Volume 33, Issue 15S, Part I of II

May 20, 2015

Journal of Clinical Oncology

Official Journal of the
American Society of Clinical Oncology

2015 ASCO Annual Meeting Proceedings

51st Annual Meeting
May 29-June 2, 2015
McCormick Place
Chicago, IL

www.jco.org

ASCO

51st
Annual Meeting of the American Society of Clinical Oncology
May 29-June 2, 2015

Chicago, Illinois

2015 Annual Meeting Proceedings Part I

(a supplement to the *Journal of Clinical Oncology*)

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JOURNAL OF CLINICAL ONCOLOGY

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CONTENTS

2015 ASCO ANNUAL MEETING PROCEEDINGS

continued on following page

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American Society of Clinical Oncology
51st Annual Meeting

2015 Abstracts

Descriptions of Scientific Sessions

Plenary Session
The Plenary Session includes abstracts selected by the Scientific Program Committee as having practice-changing findings of the highest scientific merit.

Highlights of the Day Sessions
Highlights of the Day Sessions invite expert discussants to present key findings, put abstracts into clinical context, and provide an overview of the previous day's Oral Abstract Sessions.

Oral Abstract Sessions
Oral Abstract Sessions include didactic presentations of abstracts of the highest scientific merit, as determined by the Scientific Program Committee. Experts in the field serve as discussants and provide comprehensive themed discussions of the findings from the abstracts.

Clinical Science Symposia
Clinical Science Symposia provide a forum for science in oncology, combining didactic lectures on a specific topic with the presentation of abstracts. Experts in the field serve as discussants to place studies in the appropriate context and critically discuss the conclusions in terms of their applicability to clinical practice. New this year, three special Clinical Science Symposia will be designated around specific pathways that cut across cancer types.

Poster Discussion Sessions
Select posters from the Poster Sessions will be discussed by expert discussants, with the abstract authors participating as panel members. These sessions will be followed by networking with the discussants and authors.

Poster Sessions
Poster Sessions include selected abstracts of clinical research in poster format. Trials in Progress (TPS) abstracts are presented within a track's Poster Session.

Publication-Only Abstracts
Publication-only abstracts were selected to be published online in conjunction with the Annual Meeting, but not to be presented at the Meeting.

All presented and publication-only abstracts are citable to this Journal of Clinical Oncology *supplement. For citation examples, please see the Letter from the Editor.*

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2015 Annual Meeting. Abstracts selected for electronic publication only are available in full-text versions online through ASCO.org and JCO.org. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Annual Meeting Program or the iPlanner, the online version of the Annual Meeting Program, available at am.asco.org.

Dates and times are subject to change.
All modifications will be posted on am.asco.org.

The deadline for abstract submission for the 2016 Annual Meeting is
Tuesday, February 2, 2016, at 11:59 PM (EST).

Letter from the Editor

The *2015 ASCO Annual Meeting Proceedings Part I* (a supplement to the *Journal of Clinical Oncology*) is an enduring record of the more than 2,800 abstracts selected by the ASCO Scientific Program Committee for presentation at the 51st ASCO Annual Meeting. Accepted abstracts not presented at the meeting are included in the online supplement to the May 20 issue of *Journal of Clinical Oncology* at JCO.org.

The majority of abstracts selected for presentation are included here in full and are categorized by scientific track. After the Annual Meeting, abstracts can be accessed online through ASCO University's Meeting Library (meetinglibrary.asco.org/abstracts). Online abstracts include the full list of abstract authors and their disclosure information.

Late-Breaking Abstracts are represented here by abstract title and presenting author only. The full-text versions of these abstracts will be publicly released through ASCO.org during the Annual Meeting. Late-Breaking Abstracts will also be included in the *2015 ASCO Annual Meeting Proceedings Part II*, an online supplement to the June 20 issue of *Journal of Clinical Oncology* on JCO.org. Print versions of these abstracts will be available onsite at the Annual Meeting in the *ASCO Daily News*.

All abstracts carry *Journal of Clinical Oncology* citations. The following are citation examples for print and electronic abstracts:

J Clin Oncol 33:5s, 2015 (suppl; abstr LBA1)

J Clin Oncol 33, 2015 (suppl; abstr e12000)

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Michael A. Carducci, MD
Editor, *2015 ASCO Annual Meeting Proceedings*

JOURNAL OF CLINICAL ONCOLOGY

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3. Institutional online access, whether an online-only or bundled subscription, is for a single-site license, which allows an unlimited number of concurrent users from that site.
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5. Subscribers outside the US, add $100 per print subscription for expedited delivery.
6. Single-issue price: $40 US, $50 international.
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8. Except on Tier 5 orders, the publisher allows for a 5% discount to recognized subscription agents.

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ASCO Abstracts Policy

Public Release of Abstracts

The abstracts published in the *2015 ASCO Annual Meeting Proceedings Part I*, including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 13, 2015. These abstracts are publicly available online through ASCO.org, the official website of the Society. Late-Breaking Abstracts (LBAs), which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a press briefing or scientific presentation on Friday, May 29, will be publicly released Friday, May 29, through ASCO.org at 2:00 PM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.
- Late-Breaking Abstracts presented in a press briefing or scientific presentation on Saturday, May 30, will be publicly released Saturday, May 30, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.
- Late-Breaking Abstracts presented in a press briefing or scientific presentation on Sunday, May 31, will be publicly released Sunday, May 31, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.
- Late-Breaking Abstracts presented in a press briefing or scientific presentation on Monday, June 1, or Tuesday, June 2, will be publicly released Monday, June 1, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on ASCO.org.

Abstract Notice

All abstracts presented at and published in conjunction with the Annual Meeting are included in online supplements to the *Journal of Clinical Oncology*. The abstracts released on May 13, 2015, are included in the May 20 (Vol. 33, No. 15S) issue (*2015 Annual Meeting Proceedings Part I*), and the Late-Breaking Abstracts, released on a daily basis during the Meeting, are included in the June 20 (Vol. 33, No. 18S) issue (*2015 Annual Meeting Proceedings Part II*).

ASCO's Policy for Relationships with Companies

In compliance with standards established by ASCO's Policy for Relationships with Companies (Conflict of Interest; J Clin Oncol. 2013;31[16]:2043–2043) and the Accreditation Council for Continuing Medical Information (ACCME), ASCO's intent is to promote balance, independence, objectivity, and scientific rigor through the disclosure of financial and other interests, and in the identification and management of potential conflicts. According to the ASCO's Policy for Relationships with Companies, all authors are expected to provide general disclosure information for 11 disclosure categories of relationships with for-profit health care companies.

The requirements in ASCO Conflict of Interest Policy apply to all abstract authors. Authors may enter their own disclosures using the ASCO Disclosure Management System online at coi.asco.org. By establishing a disclosure on coi.asco.org, authors will have a unified disclosure across all ASCO activities, including volunteer service, journals, and abstracts submissions. If an author has provided disclosure through ASCO Disclosure Management System, the information will automatically populate in the submission site.

Alternatively, a submitting author can enter disclosure information from coauthors who opt not to use the ASCO Disclosure Management System through the Abstract Submitter program. Copies of the Disclosure Form can be sent to coauthors for completion and returned to the submitting author before submission of the abstract.

Per the Implementation Plan to Manage Relationships with Companies for CME Activities, all oral abstract presenters will be subject to the same disclosure review and management strategies as faculty who participate in ASCO CME activities.

Please visit asco.org/rwc for more information on the ASCO Conflict of Interest Policy and the Conflict of Interest Policy Implementation Plan for CME Activities.

Additional Disclosure Questions for First, Last, and Corresponding Authors of Original Research

The first, last, and corresponding authors are required to answer additional questions specific to their abstract. ASCO will not enforce restrictions listed in ASCO's Policy for Relationships with Companies on first, last, and corresponding authors and will reconsider whether to do so after a period of data gathering and analysis that will continue at least through April 22, 2016. Financial relationships of first, last, and corresponding authors are still required to be disclosed and will be managed in accordance with ASCO procedures.

ABSTRACTS
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SPECIAL AWARD LECTURE ABSTRACTS

David A. Karnofsky Memorial Award and Lecture
Saturday, May 30, 9:30 AM

PD-1 pathway blockade: A common denominator for cancer therapy.

Suzanne L. Topalian, MD; Johns Hopkins Kimmel Cancer Center; Johns Hopkins Kimmel Cancer Center, Baltimore, MD

In the current era in oncology emphasizing personalized therapy, PD-1 pathway blockade is distinguished by its "common denominator" approach. The genetic diversity found in most human cancers creates challenges for therapies directed against individual mutations but exposes a panoply of new targets for potential immune recognition. However, immune cells that recognize and are poised to attack cancer cells are held in check at the tumor site by suppressive molecular pathways (so-called "immune checkpoints"). Nearly twenty years ago, laboratory studies revealed that blocking the prototypical immune checkpoint Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) could mediate tumor regression in murine models, leading to the clinical development and approval of anti-CTLA-4 (ipilimumab) for treating patients with advanced melanoma in 2011. More recently, drugs blocking the distinct checkpoints Programmed Death 1 (PD-1) and its major binding partner PD-L1 have shown great promise in treating diverse cancer types. The realization that non-small-cell lung cancer is susceptible to anti-PD-1/PD-L1 immediately broadened the horizon for cancer immunotherapy as a general treatment modality–lung and other common epithelial cancers had not previously responded to various immunotherapies and were thought to be relatively "non-immunogenic." Durable regressions of advanced treatment-refractory kidney, bladder, ovarian, and head and neck cancers, as well as melanoma and Hodgkin's lymphoma, following PD-1 pathway blockade have fueled the intensive examination of predictive biomarkers and a growing cohort of unique checkpoint molecules as potential drug targets. These translational research efforts have provided new treatment options and are revo-lutionizing therapeutic algorithms. The complex biology of immune checkpoint pathways still contains many mysteries, and the full activity spectrum of drugs blocking these pathways, used alone or in combination, is unknown. Armed with a new scientific understanding and unprece-dented clinical opportunities, the field of immunotherapy is now standing on the threshold of even greater advances in the war against cancer.

Science of Oncology Award and Lecture
Sunday, May 31, 1:00 PM

Immune checkpoint blockade in cancer therapy: New insights and opportunities.

James P. Allison, PhD; University of Texas MD Anderson Cancer Center, Houston, TX

The existence of multiple nonredundant I inhibitory pathways that limit T cell responses offers novel strategies for mobilizing the immune system to attack cancer cells. The best characterized of these immune checkpoints is CTLA-4, which inhibits CD28 mediated costimulation. Antibodies to CTLA-4 have proven effective against multiple tumor types in both preclinical and clinical studies. Ipilimumab, an antibody to human CTLA-4, showed long term (>4.5 years) survival benefit in about 23% of patients in a randomized, placebo-controlled trial in late stage melanoma. In 2011 it was approved by the FDA for treatment of late stage melanoma and is now a standard of care for that disease. The mechanism(s) of action of anti-CTLA-4 are still being elucidated. CTLA-4 blockade results in an increase in the frequency of CD4 T cells expression ICOS (inducible costimulator) in both tumor tissues and blood. This population contains that vast majority of tumor-specific cells that produce IFNγ and TNFα Using mouse models, we have shown that the ICOS/ICOSL pathway is critical for optimal antitumor activity of anti-CTLA-4 and that ICOS is a compelling molecule to develop as a target for agonistic targeting of costimulatory checkpoints. PD-1, another checkpoint, works by interfering with T cell antigen receptor signaling, a completely different mechanism that CTLA-4. It has two ligands, PD-L1 and PD-L2, which are both expressed on dendritic cells. However, many tumor cells also express PD-L1. Antibodies to PD-1 and PD-L1 have both shown objective responses against several tumor types in clinical trials with response rates of about 25%. A recent phase II trial of a combination of anti-PD-1 and anti-CTLA-4 in melanoma showed objective responses in about 50% of late stage melanoma patients. Our studies of the mechanisms involved in the antitumor effects and of more effective combinations will be discussed.

ASCO–American Cancer Society Award and Lecture
Monday, June 1, 11:30 AM

Cancer prevention as our first best hope: Action in prevention research and cancer control.

Ernest Hawk, MD, MPH; Division of Cancer Prevention and Population Sciences, University of Texas MD Anderson Cancer Center, Houston, TX

The global context of cancer is rapidly changing as the population ages and progressively adopts unhealthy lifestyles. It is anticipated that low-to middle-income countries will bear the majority of the future cancer burden. Cancer prevention will be critical to address this growing challenge. But in order to do so, concerted efforts are needed on two fronts: (1) discovery: to better understand at a molecular and cellular level what initiates and drives early cancer development to find effective screening tools and interventions that can be administered much earlier in the disease process; and (2) dissemination: to use existing evidence to formulate and implement effective community-oriented programs involving public policy, public education, and clinical preventive services that reduce cancer risks. NCI-designated cancer centers are in a unique position to collaboratively advance prevention research and cancer control, and the Affordable Care Act is providing unprecedented opportunities to reimburse for clinical delivery of evidence-based preventive interventions. In both the clinical and population contexts, the ultimate goal is safe, timely, effective, efficient, equitable, patient-centered or culturally-tailored preventive care, sustainable across time and populations. Together, the two complementary approaches of molecular prevention and cancer control offer an optimal approach to cancer - combining adoption and maintenance of healthy lifestyles, evidence-based screening and early detection, with precision treatment of early-stage lesions. Growing evidence supports the importance of such a strategy, demonstrating significant reductions in cancer risk as well as cardiovascular-, cancer-related, and all-cause mortality in those adhering to cancer prevention recommendations. To this end, we must aspire to elevate cancer prevention and control as the first strategy to address cancer, in every regard, everywhere, and by all means—whether through molecular prevention, lifestyle modifications, screening and early detection, or policy and educational initiatives.

B. J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology
Sunday, May 31, 9:45 AM

Transforming data into activities designed for older cancer patients.

Silvio Monfardini, MD; Istituto Palazzolo, Fondazione Don Gnocchi, Milano, Italy

Clinical oncologists should be well prepared for the inevitable increase of older cancer patients in the next decades. Extensive data have been provided by many studies on the results of treatment for elderly patients in most tumor types and on the special approach needed to evaluate such patients. As a result, the International Society of Geriatric Oncology issued appropriate guidelines. Tools helping to predict treatment-related toxicity have been studied and a specific methodology for clinical trials in the elderly is now available. To acquire these data the interaction between oncologists and geriatricians has been essential. In the United States, ASCO and NCI-NIA nationwide initiatives have been emphasizing dual training and research, whereas in France a centralized universalistic approach aims to the collaboration between geriatricians and oncologists. In some other European nations, several models of care delivery and cooperation have been developed. The integrated approach built up with these national initiatives needs to be reinforced and spread, providing the background for the implementation of new research projects. Main obstacles to take action in the United States and Europe are the geriatricians shortfall and their time constraint due to being engaged with other multiple tasks at their institutions other than overhelming numbers of older cancer patients. Local health care situations differ, but the best suited modality of cooperation among oncologists, geriatricians, and allied health professionals should always be found. Innovation through interaction with geriatricians should be brought into surgical oncology and even more in radiotherapy. A greater interaction is also necessary to study how to deliver optimal post-treatment care to older cancer survivors. Studies are also needed for frail cancer patients, the majority of whom are located in nursing homes.

Pediatric Oncology Award and Lecture Childhood cancer survivors: A lifetime of risk and responsibility.
Saturday, May 30, 1:15 PM

An autobiography of "we."

Stephen E. Sallan, MD; Dana-Farber Cancer Institute, Boston, MA

Simultaneously stunning and yet unsurprising, over the past 40 years the collective endeavors of a relatively small community of pediatric investigators have fundamentally impacted the field of childhood cancer. Cure is expected for the vast majority of affected children. Today's research focuses on currently intractable variants of disease, more precisely targeted therapies, and diminution of the sequelae of curative treatments. With an emphasis on training and mentorship, and in recognition that every successful endeavor represents the intertwined and inseparable contributions of many individuals, this presentation will encompass the common ground and collective attributes of the pediatric oncology community. The community's commitment to discovery in the context of clinical trials and the importance of the two-way street between clinical investigators and basic science laboratories will be addressed. In essence, the presentation will consider the too often overlooked "sociology" of our community: Who are we? How did we get here? How do we accomplish our work? Where are we going?—An overview of our collective career journeys as one transitions from "I to We to Them."

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LBA1 **Plenary Session, Sun, 1:00 PM-4:00 PM**

Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067). *First Author: Jedd D. Wolchok, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, May 31, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA2 **Plenary Session, Sun, 1:00 PM-4:00 PM**

Reduction in late mortality among 5-year survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Gregory T. Armstrong, St. Jude Children's Research Hospital, Memphis, TN*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, May 31, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA3 **Plenary Session, Sun, 1:00 PM-4:00 PM**

Elective versus therapeutic neck dissection in the clinically node negative early oral cancer: A randomised control trial (RCT). *First Author: Anil D'Cruz, Tata Memorial Hospital, Mumbai, India*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, May 31, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA4 **Plenary Session, Sun, 1:00 PM-4:00 PM**

NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. *First Author: Paul D. Brown, The University of Texas MD Anderson Cancer Center, Houston, TX*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, May 31, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA100 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

PD-1 blockade in tumors with mismatch repair deficiency. *First Author: Dung T. Le, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 29, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

LBA101 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. *First Author: Anthony B. El-Khoueiry, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 29, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

102 **Clinical Science Symposium, Sun, 9:45 AM-11:15 AM**

Overall survival in COMBI-d, a randomized, double-blinded, phase III study comparing the combination of dabrafenib and trametinib with dabrafenib and placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. *First Author: Georgina V. Long, Melanoma Institute Australia and The University of Sydney, North Sydney, Australia*

Background: This phase III study (NCT01584648) of dabrafenib (D) + trametinib (T) compared with D + placebo (P) demonstrated superior progression-free survival (PFS) for D+T compared with D+P (HR = 0.75 ; 95% CI: 0.57–0.99; p = 0.035) in pts with BRAF V600E/K mutant, metastatic melanoma at the primary analysis (N Engl J Med 2014;371: 1877). The interim overall survival (OS) favored D+T (40 deaths on D+T vs 55 on D+P), but did not cross the pre-planned stopping boundary for efficacy. Median time on study at the primary analysis was 9 months (0–16 months). Rates of adverse events (AEs) were similar for both arms. More pts had AEs leading to dose modifications with D+T vs D+P, and fewer hyperproliferative skin AEs were reported with D+T. The study was continued after the primary analysis to evaluate OS without crossover from D+P to D+T. **Methods:** Pts were randomized 1:1 to receive D (150mg twice daily) + T (2mg once daily) or D+P as first-line therapy. Eligible pts were age 18 or older, ECOG performance status ≤ 1, and had histologically confirmed unresectable stage IIIC or IV, BRAF V600E/K mutant cutaneous melanoma. The primary endpoint was investigator-assessed PFS; secondary endpoints were OS, overall response rate (ORR), duration of response (DoR), and safety. The final statistical OS comparison was to be initiated when 220 events were reported. **Results:** From May 2012 to January 2013, 423 pts were randomized (211 to D+T, 212 to D+P). The 220th death was reported on Jan 12, 2015; analysis is expected to be completed in Mar 2015. Estimated median time on study at data cut off is 20 months (0-31 months). **Conclusions:** The statistical analysis will evaluate the superiority of D+T vs D+P for OS. A 2-year OS landmark analysis, updated PFS, ORR, DoR, and safety will be presented. Clinical trial information: NCT01584648.

103 **Clinical Science Symposium, Sun, 9:45 AM-11:15 AM**

Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with *BRAF* V600E mutated (BRAFm) metastatic colorectal cancer (mCRC). *First Author: Chloe Evelyn Atreya, University of California, San Francisco, San Francisco, CA*

Background: *BRAF* V600E mutations occur in 5–10% of mCRC and confer a poor prognosis. Unlike BRAFm melanoma, BRAF and MEK inhibitors have minimal activity in BRAFm mCRC. Preclinical data suggest that combined inhibition of the EGFR and MAPK pathways is required to maximally inhibit growth of BRAFm mCRC. This study evaluates the activity of the combination of P with D and/or T in BRAFm mCRC. **Methods:** Eligible pts with BRAFm mCRC received doublet, D+P or T+P, or triplet, D+T+P. **Results:** Doublet (D+P): 20 pts received the full doublet dose (D 150mg twice daily [BID] + P 6mg/kg every 2 weeks [Q2W]). Triplet: 35 pts received D+T+P including 24 pts that received full triplet dose (D 150mg BID + T 2mg once daily [QD] + P 6mg/kg Q2W). No dose-limiting toxicities were observed. As of October 20, 2014, the most common adverse events were dermatitis acneiform (Grade [G] 1/2 55%) and fatigue (G 1/2 45%) for D+P, and diarrhea (G1/2 60%, G3 9%) and dermatitis acneiform (G1/2 47%; G3 9%) for triplet. The confirmed response rate for D+P was 10% and for D+T+P was 26% (Table 1). Treatment with either regimen reduced levels of pERK in on-treatment biopsies relative to pre-dose biopsies (median reduction D+P 23%; D+T+P 54%). Pts are currently being enrolled to T+P. Updated results including progression-free survival and duration of response will be presented. **Conclusions:** Encouraging clinical activity with acceptable tolerability is seen with the triplet D+T+P in BRAFm mCRC. Clinical trial information: NCT01750918.

Investigator–assessed best response with confirmation (RECIST 1.1).

	D 150 mg BID+ P 6mg/kg Q2W N = 20	D 150 mg BID, T 1.5 mg QD, P 4.8 mg/kg Q2W N = 3	D 150 mg BID, T 2 mg QD, P 4.8 mg/kg Q2W N = 4	D 150 mg BID, T 1.5 mg QD, P 6 mg/kg Q2W N = 4	D 150 mg BID, T 2 mg QD, P 6 mg/kg Q2W N=24	D+T+P Total N = 35
Complete response, n (%)	1 (5)	0	1 (25)	0	0	1 (3)
Partial response, n (%)	1 (5)	2 (67)	1 (25)	0	5 (21)	8 (23)
Stable disease, n (%)	16 (80)	1 (33)	2 (50)	2 (50)	15 (63)	20 (57)
Progressive disease, n (%)	2 (10)	0	0	2 (50)	3 (13)	5 (14)
Not evaluable, n (%)	0	0	0	0	1 (4)	1 (3)
Response rate (CR+PR), n (%)	2 (10)	2 (67)	2 (50)	0	5 (21)	9 (26)
95% confidence interval, %	1.2–31.7	9.4–99.2	6.8–93.2	0.0–60.2	7.1–42.2	12.5–43.3

104 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

A pharmacokinetic (PK) and pharmacodynamic (PD) biomarker-driven phase I study of intermittent, low dose intensity schedules of the dual MEK/RAF inhibitor, RO5126766 (RO) in patients (pts) with advanced solid tumors. *First Author: Maria Jose de Miguel Luken, Royal Marsden Hospital/ Institute of Cancer Research, Sutton, United Kingdom*

Background: RO5126766 is a novel dual MEK-RAF inhibitor. A previous phase I study explored high dose intensity schedules that were limited by a $t_{1/2}$ of 60 hours and a challenging toxicity profile. We hypothesised that schedules that achieve significant target modulation but a lower dose intensity due to intermittent dosing will lead to clinically effective and tolerable schedules of RO5126766. **Methods:** The aims of this investigator-initiated study (EudraCT: 2012-001040-22) were to determine the tolerability, PK, PD and preliminary antitumor activity of 2 dosing schedules: orally once daily on Mon-Wed-Fri (MWF) and Mon & Thu (MT). An expansion cohort mandated patients (pts) with *K-* or *N-RAS/B-RAF* mutations. Plasma PK and phosphorylated (p)-ERK in peripheral blood mononuclear cell (PBMCs) were analysed. Tumor PD was assessed in pre- and post-treatment tumor biopsies and diffusion-weighted MRI (DWI). **Results:** To date, 29 pts have been treated. MWF schedule; 3.2 mg and 4 mg (n = 7 each) and MT schedule; 4 mg (n = 8) and expansion cohort (n = 7). Dose-limiting toxicities (DLTs) on the MWF schedule were G3 blurred vision (n = 1) at 4 mg, and G3 skin rash and G4 creatine kinase (CK) elevation (n = 2) at 3.2 mg. No DLTs were recorded in the MT schedule. Most common toxicities were rash, CK elevation, fatigue, mucositis and diarrhea. PK profile at 4 mg MT showed a C_{max} of 247 ng/mL and an AUC of 3,580 ng.hr/mL, consistent with growth inhibition in xenograft models. Maximal PD inhibition of p-ERK in PBMCs was 83% at 3.2 mg, thus both 3.2 mg and 4 mg were in the pharmacodynamically active range. Based on the tolerability, PK and PD profiles, 4 mg MT was declared the recommended phase 2 dose (RP2D). At the RP2D, 3/7 (42.9%) pts with *KRAS* mutations (NSCLC, ovarian and endometrial cancers) achieved RECIST confirmed partial responses and DWI showed increased apparent diffusion coefficient (ADC) at 15 days post-dose in these pts. Recruitment to the expansion cohort is ongoing. **Conclusions:** The RP2D of RO5126766 was defined as 4 mg orally, delivered twice a week, MT, and is associated with preliminary promising single agent activity in *KRAS* mutant tumors. Clinical trial information: 2012-001040-22.

105 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Phase I study of combination vemurafenib, carboplatin, and paclitaxel in patients (pts) with *BRAF*-mutant advanced cancer. *First Author: Shumei Kato, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Although BRAF inhibitors have demonstrated efficacy, resistance develops in most pts. We hypothesized that BRAF inhibitor vemurafenib, in combination with carboplatin and paclitaxel, would be well-tolerated and overcome resistance. **Methods**: We designed a phase I study (3+3 design) to determine safety of vemurafenib (480-960 mg twice a day) with carboplatin (AUC 5-6 q3 weeks) and paclitaxel (75-175 mg/m^2 q3 weeks). Endpoints included maximum tolerated dose (MTD), dose limiting toxicity (DLT), and response (RECIST 1.1). **Results**: To date, 19 pts have enrolled. Pts received vemurafenib (480-720 mg twice a day), carboplatin (AUC 5-6) q3 wks, and paclitaxel (100-135 mg/m^2) q3 wks. Median age was 53 yrs (range 33-75) with median of 4 prior systemic therapies (range 1-7). Eleven pts (58%) had received prior BRAF inhibitors, 3 pts (16%) MEK inhibitors, 8 pts (42%) platinum therapy, and 3 pts (16%) taxane therapy. Pts (13/19 [68.4%] with melanoma and n = 1 pt each of cholangiocarcinoma, histiocytoma, papillary thyroid [PTC], anal, unknown primary, pancreatic cancer) had *BRAF* V600E (n = 15), V600K (n = 1) or other *BRAF* mutation (n = 1 each for R6712, del N486-P490, and D459G). MTD has not yet been reached. Two pts had DLTs (G2 creatinine elevated >7 days [n = 1], G3 transaminitis and G4 thrombocytopenia [n = 1]). Five pts had grade ≥ 3 drug-related toxicity with neutropenia (n = 5), thrombocytopenia (n = 5), fatigue (n = 4), anemia (n = 3), and hyponatremia (n = 2). Six out of 19 pts (32%) had objective response (all melanoma pts with *BRAF*V600E [n = 5] and V600K [n = 1] mutation), including 1 complete and 5 partial responses. Four of the 6 responding pts had progressed on prior vemurafenib. Of 11 pts who had received a prior BRAF inhibitor, 4 (36%) achieved objective response. One PTC pt with V600E mutation had prolonged stable disease of 24 months. Among pts with melanoma, response rate was 46% (6/13 pts), with median PFS of 4.9 months (range 0.2–18.4). **Conclusions**: Combination vemurafenib, carboplatin, and paclitaxel is tolerated in pts with advanced cancer. Responses were observed in melanoma pts previously resistant to BRAF inhibitors, suggesting that the combination may overcome resistance. MTD has not yet been reached, and dose escalation continues. Clinical trial information: NCT01636622.

106 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Successful implementation of a novel trial model: The Signature program. *First Author: Julio Antonio Peguero, Oncology Consultants PA, Houston, TX*

Background: Here we describe 8 ongoing single agent clinical protocols under Novartis' "Signature" program involving buparlisib (BKM120, PI3Ki), dovitinib (TKI258, multikinase inhibitor), binimetinib (MEK162, MEKi), encorafenib (LGX818, RAFi), ribociclib (LEE011, CDK4/6i), BGJ398 (FGFRi), ceritinib (LDK378, ALKi) and sonidegib (LDE225; SMOi). These are tissue-agnostic, genetic alteration-specific (mutation, amplification, translocation, etc.) protocols using patients (pts) identified via standard-of-care profiling. This brings the 'Protocol to the Patient' for pts with actionable genetic alterations and who would like access to drugs targeting those alterations. **Methods:** Pts with advanced solid and hematologic cancers and no standard therapeutic options are eligible. Pts are preidentified with a local test performed in a CLIA laboratory for an actionable genetic alteration. Indications where existing data showed no benefit, or key studies were planned, were excluded from accrual. The primary objective is to assess clinical benefit (SD or better for ≥ 16 weeks) for each compound. A novel adaptive statistical design is used to cluster pts of like indications into cohorts for independent analysis for futility (minimum 10 pts) or efficacy (minimum 15 pts). **Results:** Between March 2013 – January 2015, 16 academic and 151 unique community/network sites have dosed 368 pts; buparlisib (142), dovitinib (73), binimetinib (90), encorafenib (9), ribociclib (30), BGJ398 (12), ceritinib (3) and sonidegib (9) with completed cohorts for buparlisib (CRC, ovarian, sarcomas, HNSCC, cervix), dovitinib (CRC, GIST), and binimetinib (lung). The average startup timeline was 5.2 weeks.The most frequent genetic alterations were RAS mutation (68%), PIK3CA mutation (55%), and PTEN loss (41%). Preliminary activity was observed in various tumors; buparlisib (vaginal, HNSCC), dovitinib (ovarian), and binimetinib (AML, ovarian, thyroid). **Conclusions:** This program allows rapid enrollment of molecularly profiled pts with genetic alterations linked to cognate targeted agents. Early signs of clinical activity suggest potential for detection of new indications using a pt-sparing design that could lead to subsequent confirmatory trials.

107 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Prospective evaluation of circulating tumor DNA sequencing in pancreatobiliary carcinomas. *First Author: Eric Andrew Collisson, UC San Francisco, San Francisco, CA*

Background: Pancreatobiliary carcinomas (PC) carry a poor prognosis but have not yet benefitted from the revolution in precision oncology, in part because biopsy tissue is often inadequate for molecular characterization. Cell-free DNA (cfDNA) sequencing tests may provide access to genetic testing and monitoring for advanced PC patients. **Methods:** Twenty-five advanced PC patients were enrolled prospectively in a trial to assess the feasibility, accuracy, and clinical utility of cfDNA next-generation sequencing (NGS) of 54 cancer genes. cfDNA mutations were compared to those detected by biopsy-based NGS tests, and the concordance of the two was determined. cfDNA sequencing in disease monitoring was compared to changes in secreted tumor markers in a subset of patients. **Results:** The NGS-based cfDNA test detected cancer mutations in 21 of 25 (84%) advanced PC patients and provided actionable findings for four patients. Multi-gene sequencing data was available from both blood-based and biopsy-based methods for 17 patients. Over 90% of mutations detected by the biopsy-based genetic tests were detected in cfDNA in these 17 evaluable patients. Four additional mutations were detected by cfDNA sequencing that were not detected in tumor tissue. Tumor biopsy NGS failed for 8 patients, equating to a considerably higher failure rate (32%) than the overall failure rate reported by commercial vendors. Three cfDNA mutations in these patients suggested a new therapeutic option. An activating EGFR-exon19 deletion was observed in cfDNA for one patient, which was later confirmed by a biopsy test and empowered successful treatment with erlotinib. The average diagnostic accuracy of cfDNA sequencing was 97%, with 92% average sensitivity and 100% specificity across the cohort. Changes in cfDNA mutation frequencies correlated with changes in tumor marker measurements (Pearson's r = 0.7). **Conclusions:** cfDNA sequencing is a clinically practicable alternative to biopsy-based tumor DNA sequencing in PC. cfDNA from most PCs showed high mutational concordance with tissue biopsy, and showed high tumor-burden concordance with tumor markers. cfDNA sequencing should be considered for prospective therapeutic trials in pancreatobiliary cancers.

108 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Circulating tumor cells (CTC) and pathological complete response (pCR) as independent prognostic factors in inflammatory breast cancer (IBC) in a pooled analysis of two multicentre phase II trials (BEVERLY 1 & 2) of neoadjuvant chemotherapy combined with bevacizumab. *First Author: Jean-Yves Pierga, Institut Curie, Paris, France*

Background: We have reported that CTC detection is an independent prognostic factor in 52 primary HER2+ IBC (Pierga, CCR 2014). We present a pooled analysis of two prospective trials including 152 patients (pts). Predictive and prognostic value of Circulating Endothelial Cells (CEC) for response to bevacizumab was also analyzed. **Methods:** CTC and CEC were detected in 7.5 ml and 4 ml of blood respectively in the neoadjuvant setting in IBC (T4d) pts enrolled in two phase II multicentre trials, evaluating bevacizumab (15mg/kg q3w) in combination with sequential neoadjuvant chemotherapy (CT) of 4 cycles of FEC followed by 4 cycles of docetaxel in HER2 - tumor (BEVERLY 1) or docetaxel, trastuzumab in HER2 + (BEVERLY 2). The CellSearch System, combining EpCAM immunomagnetic selection followed by anti-cytokeratin (A45B/B3) and anti-HER2 staining for CTC and CD146 IMS and CD105 staining for CEC. **Results:** From 10/08 to 09/10, 152 pts were included and 137 were evaluable for CTC and CEC. Median follow-up was 43 months. At baseline, 55 pts had ≥ 1 detectable CTC (39%). After 4 cycles of CT, a dramatic drop in CTC to a rate of 9% was observed. pCR rate was 40% and was associated with absence of hormonal receptor and HER2 + status. No correlation was found between CTC and CEC levels or pCR rate. CTC detection at baseline independently predicted 3-year disease-free survival (DFS): (70% vs. 39% for pts with < 1 vs. ≥ 1 CTC/7.5 mL [$p < 0.001$, HR 2.80 (1.65-4.76)]) and 3-year overall survival (OS) (92% vs 56% HR 4.28 $p < 0.001$). At multivariate analysis, independent prognostic parameters for DFS were absence of hormonal receptors, no pCR, and CTC detection at base-line. CEC level at baseline or variations during treatment had no prognostic value. **Conclusions:** This is the largest prospectives trial in non-metastatic IBC evaluating CTC detection. We observed a high CTC detection rate of 39%, with a strong and independent prognostic value for DFS and OS. Combination of pCR after neoadjuvant treatment, with CTC at baseline, isolates a subgroup of IBCwith excellent survival. CTC count should be part of IBC stratification in prospective trials. Clinical trial information: NCT00820547.

LBA109 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). *First Author: Luis Paz-Ares, Hospital Universitario Virgen Del Rocio, Sevilla, Spain*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 29, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

200 **Special Session, Fri, 1:00 PM-5:45 PM**

Randomized controlled trial of comparing gastrectomy (Gx) plus chemotherapy (CTX) with CTX alone in advanced gastric cancer (AGC) with a single non-curable factor: JCOG 0705/KGCA01 study (REGATTA). *First Author: Han-Kwang Yang, Department of Surgery, Seoul National University Hospital, Seoul, South Korea*

Background: The prognosis of AGC with non-curable factors is poor. Chemotherapy is the standard-of-care for those patients. However, literatures suggest that Gx may improve patients' survival. Based on these, we conducted an international randomized trial to test the role of Gx in AGC with a single non-curable factor. This trial was performed in Japan, Korea, and Singapore. **Methods:** Eligibility criteria included histologically proven gastric adenocarcinoma, cT1-3, presence of a single non-curable factor confined to either liver (H1), peritoneum (P1), or para-aortic lymph node (16a1/b2) confirmed by both CT scan and laparoscopy/laparotomy, no other distant metastasis, aged 20-75, and PS 0-1. Eligible patients were randomized to Gx followed by CTX or CTX alone. Gx with D1 lymph node dissection was recommended without resection of metastatic lesions. CTX regimen was S-1 80 mg/m2/day on days 1-21 plus CDDP 60 mg/m2 on day 8 repeated every 5 weeks. The primary endpoint was overall survival (OS). The planned sample size was 165 cases per arm, with one-sided alpha of 5%, and an 80% power detecting a 2y-survival difference of 10% (20% with CTX alone vs. 30% with Gx and CTX). **Results:** Between Feb 2008 and Aug 2013, 175 patients (95 in Japan, 80 in Korea) were randomized. 89 pts were randomized to Gx and CTX, and 86 pts were randomized to CTX alone. The first interim analysis was performed in Sep 2013, with 37% (110/294) of the planned events observed, and JCOG DSMC recommended early termination of the trial based on the overall futile effect. In the updated analysis in Dec 2014 with a median follow-up period of 14.5 months, the 2y-OS were 25.1 (95% CI: 16.2 to 34.9) % with Gx followed by CTX and 31.7 (95% CI: 21.7 to 42.2) % with CTX alone ($p = 0.68$). However, subgroup analyses suggested gastrectomy might be beneficial especially for patients with L lesion or cN2/N3. **Conclusions:** In all randomized patients, Gx followed by CTX has no survival benefit over CTX alone for AGC patients with a single non-curable factor. There is a room to re-evaluate the additional gastrectomy confined to the patients in whom distal gastrectomy suffices for tumor resection. Clinical trial information: UMIN000001012.

LBA500 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Primary results, NRG Oncology/NSABP B-35: A clinical trial of anastrozole (A) versus tamoxifen (tam) in postmenopausal patients with DCIS undergoing lumpectomy plus radiotherapy. *First Author: Richard G. Margolese, NRG Oncology/NSABP, and The Jewish General Hospital, McGill University, Montréal, QC, Canada*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

501 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Phase III trial evaluating the addition of bevacizumab to letrozole as first-line endocrine therapy for treatment of hormone-receptor positive advanced breast cancer: CALGB 40503 (Alliance). *First Author: Maura N. Dickler, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Preclinical data suggest estradiol modulates angiogenesis under both physiologic and pathologic conditions. High vascular endothelial growth factor (VEGF) levels in breast tumors have been associated with decreased response to endocrine therapy (ET). We performed a multicenter, open label phase III trial of the addition of bevacizumab (B) to first-line letrozole (L) in patients (pts) with hormone-receptor positive (HR+) advanced breast cancer to test the hypothesis that anti-VEGF therapy may delay progression on ET. **Methods:** Pts were randomized 1:1 to L (2.5 mg orally daily) or L+B (15 mg/kg intravenously every 3 weeks) within strata defined by measurable disease (Yes/No) and disease-free interval ($\leq$ / $>$ 24 months (mo)). Pts electing to receive tamoxifen by physician choice were enrolled in a parallel, randomized phase II trial. The primary endpoint was progression-free survival (PFS), defined as time from randomization to progression (RECIST v1.0) or all-cause death. Secondary endpoints were response rate, clinical benefit rate, overall survival (OS) and adverse events (CTCAE v3.0). Three hundred and fifty-two pts and 274 events were needed for 90% power to detect a hazard ratio (HR) of 0.67 (corresponding to an increase in median PFS from 6 to 9 mo). **Results:** From May 2008 to November 2011, 350 pts were randomized to the phase III trial. 343 pts received treatment and are included in the efficacy analysis. Median age was 58 (25-87). After 36 mo of additional follow-up, 258 PFS events were observed. Median PFS for L+B was 20 mo vs. 16 mo for L (HR = 0.74, 95% CI: 0.58 - 0.95; p = 0.016). There was no significant difference in OS (L+B, 47 mo vs. L, 41 mo; HR = 0.84; 95% CI, 0.61 - 1.15; p = 0.27). The most frequently reported grade 3/4 toxicities on L+B and L, respectively, were hypertension (23 vs 2%) and proteinuria (11 vs 0%). **Conclusions:** Adding B to first-line L improves PFS in HR+ advanced breast cancer with increased B-related toxicity. Updated data will be presented. Correlative studies are underway to identify potential biomarkers of response or resistance to therapy. Supported by U10CA180821, U10CA180882, CA31946, CA180888, CA180858, CA180820, CA180785. Clinical trial information: NCT00601900.

LBA502 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

PALOMA3: A double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy. *First Author: Nicholas C. Turner, Royal Marsden, London & Surrey, United Kingdom*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

503 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: SWOG/Alliance/ECOG-ACRIN/NCIC Clinical Trials Group/NRG Oncology study S0307. *First Author: Julie Gralow, University of Washington/ Seattle Cancer Care Alliance, Seattle, WA*

Background: Randomized trials and a recent meta-analysis suggest that adjuvant bisphosphonates can decrease recurrence and death, primarily in a postmenopausal population. SWOG S0307 compares efficacy of 3 bisphosphonates in early stage breast cancer. **Methods:** Patients with stage I-III breast cancer receiving adjuvant systemic therapy were randomized to receive 3 years of clodronate (CLOD) (1600 mg po qd), ibandronate (IBAN) (50 mg po qd) or zoledronic acid (ZA) (4 mg IV q month x 6, then q3 months x 2.5 years). The primary endpoint was disease-free survival (DFS). The target accrual of 5,400 gave $\geq$ 86% power to detect a statistically significant difference (2-sided α = 0.05) among the arms in an ITT analysis. **Results:** Late rapid accrual led to over-accrual, 6,097 patients were enrolled between 1/06-02/10. Median age was 53 with 58% post-menopausal or age 50+. 77% of tumors were ER positive, 17% HER2 positive, 16% triple negative, and 49% lymph node positive. There were more patients with grade 3/4 events with IBAN (10.5%) than CLOD (8.3%) or ZA (8.8%). Rates of ONJ were highest for ZA (1.2%), then IBAN (0.6%), followed by CLOD (0.3%). Fractures were equal across arms. 73% of patients indicated a preference for oral versus intravenous formulation if all agents showed equal efficacy. At the fourth formal interim analysis, with 56% of 1,314 expected events, the DSMC concluded that there was no realistic chance of a statistically significant difference and recommended early reporting of the trial outcomes. The primary outcome DFS did not differ across arms in a log-rank test (p = 0.71). 5-year DFS was 88% in the CLOD and ZA arms, and 87% in the IBAN arm. Overall survival was 93% in all 3 arms. Additional analyses based on age and menopausal status show no evidence of treatment differences. **Conclusions:** We found no evidence of differences in efficacy by type of bisphosphonate either in the intent to treat analysis or based on age and menopausal status. Despite differences in the type of toxicity, overall grade differed little across arms. Given that the oral study drugs are preferred by patients and approved elsewhere, efforts to make them available in the U.S. should be considered. Clinical trial information: NCT00127205.

504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Adjuvant denosumab in breast cancer: Results from 3,425 postmenopausal patients of the ABCSG-18 trial. *First Author: Michael Gnant, Medical University of Vienna, Vienna, Austria*

Background: Adjuvant endocrine therapy compromises bone health in pre- and postmenopausal breast cancer (BC) patients. Treatment-induced osteopenia, osteoporosis, and fractures are frequent side effects particularly of aromatase inhibitors (AI). Anti-resorptive treatments such as bisphosphonates have been shown to prevent and counteract these side effects of endocrine therapy, and to potentially improve survival outcomes in postmenopausal BC patients. The aim of this trial was to investigate the effects of adjuvant anti-RANK-ligand Denosumab in postmenopausal patients with early hormone receptor+ (HR+) BC receiving AI treatment. **Patients and Methods:** 3,425 postmenopausal patients with HR+ BC receiving AI were recruited in 58 sites into this prospective, randomized, double-blind, placebo-controlled, phase-III trial. Patients were randomized 1:1 to either Denosumab 60mg or placebo q6mo s.c. The primary endpoint was time from randomization to first clinical fracture, secondary endpoints included outcome (DFS, OS) and bone effects (BMD changes, vertebral fractures). **Results:** Denosumab significantly delayed the time to first clinical fracture compared to placebo (HR = 0.5, 95% CI 0.39-0.65, p $<$ 0.0001). The observed reduction in fractures between Denosumab and placebo arm (overall 92 vs 176) was similar in prognostic patient subgroups, e.g. in patients with normal bone health at baseline (n = 1,872, HR = 0.44, p $<$ 0.0001) and in patients who started the trial already osteopenic (n = 1,548, HR = 0.57, p = 0.0021). Denosumab also significantly increased BMD of the lumbar spine (9.99%), total hip (7.88%) and femoral neck (6.49%) at 36 months (compared to placebo, all adjusted p-values $<$ 0.0001). There were no differences between the Denosumab and placebo groups with respect to patient incidence adverse events (1366 vs 1334), or serious adverse events (521 vs 511). Despite proactive adjudication of potential ONJs by an independent expert panel, no ONJ case was observed. **Conclusion:** Adjuvant Denosumab significantly reduces fractures in postmenopausal BC patients receiving AI, and improves bone mineral density. Adjuvant Denosumab can be administered at this schedule with a favorable safety profile. Clinical trial information: NCT00556374.

505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). *First Author: Luca Gianni, Oncologia Medical, Ospedale San Raffaele IRCCS, Milan, Italy*

Background: InNeoSphere, four cycles of T+D, P+T+D, P+T, or P+D, followed by surgery and adjuvant chemotherapy plus conventional T, were evaluated in 417 women with locally advanced, inflammatory, or early HER2-positive breast cancer. The addition of P to T+D led to a statistically significant and clinically meaningful 16.8% increase (95% confidence interval [CI], 3.5–30.1; $P = .0141$) in pathologic complete response rate (pCR) in the breast (bpCR, ypT0/is; primary endpoint), and a 17.8% increase in total pCR in the breast and axilla (tpCR, ypT0/is, ypN0). **Methods**: A pre-planned descriptive intent-to-treat analysis was conducted 5 years after randomization of the last patient, to evaluate disease-free survival (DFS; time from surgery until progression or death) and progression-free survival (PFS; time from randomization until progression or death, equivalent to the commonly used definition of event-free survival). **Results:** Three-year survival rates, hazard ratios (HRs), and 95% CIs for the main analysis of P+T+D compared with T+D are summarized in the table. In the P+T and P+D arms, respectively, 3-year survival rates were 88% and 84% for DFS, and 81% and 82% for PFS. Across all four treatment arms pooled, for all patients who achieved tpCR versus all patients who did not achieve tpCR, the HR for DFS was 0.68 (95% CI, 0.36–1.26) and the HR for PFS was 0.54 (95% CI, 0.29–1.00). **Conclusions:** Longer-term outcomes as defined by three-year survival rates, are in line with the results of the primary endpoint (bpCR), suggesting a benefit of P added to T+D that persists over time despite use of identical adjuvant therapy in the P+T+D and T+D arms. These results also support the association between pCR and improvements in long-term outcomes. Clinical trial information: NCT00545688.

		T+D (n = 107)	P+T+D (n = 107)
DFS	3-year Kaplan–Meier survival estimate, %	85	92
	HR*	–	0.60
	(95% CI)	–	(0.28–1.27)
PFS	3-year Kaplan–Meier survival estimate, %	86	90
	HR*	–	0.69
	(95% CI)	–	(0.34–1.40)

* Compared with T+D

506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Efficacy of 12-weeks of neoadjuvant TDM1 with or without endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer: WSG-ADAPT HER2+/HR+ phase II trial. *First Author: Nadia Harbeck, University of Munich, Otterfing, Germany*

Background: Evidence suggests differential efficacy of standard neoadjuvant chemo- + targeted therapy in HER2+ early breast cancer (eBC) according to hormone-receptor (HR) status. ADAPT HER2+/HR+ aims to identify responders to dual targeted therapy, which has not been widely explored. **Methods:** 380 patients (pts) receive 12 weeks of neoadjuvant therapy. Arms A/B: T-DM1 (3.6 mg/kg q3w) ± endocrine therapy (ET) (pre-: tamoxifen; postmenopausal: aromatase inhibitor); Arm C (control): q3w trastuzumab + ET. After surgery, pts are to receive 4xEC – 12xpaclitaxel weekly (investigators' discretion) and complete 1y trastuzumab. Trial tests pCR (yPN0 and ypT0/is) in Arms A and B compared to control (C). Biomarkers are measured at baseline and after 3 weeks. **Results**: Pre-planned interim analysis (n = 130) aimed to identify an early-response biomarker (e.g. Ki-67 drop) and to validate trial assumptions. Median age was 49 years; 55% were pre-menopausal; 40% had cT1 tumors, 51% cT2; 68% had cN0, 27% cN1; 75% had G3. Median baseline Ki67 was 30%. In all arms, 95-100% received all 4 therapy cycles. 15 SAEs occurred in 12 pts (A:4; B:6; C:2), majority are CTC grades 2 (9) or 3 (4); all pts completely recovered without sequelae. Overall pCR rate was 30.8%: A: 40.5%, B: 45.8%, C: 6.7%. The difference between either arm A or B vs. C was significant (p $<$ 0.001), but not A vs. B. Exploratory analysis suggests benefit of adding ET to T-DM1 in pre- (pCR: 28.6% for T-DM1 single agent vs. 47.6% with ET) but not in postmenopausal pts (pCR: 64.3% vs. 50%). Ki-67 quantification in the 3-week biopsy was not possible in 43.1%, mostly due to low tumor cell counts ($<$ 500); of the remaining tumors, 21.6% (16/74) had Ki-67 ≤ 10% after first cycle. Final data set is required to substantiate these findings which may also be impacted by the different ET options (Tam vs. AI). **Conclusions:** The interim analysis demonstrates for the first time clinically meaningful pCR rates ($>$ 40%) after only 12 weeks of T-DM1 ± ET without systemic chemotherapy in HER2+/HR+ eBC. Ongoing biomarker analyses include PI3K mutations and intrinsic subtypes. In 1/2015, registration phase was completed at 449 pts. Clinical trial information: NCT01745965.

507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. *First Author: Paul Anthony Ellis, Guy's Hospital and Sarah Cannon Research Institute, London, United Kingdom*

Background: In phase II and III studies, treatment with T-DM1 or with P + H + docetaxel has shown statistically significant increases in progression-free survival (PFS) and overall survival (OS) vs control regimens in patients with HER2-positive MBC. The combination of T-DM1 + P resulted in synergistic inhibition of tumor cell line proliferation in vitro. This and preliminary data from a phase II clinical trial provided the rationale for further study. **Methods:** In MARIANNE (NCT01120184), patients with centrally assessed HER2-positive (IHC3+ or ISH+) progressive/recurrent locally advanced BC or previously untreated MBC with a ≥ 6-month interval since treatment in the (neo)adjuvant setting with taxanes or vinca alkaloids were randomized 1:1:1 to HT (docetaxel or paclitaxel + H), T-DM1 (T-DM1 + placebo, hereafter T-DM1), or T-DM1 + P, at standard doses. The primary end point was PFS assessed by independent review. Comparisons between HT and T-DM1 or T-DM1 + P were considered separately. PFS was tested first for non-inferiority and for superiority only if non-inferiority was achieved. **Results:** At the clinical cutoff date, September 16, 2014, 365 patients had been randomized to HT, 367 to T-DM1, and 363 to T-DM1 + P. In each arm, approximately 31% of patients had prior (neo)adjuvant treatment with HER2-directed therapy. Approximately 37% overall had de novo disease. The study met the PFS non-inferiority end point, but not the superiority end point. OS was similar across treatment arms. **Conclusions:** These data demonstrate non-inferiority in PFS between T-DM1–containing arms and control. T-DM1–containing regimens were associated with a different toxicity profile than the control regimen. Clinical trial information: NCT01120184.

Outcome	HT	T-DM1	T-DM1 + P
Median follow-up, mo	34.8	34.9	34.7
Median PFS, mo	13.7	14.1	15.2
HR [97.5% CI]	-	0.91[0.73–1.13], p = 0.31 vs HT	0.87[0.69–1.08], p = 0.14 vs HT 0.91[0.73–1.13], p = 0.31 vs T-DM1
ORR, %	67.9	59.7	64.2
Median duration of response, mo	12.5	20.7	21.2
Grade 3–5 AEs, %	54.1	45.4	46.2
Most common grade 3–5 AEs, %			
Neutropenia	19.8	4.4	2.7
Febrile neutropenia	6.5	0	0
Anemia	2.8	4.7	6.0
AST increased	0.3	6.6	3.0
Thrombocytopenia	0	6.4	7.9

508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: Primary analysis at 2 years of a phase 3, randomized, placebo-controlled trial (ExteNET). *First Author: Arlene Chan, Breast Cancer Research Centre - WA & Curtin University, Perth, WA, Australia*

Background: Neratinib (N) is an irreversible pan-HER tyrosine kinase inhibitor with clinical efficacy in trastuzumab (T) pre-treated HER2-positive (HER2+) metastatic breast cancer. In HER2+ early breast cancer (EBC), a significant proportion of patients (pts) recur with invasive disease despite T-containing adjuvant therapy. **Methods:** Women with stage 1–3c EBC with the last T dose ≤2y (later modified to stage 2–3c and ≤1y, respectively) and locally confirmed HER2+ were eligible. Pts were randomized to N 240mg PO once daily or placebo (P) for 12m, stratified by ER/PR, nodal status and T schedule. A global amendment reduced follow-up to 2y from study entry. A current amendment restores the original 5-y follow-up. Invasive DFS (IDFS) at 2y is the primary endpoint and other secondary endpoints include DFS + DCIS, distant DFS (DDFS), CNS incidence, and patient-reported outcomes. Overall survival (OS) is an event-driven secondary endpoint. Efficacy analyses were ITT using a stratified Cox model and log-rank test (1-sided α=0.025). **Results:** 2,821 pts were randomized between 07/2009 and 10/2011 (1,409 N; 1,412 P). Median time from last T was 4.4m N vs 4.7m P. Baseline characteristics were balanced between arms. Efficacy results are shown below. Pre-planned subset analyses showed a lower IDFS HR in ER/PR+ pts (n=1,616; HR=0.51 [0.33–0.77]) and in a centrally confirmed HER2+ cohort (HR=0.52 [0.34–0.79]). Diarrhea was the most common adverse event (AE) for N pts with 40% G3 (1pt G4). Other individual AEs ≥G3 occurred in < 4% N pts. Ejection fraction decrease ≥G2 was seen in 1.3% N vs 1.1% P pts. Mean relative dose intensity (RDI) was 88% in N vs 98% in P pts. **Conclusions:** ExteNET demonstrates that 12m of N following standard chemotherapy + T improves IDFS and DFS-DCIS at 2y in HER2+ EBC. Diarrhea, the most common AE, was manageable. Additional follow-up will allow assessment of 5-y IDFS and OS. ClinicalTrials.gov: NCT00878709. Clinical trial information: NCT00878709.

Efficacy endpoint	2-y rate, % N (n=1,409)	2-y rate, % P (n=1,412)	HR (95% CI)	P-value (1-sided) stratified log rank
IDFS	93.9	91.6	0.67 (0.50–0.91)	0.0046
DFS-DCIS	93.9	91.0	0.63 (0.46–0.84)	0.0009
DDFS	95.1	93.7	0.75 (0.53–1.05)	0.0447

509 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Meta-analysis of breast cancer expression data using published gene signatures to reveal key cellular processes implicated in chemosensitivity and resistance. *First Author: Daniel G. Stover, Dana Farber Cancer Inst, Brookline, MA*

Background: Although many pathways and cell states are implicated in therapeutic resistance, predicting response to chemotherapy remains a challenge. **Methods:** We assembled expression data and pathologic complete response (pCR) versus residual disease (RD) status for 1,507 breast cancer samples collected prior to neoadjuvant chemotherapy. For each sample, we evaluated 118 published gene signatures including signaling, lineage, cell state, immune, and microenvironmental processes. **Results:** Among all signatures, the strongest predictors of pCR vs. RD were proliferation-related. Microarray data from a breast epithelial cell morphogenesis assay demonstrated that five separate proliferation signatures correlated with in vitro proliferation. To assess how proliferation contributes to chemosensitivity, we evaluated genes differentially expressed in patients with pCR versus RD (FDR-adjusted $p < 0.05$, limma) before and after normalizing data for proliferation using two distinct proliferation signatures. Among ER+ breast cancer and ER+ subsets Luminal A and B, > 95% of differentially expressed genes were proliferation-associated, suggesting that proliferation differences account for most of the variation in ER+ chemosensitivity. In comparison, among triple-negative breast cancers (TNBCs) and the basal-like subset, only 72.0% and 35.4% of differentially expressed genes, respectively, were proliferation-associated. For TNBCs, signatures associated with chemotherapy response clustered into five key areas: proliferation, mesenchymal phenotype, TGF-beta signaling/stromal features, cyclin and Src activation, and ER signaling (possibly low-level not detected by IHC). Stratifying 175 TNBCs with zero (N0) or few positive lymph nodes (N1) by high versus low activity of three signatures—proliferation, epithelial-to-mesenchymal transition, and Src signaling—was highly predictive of failure to achieve pCR (negative-predictive value 0.965; 95% CI 0.912-0.990). **Conclusions:** Interrogating multiple signatures in a large expression data set allows insights into key processes associated with chemoresistance and sensitivity in breast cancer.

510 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Prognostic significance of tumor-infiltrating CD8+ and FOXP3+ lymphocytes in residual tumors and alterations in these parameters after neoadjuvant chemotherapy in triple-negative breast cancer. *First Author: Minoru Miyashita, Tohoku University Graduate School of Medicine, Sendai, Japan*

Background: A reliable marker is needed to identify high-risk patients eligible for post-neoadjuvant trials of new investigational drugs for breast cancer. We investigated the prognostic value of CD8+ TILs and FOXP3+ TILs in residual tumors after neoadjuvant chemotherapy (NAC) and changes in these parameters before and after NAC in patients with triple-negative breast cancer (TNBC). **Methods:** One hundred and thirty-one TNBC patients who received NAC were identified. CD8+ TIL and FOXP3+ TIL in residual tumors and biopsy specimens were investigated. The CD8+ TIL and FOXP3+ TIL status of the residual tumors was assessed, and the rates of changes in these cancers caused by NAC were calculated. **Results:** TNBC patients with high CD8+ TIL levels or a high CD8/FOXP3 ratio in residual tumors had significantly better recurrence-free survival (RFS) and breast cancer-specific survival (BCSS) than patients with low values of these parameters. In multivariate analyses, CD8+ TIL exhibited strong prognostic significance for RFS, with a hazard ratio (HR) of 3.44 (95%CI, 1.74-7.19, $P = 0.0003$). The CD8/FOXP3 ratio was also significantly correlated with RFS (HR = 2.00, 95%CI, 1.01-4.26, $P = 0.049$). TNBC with larger residual tumor size and positive lymph node status was independently associated with worse RFS ($P = 0.0032$ and $P = 0.0090$, respectively). High CD8+ TIL levels were a markedly powerful indicator of improved BCSS, with an HR of 3.58 (95%CI, 1.48-9.58, $P = 0.004$). Nodal status was also associated with BCSS ($P = 0.003$). TNBC with a high rate of CD8+ TIL changes was associated with significantly better RFS compared to the low group ($P = 0.011$). Higher rates of changes in the CD8/FOXP3 ratio were significantly correlated with both better RFS and BCSS compared to lower rates ($P = 0.011$ and $P = 0.023$, respectively). **Conclusions:** This study is the first to demonstrate that high CD8+ TIL and a high CD8/FOXP3 ratio in residual tumors and increases in these parameters after NAC accurately predict improved prognosis in TNBC patients with non-pCR following NAC. These parameters may be a surrogate for adjuvant treatment in patients with residual disease in the neoadjuvant setting.

511 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Correlation of *PIK3CA* mutation with pathological complete response in primary HER2-positive breast cancer: Combined analysis of 967 patients from three prospective clinical trials. *First Author: Sibylle Loibl, German Breast Group, Neu-Isenburg, Germany*

Background: The predictive value of *PIK3CA* mutations in HER2+ BC has been shown conclusively. Data on subgroup analyses are lacking. **Methods:** We combined data from three studies evaluating *PIK3CA* mutations as predictor for pCR: the neoadjuvant GEPAR studies (n = 504) (Loibl et al. *JCO* 2014), the Neo-ALTTO study (n = 355) (Majewski et al. *JCO* 2015) and the CHERLOB study (n = 108) (*ESMO* 2014). Patients received either trastuzumab (T), lapatinib (L) or the combination T/L in addition to taxane-based chemotherapy. *PIK3CA* was genotyped in tumor biopsies prior to therapy. **Results:** 967 patients were included. Median age was 48 (range 21-80); most tumors were cT1-2 (69.5%); cN+ (61.7%); ductal invasive (93.4%), grade 3 (56.2%); HR+ (56.2%). Overall, 21.7% had at least one mutation, 7.2% in exon 9 and 14.5% in exon 20. *PIK3CA* mutations were equally frequent in the HR+ compared to the HR- group: 21.7% in both groups. Overall, pCR rate was significantly lower in the *PIK3CA* mutant (mut) compared to the wild type (wt) group (16.2% vs 29.6%; $p < 0.001$). There was no difference in pCR rate whether the mutation was in exon 9 (15.7%) or exon 20 (16.4%). Within the HR+ subgroup the *PIK3CA* mut pts had a pCR rate of only 7.6% compared to 24.2% in the wt group ($p < 0.001$). In contrast, the difference in pCR (27.2% vs 36.4%) according to *PIK3CA*mutation status was not significant in the HER2+/HR- group ($p = 0.125$; interaction $p = 0.036$). The pCR rate for mut vs wt was 20.3% vs 27.1% for T ($p = 0.343$); 11.3% vs 16.9% for L (0.369) and 16.7% vs 39.1% for T/ L ($p < 0.001$). In the HR+ T/L group the pCR rate was 5.5% vs 33.9% (interaction $p = 0.008$). **Conclusions:** This metaanalysis confirms a significantly lower pCR rate in HER+, *PIK3CA* mutant tumors after anti-HER2 treatment. Patients with a HER2+/HR+/*PIK3CA* mutant tumor had a pCR rate of 5.5% only when treated with double-blockade and might be considered for alternative treatment. The project was funded within the EU-FP7 project RESPONSIFY No 278659.

% pCR	All cases Mut	All cases wt	HR-ve Mut	HR-ve wt	HR+ve Mut	HR+ve wt
All Treatments	16.2	29.6	27.2	36.4	7.6	24.4
T	20.3	27.1	25.0	34.8	14.3	20.9
L	11.3	16.9	18.5	22.9	5.7	12.3
T/L	16.7	39.1	37.9	46.0	5.5	33.9

512 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Predictive biomarkers of everolimus efficacy in HER2+ advanced breast cancer: Combined exploratory analysis from BOLERO-1 and BOLERO-3. *First Author: Dennis J. Slamon, School of Medicine/Translational Oncology Research Laboratory, University of California, Los Angeles, Los Angeles, CA*

Background: Two phase 3 trials BOLERO-1 and BOLERO-3 evaluated the addition of everolimus (EVE) to trastuzumab (TRAS) + chemotherapy in HER2+ advanced breast cancer (ABC). In BOL-3, heavily pretreated patients (pts) derived a statistically significant benefit from EVE, while BOL-1 (first-line EVE) did not meet the primary endpoints. This analysis aimed to identify biomarkers predictive of EVE efficacy using data from both trials. **Methods:** Exons of 282 cancer related genes were analyzed by next generation sequencing (NGS). PTEN levels were determined by IHC. Hyperactive PI3K pathway was defined as pts with low PTEN or known PIK3CA or AKT1 E17K mutation (narrow def) or mutation in any member of the PI3K/Akt/mTOR pathway (broad def). Correlations between biomarkers and PFS were evaluated by uni- and multi-variate Cox models. **Results:** Five hundred and sixty-one archival tumor samples (BOL-1 302; BOL-3 259) were successfully analyzed. PI3K pathway gene alterations were seen in ~45% of samples. A trend of greater benefit from EVE was observed in pts with PI3K pathway activation (individual trials). In a combined analysis from both trials, pts with PIK3CA mutations (HR = 0.69) or low PTEN (HR = 0.5) derived more benefit from EVE. A robust positive correlation between PI3K hyperactivity and PFS benefit was observed using both narrow def (HR = 0.67 vs normal PI3K activity HR = 1.2) and broad def (HR = 0.61 vs normal PI3K activity HR = 1.38). In a multivariate analysis, interaction between PI3K status and treatment effect was statistically significant (p = 0.016). **Conclusions:** This exploratory analysis suggests that pts with hyperactive PI3K signaling pathway derive greater benefit from adding EVE to TRAS + chemotherapy in HER2+ ABC. Clinical trial information: NCT00876395, NCT01007942.

			BOL-1			BOL-3		
		Tx	n/N*	Median PFS (mo)	HR	n/N*	Median PFS (mo)	HR
PIK3CA	Wild type	PBO	31/48	17.1	1.13	66/82	6.6	1.04
		EVE	51/89	18.5		58/77	6.8	
	Mutant	PBO	17/19	7.6	0.70	37/42	5.7	0.67
		EVE	30/39	12.0		28/29	6.9	
PTEN	Normal	PBO	53/90	13.8	1.02	93/110	6.7	1.03
		EVE	87/163	16.1		84/107	6.8	
	Low	PBO	12/18	16.8	0.56	12/15	5.5	0.49
		EVE	17/31	23.5		13/15	9.5	
PI3K pathway	Normal	PBO	26/41	17.1	1.18	57/70	6.97	1.15
		EVE	40/72	18.2		49/67	6.83	
	Hyperactive	PBO	27/35	10.9	0.72	46/54	5.59	0.63
		EVE	44/66	13.9		39/42	6.93	

*n = no. of events; N = no. of pts.

513 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Validation of prediction of distant recurrence (DR) by Prosigna (PAM50) in subgroups of a Danish Breast Cancer Cooperative Group (DBCG) cohort of node-positive (N1), hormone receptor positive (HR+), postmenopausal early breast cancer (EBC) patients allocated 5yr of endocrine therapy (ET). *First Author: Bent Ejlertsen, The Danish Breast Cancer Cooperative Group, DBCG Secretariat, Rigshospitalet, Copenhagen, Denmark*

Background: N1, HR+ EBC patients are routinely treated with both ET and chemotherapy (CT). Identification of N1 patients with good outcome who may be spared CT remains an elusive goal. In a combined analysis of 2 randomized trials, Prosigna (PAM50) risk of recurrence (ROR) score identified low risk N1 patients with outcome equivalent to N0 disease. We examined the ability of ROR to predict 10yr DR for patients with 1, 2 or 3+ nodes in a comprehensive nationwide cohort from Denmark to identify N1 women who may be spared overtreatment with CT. **Methods:** Using the population based DBCG database primary FFPE tumor blocks and follow-up data were collected from all Danish women diagnosed from 2000-2003 with HR+, postmenopausal, N1 EBC treated with ET alone (N = 1,480). PAM50 on the NanoString nCounter Analysis System categorized patients as Low, Intermediate, or High risk using pre-specified cutoffs varied by number of positive nodes. Multivariate analyses were performed to assess the ability of PAM50 to predict DR in patients with 1, 2, or 3+ nodes. **Results:** 1,466 (99%) passed PAM50 QC. Median follow-up was 9.25 years. Risk of 10yr DR based on the number of positive nodes and PAM50 is shown in the Table. Including ROR in a Fine and Gray's multivariate proportional sub-hazards model improved outcome prediction for patients with 1, 2, and 3+ nodes (P < 0.0001, 0.0001, 0.008 respectively). **Conclusions:** Prosigna (PAM50) improves outcome prediction in N1 patients over standard variables. PAM50 can identify at least 37% of patients with 1 and 15% with 2 positive nodes who have an excellent prognosis and may be spared adjuvant CT in a real world setting.

	DR risk by Risk Group % [95%CI]			DR risk by Subtype % [95%CI]	
Nodes (N)	**Low (N)**	**Intermediate (N)**	**High (N)**	**Luminal A (N)**	**Luminal B (N)**
1+ Node (809)	3.6 [1.7-6.5] (298)	15 [10-21] (237)	21 [16-27] (274)	8.5 [5.9-12] (509)	18 [13-24] (248)
2+ Nodes (426)	4.6 [1.2-11] (65)	8.7 [4.4-15] (137)	21 [15-27] (224)	8.8 [5.4-13] (250)	20 [14-27] (142)
3+ Nodes (231)	-	0 [NA] (26)	26 [20-33] (205)	9.4 [4.7-16] (124)	39 [26-51] (85)

514 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Final analysis of a randomized comparison of letrozole (Let) vs observation (Obs) as late reintroduction of adjuvant endocrine therapy (AET) for postmenopausal women with hormone receptor positive (HR+) breast cancer (BC) after completion of prior AET: ANZBCTG 0501 (LATER). *First Author: Nicholas Zdenkowski, Australia and New Zealand Breast Cancer Trials Group, Newcastle, Australia*

Background: AET for postmenopausal women with HR+ early BC has until recently been limited to 5 yrs of tamoxifen, an aromatase inhibitor or a sequential combination of these. However, after 5 yrs of AET, BC events continue to occur at a high rate (2% per yr) for at least another 10 yrs. The LATER trial was designed to compare 5 yrs of Let 2.5mg daily as late reintroduction of AET to Obs (= usual care) in postmenopausal women after ≥ 4 yrs of AET. **Methods:** LATER was a prospective open label randomized trial for postmenopausal women who were BC free and had completed ≥ 4 yrs of AET for HR+ early BC more than 1 yr prior to study entry. The primary outcome was the rate of invasive BC events (defined as new invasive primary, local, regional or distant recurrence or contralateral BC) for Let arm compared to Obs. Secondary outcomes included disease-free survival (DFS), overall survival (OS) and toxicity. To reject the null hypothesis in favor of a 60% reduction in the primary outcome with β = 0.10 and 2α = 0.05, 1700 patients were required. In Oct 2014 the independent data and safety monitoring committee recommended to cease trial follow up and to release the data for analysis due to a low event rate. **Results:** Between May 2007 and March 2012, 360 patients were randomized (181 Let; 179 Obs), after which enrolment ceased due to a low accrual rate. Patients completed prior AET a median of 2.5 yrs before randomization. N+ 33.9%, N- 60.0%, unknown 6.1%. Prior AET was aromatase inhibitor only in 11.1%, SERM in 50.6% and a sequential combination in 38.3%. In the ITT population, at a median 3.0 yrs follow-up, 1.1% of patients in the Let arm had experienced an invasive BC event vs 8.4% in the Obs arm (difference 7.3%, 95% CI 2.9-11.6, p = 0.001, conditional binomial exact test). DFS events occurred in 6.1% vs 11.7% (p = 0.06) and death in 1.7% vs 2.2% (p = 0.70) in the Let and Obs arms respectively. **Conclusion:** In postmenopausal women who had completed ≥ 4 yrs of AET for HR+ early BC, Let significantly reduced the incidence of late invasive BC events. Clinical trial information ACTRN 012607000137493. Clinical trial information: 01260700013749.

515 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Ovarian function suppression, symptom burden, and quality of life in young women with breast cancer: A prospective study. *First Author: Shoshana M. Rosenberg, Dana-Farber Cancer Institute, Boston, MA*

Background: Recent clinical trial data have demonstrated that ovarian function suppression (OS) in addition to tamoxifen (T) or aromatase inhibitors (AI) can improve breast cancer free survival in young women with hormone positive (HR+) breast cancer. We evaluated the impact of OS on quality of life (QOL) in young women, a population at risk for worse QOL outcomes and survival. **Methods:** Patient reported symptom and QOL data were collected 1 year after dx as part a cohort study enrolling women newly dx'd with breast cancer age ≤40. Severity of symptoms (Breast Cancer Prevention Trial checklist) was compared between women on OS+T vs. T alone by Fisher's exact test. For QOL (Cancer Rehabilitation Evaluation System (CARES) physical, psychosocial, sexual subscales), differences in mean scores between groups were compared with t-tests. All were stratified by receipt of chemotherapy. Due to small numbers, women on AIs were excluded. **Results:** Of444 women with Stage 0-III, HR+ disease on T, 106 (24%) reported OS use. The Table details symptom prevalence (% at least moderately bothersome) by group. Among women who had chemo (n=333), women on OS had higher (p≤.05) mean CARES scores (worse QOL) on all 3 subscales. Mean scores for women who did not receive chemo (n=111) were not significantly different between groups. **Conclusions:** Young breast cancer survivors on endocrine therapy have a high symptom burden which should be considered in treatment decision making and survivorship care. Women on OS+T experience more vasomotor and (in those who received chemo) greater cognition issues, and poorer QOL in the early survivorship period compared to T alone. Early intervention to reduce symptom burden should be offered to young women to potentially improve QOL, enhance adherence and optimize survival.

	Chemo			No chemo		
	OS+T N (%)	T N (%)	p	OS +T N (%)	T N (%)	p
Hot flashes	45 (59)	99 (39)	0.002	23 (77)	24 (30)	<0.0001
Night sweats	36 (47)	86 (33)	0.03	19 (63)	28 (35)	0.009
Vaginal dryness	27 (36)	71 (28)	0.20	10 (33)	13 (16)	0.06
Difficulty concentrating	32 (42)	69 (27)	0.02	5 (17)	17 (21)	0.79
Easily distracted	30 (39)	67 (26)	0.03	6 (20)	18 (22)	-
Weight gain	16 (21)	29 (11)	0.04	2 (7)	7 (9)	-
Unhappy with appearance	37 (49)	86 (34)	0.02	5 (17)	21 (26)	0.45

516 Poster Discussion Session; Displayed in Poster Session (Board #4), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Tumor *PIK3CA* genotype and prognosis: A pooled analysis of 4,241 patients (pts) with early-stage breast cancer (BC). *First Author: Dimitrios Zardavas, Breast International Group, Brussels, Belgium*

Background: *PIK3CA* mutations (mt) are frequently observed in BC but their clinical relevance is unclear. We performed an individual pt data pooled-analysis to evaluate the prognostic impact of *PIK3CA* status on early-stage BC. **Methods:** Participating studies were identified by literature search. Associations of *PIK3CA* status with clinicopathologic characteristics were tested. Cox regression models were applied adjusting for age, tumor size, nodes, grade, ER and HER2 status, treatment and study. Invasive disease-free survival (IDFS) was the primary endpoint, followed by distant disease-free survival (DDFS), overall and by BC subtypes. **Results**: Data from 16 studies were included. Median age was 56yrs (18-96) and median follow-up was 6.5yrs; 1384 pts (33%) received chemotherapy, 1147 (27%) endocrine monotherapy, 816 (19%) both and 894 (21%) none/unknown. *PIK3CA* mt occurred in 26.9%: 55.2% exon 20 and 36.2% exon 9. They were associated with ER+ tumors, increasing age, lower grade (all $p < 0.001$) and smaller size ($p = 0.04$). Incidence of *PIK3CA* mt was 15%, 23%, 32% in the ER-/HER2-, HER2+ and ER+/HER2- subtypes respectively ($p < 0.001$). In the univariate analysis, *PIK3CA* mt were associated with better IDFS: HR = 0.85 [95%CI:0.75-0.96]; p = 0.0009. A statistically significant non-proportional prognostic effect was observed ($p = 0.02$): during the first 3 yrs *PIK3CA* mt had better IDFS (HR = 0.73 [0.60-0.88]) compared to after 3yrs (IDFS HR = 0.96[0.8-1.1]; P interaction:0.03). There was no significant interaction by BC subtype ($p = 0.6$) and no significant differences by exon 9 or 20 site ($p = 0.7$). In the multivariate analysis, *PIK3CA* status did not remain statistically significant overall (HR = 0.94 [0.8-1.2]; p = 0.6) nor in the first 3 yrs. Results were similar for the DDFS endpoint. In further analyses, a significant interaction between *PIK3CA* status and age was found, remaining after adjustment ($P = 0.04$). *PIK3CA* mutant BCs had significantly better IDFS in women $\leq$ 50yrs (HR = 0.65 [0.4-0.95]) but not $>$ 50yrs (HR = 1.10 [0.9-1.4]; Pint = 0.01). **Conclusions:** *PIK3CA* mutations are associated with a better prognosis. This effect is greatest in young women for whom *PIK3CA* status could potentially refine treatment decisions.

517 Poster Discussion Session; Displayed in Poster Session (Board #5), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

HER3 and paxillin signaling in ER+ HER2- metastatic breast cancer (MBC) patients receiving letrozole (L) vs letrozole plus dasatinib (L+D) in a randomized phase II trial. *First Author: Joyce O'Shaughnessy, Baylor Sammons Cancer Ctr US Onc, Dallas, TX*

Background: BC invasion is mediated by Src and its downstream target, the adhesion protein, paxillin (Pax). A randomized phase II trial of L + the Src inhibitor dasatinib demonstrated that L+D improved median PFS to 20 mos from 10 mos with L alone as first-line therapy for ER+ HER2-negative MBC (Paul D. SABCS 2013, S3-07). We conducted reverse phase protein microarray (RPMA) on pts' primary BCs to identify phosphoproteins associated with recurrence and with outcome on L vs L+D. **Methods:** 48 pts' FFPE primary breast cancers were acceptable for RPMA at a CLIA-certified laboratory (Theranostics Health, Rockville, MD). Immunostaining was carried out with 20 antibodies directed against HER pathway proteins, MET, Src, and Pax. Student t-test or Mann-Whitney U test and Spearman correlation coefficient (ρ) were used to assess biomarker association with PFS $<$ 6 mos vs $>$ 6 mos by treatment arm (unpaired 2 tails, p value). **Results:** Median PFS for the 48 pts was 19.2 mos for L+D (N=21) vs 9.2 mos for L (N=27). ~90% of the BCs overexpressed HER3, p-mTOR, p-4EBP1, p-JAK2, p-STAT3 and 50% overexpressed p-Pax. Across all pts, protein linkage Pearson correlations (r) showed strong associations between p-Pax & p-HER2 (r=0.74), HER3 & p-HER2 (r=0.79), p-HER1 & p-HER2 (r=0.82), HER3 & p-MET (r=0.72) and p-Pax & p-MET (SR=0.93). Evaluating all 48 pts, PFS $<$ 6 mos was correlated with HER3 expression ($p< 0.01$), p-HER3 (p=0.02), p-HER2 (p=0.04) and HER1 (p=0.05). Evaluating L vs L+D pts, PFS $<$ 6 mos was associated with HER3 ($p< 0.01$), p-HER3 (p=0.03), p-HER2 (p=0.07), HER1 (p=0.05), p-Pax (p=0.02), and p-Met (p=0.05) expression only in L alone pts and not in L+D pts. PFS $<$ 6 mos with L+D was associated with p-Src (ρ=0.9, p=0.04) and p-Pax (ρ=0.71, p=0.11)]. p-Pax expression was inversely correlated with prolonged PFS in L alone (ρ= -0.7, p=0.04) but not in L+D pts. **Conclusions:** Primary ER+ HER2- BCs that recurred expressed high levels of HER3 and downstream phosphoproteins. HER3 overexpression correlated with p-HER2, p-HER1, p-MET, and p-Pax expression and predicted for short PFS with L alone but not with L+D. These findings suggest that dasatinib may inhibit HER3 signaling in ER+ HER2- MBC pts.

518 Poster Discussion Session; Displayed in Poster Session (Board #6), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

DNA methylation in serum as an independent marker of outcome and treatment response in TBCRC 005: A prospective study in metastatic breast cancer (MBC) patients. *First Author: Kala Visvanathan, Johns Hopkins Kimmel Cancer Center and Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

Background: Accurate markers are needed to assess the effect of therapies early in MBC. Emerging studies suggest that methylated tumor DNA in blood can predict poor prognosis. In the TBCRC 005 multi-site prospective biomarker study we tested whether serum DNA methylation assessed by the cMethDNA assay (PMID 2437128) is predictive of disease outcomes in MBC and compared our results to circulating tumor cells (CTC). **Methods:** Serum was collected from 2007-2009, and methylation of *AKR1B1, HOXB4, RASFGR2, RASSF1A, HIST1H3C, TM6SF1* loci were determined in duplicate serum samples from 141 women with measurable MBC at baseline, week 3-4 and week 8-12. For each patient, the cumulative methylation index (CMI) was calculated, log-transformed, and modeled as a continuous or binary variable. The study specific cut-point was based on maximally selected logrank statistic and unbiased point estimates were obtained by cross-validation. Cox proportional hazard models were used to evaluate association between CMI at baseline and week 3-4, with PD at first re-staging, PFS, and OS. The added value of CMI to prognostic factors including CTC was assessed using the likelihood ratio test and concordance probability estimates. **Results:** Median age was 56 years; 89% white; 60% HR+/HER2-. Patients with high CMI at week 3-4 had a median OS of 12.8 months compared to 22.6 months among those with a low CMI. PFS results were similar. An increase in CMI units at 3-4 weeks was associated with PD ($P = 0.003$), PFS ($P = 0.008$), and OS ($P < 0.001$) in multivariate analyses. In joint models both CMI and CTC were predictive of PFS and OS. Furthermore, an increase in CMI from baseline to week 3-4 was significantly associated with PD (HR 1.58, CI 1.21-2.05, $P < 0.001$), worse PFS (HR 1.22, CI 1.10-1.35, $P < 0.001$) and OS (HR 1.10, CI 0.99-1.22, $P = 0.077$). Change in CTC between the same time points was not associated with disease outcomes. **Conclusions:** This is the most comprehensive study to date of DNA methylation in blood of MBC patients. The cMethDNA CMI of this gene marker set is an independent prognostic factor in MBC and is promising as useful marker for risk stratification and early assessment of treatment.

519 Poster Discussion Session; Displayed in Poster Session (Board #7), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Oncotype DX in *BRCA*-associated vs. sporadic breast cancers: Differences based on germline mutation status and potential implications for adjuvant systemic therapy (AST). *First Author: Payal Deepak Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Biological differences between *BRCA*-associated and sporadic breast cancer (BC) could warrant different recommendations for AST among patients (pts) with phenotypically similar cancers. Onco*type* DX (Genomic Health Inc., CA) is prognostic, quantifies predicted benefit of AST, and is used to guide clinical decisions in pts with early-stage hormone receptor-positive (HR+) BC. The results of this assay have not been described in pts with deleterious germline *BRCA(gB)* mutations. **Methods:** Pts seen at MSKCC for HR+, stage I/II, node-negative BC with Onco*type* DX results, were retrospectively ascertained and medical records reviewed. *B1/2* mutation carriers (cases) were identified and matched 1:2 to noncarriers (controls), based on age at diagnosis and tumor size. Two sample nonparametric tests were used to compare *B1* vs. *B2* pts. Conditional logistic regression (SAS v 9.4) assessed differences in Oncotype DX recurrence scores (RS) and risk stratification by mutational status. **Results:** 50 cases (*B1*: n = 19, *B2*: n = 31) and 100 controls were included. Cases and controls were well-matched for age ($p = 0.9$) and tumor size ($p = 0.6$). Cases were more likely to have high-grade tumors ($p = 0.004$). Median RS was 23 for *B1* and 24 for *B2* carriers ($p = 0.6$). Stratification into low-, intermediate-, and high-risk categories was similar between *B1* and *B2* carriers ($p = 0.3$). Median RS was significantly higher for cases than for controls (RS 24 vs. 16, $p < 0.0001$). Risk stratification also differed based on mutational status ($p = 0.0002$). Cases had more high-risk (28% vs. 7%) and intermediate-risk (56% vs. 36%) disease than controls. Cases had less low-risk disease than controls (16% vs. 57%). Cases were significantly more likely to receive AST (74% vs. 46%, $p = 0.002$). **Conclusions:** Presence of a *gB1/2* mutation may be a biomarker for intrinsically less favorable disease in pts with early-stage, HR+ BC. Few affected *gB* carriers have RS indicating clear absence of benefit from AST. Increased use of, and benefit from, AST in *gB* carriers may mitigate otherwise inferior outcomes, accounting for the similar prognoses for carriers and noncarriers reported in the literature.

520 Poster Discussion Session; Displayed in Poster Session (Board #8), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Efficacy of the PARP inhibitor (PI) ABT-888 (veliparib [vel]) either with carboplatin (carb) or as a single agent followed by post-progression therapy in combination with carb in patients (pts) with *BRCA1*- or *BRCA2*-(*BRCA*)-associated metastatic breast cancer (MBC). *First Author: George Somlo, City of Hope, Duarte, CA*

Background: Based on the concept of synthetic lethality combining platinum agents and PIs should benefit patients (pts) with *BRCA*-associated MBC. We report mature outcomes with vel alone, or with carb. **Methods:** Pts with germline *BRCA*-associated MBC, ECOG performance status of ≤ 2, without prior PI treatment were included. In phase I the maximum tolerated dose (MTD) of carb (AUC of 5) IV every 21 days, and vel 150 mg BID were defined. In phase II, pts received vel 400 mg BID and upon progression, carb and vel at the MTD. **Results:** Between 6/2010 and 4/2014, 72 evaluable pts (28 in phase I, 44 in phase II) with *BRCA1* (34 patients) or *BRCA2* (37 patients) mutations (1 pt had both) and with MBC were enrolled. The median age was 44-years (range; 28-68); 49% of pts had hormone receptor + MBC. Pts received a median of 1 (0 – 5) prior chemo-regimen for MBC. Response rate (RR) for the 28 pts in phase I was 50% [CR rate 18%] and 2 pts remain in CR at 43+ and 34+ cycles, both are on vel maintenance, alone; median progression-free survival (PFS) was 8.5 mos (95% CI 7.3-10.1), and median TTF was 8.3 mos (6.9-9.5). For 44 phase II pts treated with vel, the median PFS was 5.2 months (4.0-6.4) and including their cross-over carb/vel treatment the cumulative TTF was 6.7 months (4.6-8.5); 13/44 (30%) responded to vel; 2 pts are still on vel (1 with a PR at 14 cycles, 1 with a CR at 25 cycles); 1 pt converted to PR after cross-over to carb/vel. OS was 18.8 months (95% CI 15.0-26.3) for the 28 pts treated with the combination of carbo/vel, and 12.6 months (95% CI 11.7-NR) for the 44 pts treated with vel followed by carbo/vel ($p < 0.1$). In phase I, dose delay or adjustment was needed in 1/3 of the pts treated at the MTD within the first 3 cycles due to cytopenias. In phase II, 8/44 (18%) required dose adjustment on single agent vel, and 5 pts required dose adjustment after cross-over to carb/vel. **Conclusions:** The trend for longer TTF with the carb/vel combination first vs. vel followed by carb/vel, combined with the improved time OS suggest that carb/vel followed by vel maintenance deserves further testing in a randomized prospective trial. Clinical trial information: NCT01149083.

521 Poster Discussion Session; Displayed in Poster Session (Board #9), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

DNA repair deficiency biomarkers and identification of ER-positive breast cancer patients who may benefit from veliparib/carboplatin: Results from the I-SPY 2 trial. *First Author: Laura van't Veer, UC San Francisco, San Francisco, CA*

Background: In the I-SPY 2 TRIAL, HER2- patients were adaptively randomized to receive standard chemotherapy or the PARP inhibitor veliparib with carboplatin (V/C) and chemotherapy. V/C graduated in the triple-negative (TN) subtype, and we've previously shown that DNA repair deficiency signatures [BRCAness and PARPi-7] may predict V/C response. Here we combine these signatures into a composite measure of DNA repair deficiency. **Methods**: 115 HER2- patients (V/C: 71 and concurrent controls: 44) are considered in this analysis. BRCA1/2 germline mutation is assessed by Myriad Genetics. The PARPi-7 and BRCAness signature scores are computed from Agilent 44K array data. A patient is predicted DNA repair deficient if carrying a BRCA1/2 mutation or BRCA-like or PARPi7-high. We modify the I-SPY 2 Bayesian model to include DNA repair deficiency status to estimate the predictive probability of V/C demonstrating superiority to control in a 1:1 randomized phase 3 trial of 300 'biomarker-positive' patients. Our study is exploratory with no claims for generalizability and does not adjust for multiplicities of other biomarkers outside this study. **Results:** 15 patients are BRCA1/2 mutation carriers, of which 13 are PARPi7-high or BRCA-like. Comparing PARPi7 and BRCAness (62 PARPi7-low, 53 PARPi7-high; 59 non-BRCA1-like, 56 BRCA1-like) we find only moderate concordance (64%; kappa = 0.29). Altogether, 77 patients are predicted to be DNA repair deficient by one of these measures. 38% (21/56) of HR+/HER2- patients are predicted DNA repair deficient, along with nearly all (56/59) TN. In the V/C arm, 5/13 HR+/HER2- DNA repair deficient patients and 22/38 TN patients had a pCR (vs 0/8 and 5/21 controls respectively). When DNA repair deficient HR+/HER2- patients are added to the TN subset, the probability of phase 3 success is 94%, which is comparable to the graduating TN signature [97% in this model] while increasing patient prevalence. **Conclusions:** Our exploratory analysis suggests that 38% of HR+/HER2- patients in I-SPY 2 are DNA repair deficient and may benefit from V/C. If validated, DNA repair deficiency biomarkers may be used to select HR+/HER2- patients for future PARP inhibitor trials.

522 Poster Discussion Session; Displayed in Poster Session (Board #10), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A phase Ib study of abemaciclib with therapies for metastatic breast cancer. *First Author: Sara M. Tolaney, Dana Farber Cancer Institute, Boston, MA*

Background: Abemaciclib, an inhibitor of cyclin dependent kinases CDK4 and CDK6, demonstrated safety and clinical activity as a single agent for hormone receptor positive (HR+) metastatic breast cancer (MBC) irrespective of *HER2* amplification (Tolaney, SABCS 2014). This study (NCT02057133) evaluates safety, pharmacokinetics (PK), and antitumor activity of abemaciclib combined with endocrine or HER2-targeted therapies for MBC. **Methods:** Patients (pts) in 6 cohorts received abemaciclib 150-200 mg every 12 hours (Q12H) with letrozole 2.5 mg/d (Part A), anastrozole 1 mg/d (Part B), tamoxifen 20 mg/d (Part C), exemestane 25 mg/d (Part D), exemestane 25 mg/d + everolimus 5 mg/d (Part E), or trastuzumab 6-8 mg/kg every 21 days (Part F). Pts in Parts A-E had HR+, HER2- MBC and in Part F had HER2+ MBC. Eligibility included measurable disease or nonmeasurable bone disease by RECIST v1.1, ECOG performance status ≤ 1, no prior chemotherapy for metastatic disease (Parts A-E), and ≥ 1 chemotherapy regimen for metastatic disease (Part F). Abemaciclib was given continuously until progression. Patients were assessed every 28 days in Parts A-E and every 21 days in Part F. Dose escalation cohorts of ≥ 3 pts receiving abemaciclib at 150 mg and 200 mg Q12H were included in Parts E and F. **Results:** A total of 65 pts started treatment with abemaciclib (200mg Q12H) by 16-Dec-2014 in Parts A-D. Pts had a median age of 57 years (range: 28-77) and a median of 3 prior systemic therapies (range: 1-8) for breast cancer. The most common ($\geq$ 20% overall in Parts A-D) possibly related treatment-emergent adverse events (TEAEs) (all grades %, G3 %) were diarrhea (95, 31), fatigue (71, 14), nausea (62, 6), neutropenia (31, 17), abdominal pain (31, 3), decreased appetite (29, 0), vomiting (28, 3), and anemia (25, 0). Diarrhea was manageable with antidiarrheal agents or dose reduction. No G4/5 TEAEs occurred. The disease control rate (CR + PR + SD) was 67% for Parts A+B [nonsteroidal aromatase inhibitors (36 pts)] with 2 confirmed PRs and 75% for Part C [tamoxifen (16 pts)]. Safety, PK, and efficacy results will be updated at presentation. **Conclusions:** Combinations of abemaciclib with endocrine therapies demonstrate manageable safety and early clinical evidence of antitumor activity. Clinical trial information: NCT02057133.

523 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Updated findings of a first-in-human, phase I study of margetuximab (M), an Fc-optimized chimeric monoclonal antibody (MAb), in patients (pts) with HER2-positive advanced solid tumors. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: Fc-dependent mechanisms such as antibody-dependent cellular cytotoxicity (ADCC) may be important for the activity of MAbs. M is a MAb to HER2 engineered for increased Fc-domain binding affinity to both low affinity variants of the activating Fcγ receptor, CD16A. In preclinical studies, M showed enhanced ADCC compared to an unmodified precursor. Results from the initial dose escalation have previously been reported. Here we describe pharmacokinetics (PK), safety and activity data for the expansion cohort and an alternative schedule, including responses in patients with refractory breast cancer (BC). **Methods:** Pts with refractory carcinomas that overexpress HER2 for whom no standard therapy was available were enrolled. Pt cohorts received escalating doses of M weekly for 3 of every 4 weeks (Regimen A) or every 3 weeks (Regimen B) by intravenous infusion in a 3+3 (Regimen A) or 6+6 (Regimen B) design. Additional safety and activity data were obtained in expansion cohorts of each regimen. Tumor response was determined using RECISTv1.1. PK was evaluated during all cycles. **Results:** Fifty-two patients received M (34 patients received 0.1 to 6.0 mg/kg in Regimen A and 18 patients received 10 to 18 mg/kg in Regimen B). The maximum tolerated dose was not exceeded for either regimen. Treatment was well-tolerated, with mostly Grade 1 and 2 toxicities consisting of infusion-related reactions and constitutional symptoms such as pyrexia, nausea, anemia, diarrhea, and fatigue. Partial responses were observed in 8 patients and stable disease in 21 patients. Tumor reductions were observed in 11 of 19 patients with BC, including 4 patients with confirmed partial responses, 3 of whom had received prior trastuzumab and lapatinib, with several durable responses of $>$ 30 weeks. Median progression free survival for patients with BC was 169 days. PK analysis showed that doses of 3 mg/kg in Regimen A and all doses in Regimen B achieved steady state trough levels sufficient to inhibit HER2 signaling. **Conclusions:** The results indicate that M is tolerated well and has promising activity in HER2-positive tumors including BC. Further development is ongoing. Clinical trial information: NCT01148849.

524 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Adaptively randomized trial of neoadjuvant chemotherapy with or without the Akt inhibitor MK-2206: Graduation results from the I-SPY 2 Trial. *First Author: Debu Tripathy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: A key node of growth and survival signaling pathways is the Akt serine/threonine kinase that activates mTOR and downstream effectors. I-SPY 2 is a randomized neoadjuvant trial to test agents and combinations added to standard chemotherapy. Pathological complete response (pCR) defined as absence of invasive cancer in breast and nodes is the primary endpoint. We report efficacy results for allosteric Akt inhibitor MK-2206. **Methods:** Women with invasive breast cancer ≥2.5 cm on exam or ≥2 cm on imaging were adaptively randomized to 12 weekly paclitaxel (and trastuzumab if HER2+) cycles (control) or in combination with one of several experimental agents followed by doxorubicin/cyclophosphamide x 4. Patients (pts) are stratified to 8 subsets based on hormone-receptor (HR), HER2, and MammaPrint statuses, with combinations of subsets defining agent signatures. MK-2206 135 mg daily by mouth was evaluated in all 8 subsets. Adaptive assignment to the experimental arms was based on current Bayesian probabilities of superiority over control. Graduation by signature and futility stopping was based on Bayesian predictive probability of success in a 2-arm, N=300 Phase 3 randomized 1:1 trial with pCR endpoint. **Results:** MK-2206 graduated in the first 3 signatures in the table. Accrual ended with 93 patients assigned to that arm and when 56 pts had been concurrently randomized to control. Final posterior and predictive probabilities are shown for all 10 signatures. **Conclusions:** MK-2206 improves pCR rates compared to standard chemotherapy in several breast cancer signatures, defined mostly by HR- and HER2+, sufficiently for evaluation in a Phase 3 neoadjuvant trial powered for event-free survival. Safety data will be presented. Clinical trial information: NCT01042379.

Signature	Estimated pCR Rate			Probability MK2206 Superior to Control	Predictive Probability Success Phase 3
	MK-2206 N=93	Control N=56	Difference		
HR-/HER2+	64.1	35.7	28.4	97.3	87.0
HR-	46.7	26.1	20.6	98.6	82.7
HER2+	49.6	28.9	20.7	95.1	77.7
HR-/HER2-	40.2	22.4	17.8	96.8	75.9
MP+	39.3	22.5	16.8	97.0	74.1
All	35.2	21.1	14.1	97.9	68.6
HR+/HER2+	35.8	22.4	13.4	85.4	61.3
HER2-	29.3	18.0	11.3	95.0	59.0
HR+	22.8	15.9	6.9	81.8	42.5
HR+/HER2-	17.1	13.0	4.1	72.7	31.7

525 Poster Session (Board #13), Sat, 8:00 AM-11:30 AM

Molecular profiling of ER weakly-positive breast cancer. *First Author: Brandon S. Sheffield, University of British Columbia, Department of Laboratory Medicine and Pathology, Vancouver, BC, Canada*

Background: The estrogen receptor (ER) is a key predictive biomarker in the treatment of breast cancer. Luminal subtypes of breast cancer express *ESR1*, and are eligible for hormonal therapy. Standard laboratory assessment of ER status is currently immunohistochemistry (IHC)-based. Since the introduction of ER IHC, the threshold for positivity has decreased from 10% to ≥ 1% of tumor cells whilst methodological advances have increased the sensitivity of IHC detection. These trends have led to considerable uncertainty regarding the use of hormonal therapy in the setting of ER weakly-positive tumors. We report intrinsic subtype classification on a cohort of ER weakly-positive early stage cancers and discuss the implications on clinical treatment. **Methods:** Consecutive cases of untreated, surgically resected primary breast cancer were retrospectively identified from 4 tertiary care centres in British Columbia, Canada. All participating centres engage in routine external proficiency testing for breast biomarkers. Based upon the semiquantitative Allred score, combining staining intensity and percentage of tumor cells, ER-negative (Allred 0 and 2) and ER weakly-positive (Allred 3-5) cases were included. Gene expression profiling was performed using qRT-PCR. Intrinsic subtype prediction was made based upon the PAM50 gene expression signature. **Results:** 153 cases were included in the series; 62 cases originally diagnosed as ER weakly-positive and 91 ER-negative. Weak ER signal by IHC correlated poorly with *ESR1* gene expression by qRT-PCR (R^2 =0.2 [0.1-0.3, 95% CI]). Of the 62 cases originally assessed as ER weakly-positive, only 6 (10%) were confirmed as luminal subtype by gene expression profiling with the remaining cases showing basal-like or HER2-enriched subtypes (90%). In this highly enriched ER weakly-positive cohort, the positive predictive value of low-level ER staining for luminal subtype was extremely poor (8% [3%-18%, 95% CI]). **Conclusions:** Weak ER expression by IHC is a poor correlate of both luminal subtype and *ESR1* expression in breast cancer. In the setting of highly sensitive and robust IHC methodology, cutoffs for ER status determination and subsequent systemic therapy may need to be revisited.

526 Poster Session (Board #14), Sat, 8:00 AM-11:30 AM

Correlation of Breast Cancer Index HOXB13/IL17BR (H/I), ER, PR and HER2 and prediction of relative endocrine benefit from tamoxifen and anastrozole in HR+ breast cancer: A TransATAC study. *First Author: Yi Zhang, bioTheranostics, San Diego, CA*

Background: Estrogen receptor (ER) expression is a critical determinant of endocrine response, however additional biomarkers are needed to complete the molecular picture of treatment benefit, response and resistance to better individualize care. Previous studies have demonstrated that H/I expression ratio predicts benefit for ER+ breast cancer patients from tamoxifen in the Stockholm adjuvant trial and from letrozole in the MA.17 extended adjuvant trial. In this correlative study, H/I was compared with ER, PR, and HER2 expression in assessing relative benefit from adjuvant anastrozole (ANA) vs tamoxifen (TAM) in HR+, LN- patients from the prospective randomized ATAC trial. **Methods:** Tumor samples from 742 HR+, LN- patients treated with 5 y of TAM or ANA were examined. Expression levels for H/I, ER, PR and HER2 were determined by RT-PCR. Cox proportional hazards models assessed the significance of the interaction between treatment and each biomarker as continuous variables, with 10-year risk of distant recurrence estimated within the 2 treatment arms separately. No adjustment for multiple testing was made. **Results:** The interaction between H/I and treatment was statistically significant ($p = 0.024$) whereas the interaction for all other biomarkers was non-significant (ER, $p = 0.17$; PR, $p = 0.054$; HER2, $p = 0.72$). Consistent with this finding, the 10-year distant recurrence rate as a function of continuous H/I indicated that the endocrine benefit with ANA compared to TAM correlated with increasing H/I. H/I expression was not highly correlated with ER, PR or HER2. **Conclusions:** In this retrospective study, H/I was the only factor that predicted differential benefit of ANA vs TAM in the adjuvant setting. Consistent with previous IHC results in TransATAC, molecular ER, PR, and HER2 were not predictive of relative treatment benefit. Taken together with previous data, these results suggest that H/I may be a useful indicator of absolute or differential endocrine benefit depending on the clinical setting. Data on utility of H/I for prediction of relative benefit require further validation.

527 Poster Session (Board #15), Sat, 8:00 AM-11:30 AM

FES PET/CT analysis to evaluate the impact of localization of breast cancer metastases on ER expression. *First Author: Hilde H. Nienhuis, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

Background: Recent data suggests that differences in locations of metastases could have implications for tumor characteristics and thus for therapy response. Limited knowledge is available in this respect about heterogeneity of the estrogen receptor (ER). ^{18}F-fluoro-17β-estradiol (FES) uptake on positron emission tomography (PET), reflects ER expression. We aimed to analyze FES uptake in tumor lesions at different sites in metastatic breast cancer patients. **Methods:** Eligible patients: biopsy proven ER positive breast cancer, post-menopausal, metastases outside the liver, no history of another metastatic malignancy, no use of ER antagonists for ≥ 5 weeks prior to FES PET. They had undergone FES PET with 64-slice mCT within the UMCG (Jan 2009 - Sept 2014). We re-analyzed FES PET and CT scans for metastases. A lesion with maximum absolute standardized uptake value (SUV_{max}) ≥ 1.5 was considered ER positive. Background tracer uptake was measured for normal tissues. CT lesions with diameter ≥ 10 mm were included. Liver lesions were not evaluated on PET given high background signal. **Results:** In 67 patients, 1,338 lesions were identified by CT (120 patients), PET (913 patients) or both (305 patients) in bone (79%), lymph nodes (15%), lungs (3%) and liver (2%). SUV_{max} of FES positive lesions varied maximally 10-fold between patients (median 1.61-15.61), and up to 11-fold within individual patients (range 1.8-19.4). Median SUV_{max} of bone, lymph nodes and lung lesions were respectively 3.21 (range 0.44-24.3); 3.26 (0.75-19.4) and 2.41 (0.54-6.46). For bone metastases median SUV_{max} varied for the sites with highest uptake in cervical spine (4.17) and lowest in sternum (2.55). Also background SUV_{max}levels differed per location with highest level in lumbal spine (1.46) and lowest in fat tissue (0.65). Lung metastases were more frequently FES negative (20%) than bone (7%, $p < 0.01$) and lymph nodes metastases (5%, $p < 0.01$). **Conclusions:** FES uptake in breast cancer metastases is heterogeneous within and between patients and differs per localization in the body, indicating the need for whole body metastases evaluation for precision medicine. *Supported by Dutch Cancer Society grants RUG 2010-4739 and 2012-5565 and ERC Advanced grant 293445.*

528 Poster Session (Board #16), Sat, 8:00 AM-11:30 AM

Breast cancer recurrence in older patients with clinically node-negative T1-T2 tumors managed without sentinel node biopsy (SNB) and without adjuvant radiation therapy. *First Author: Mervat Nabil Saleh, Memorial Hospital of Rhode Island, Pawtucket, RI*

Background: Older patients (pts) with small breast cancers who receive endocrine therapy can omit radiation without a survival disadvantage. SNB adds additional burden and may not be necessary for pts who are not planning adjuvant radiation or chemotherapy. The objective of our study was to evaluate recurrence rate with or without SNB in those pts. **Methods**: We retrospectively reviewed records of pts ≥ 60 years (y) old, diagnosed at our center between 2000 and 2014 with T1-T2, clinically node-negative, estrogen receptor-positive breast cancer, who did not receive adjuvant radiation or chemotherapy. We used Fisher's exact test to compare characteristics, and Gray's test for cumulative incidence function (CIF) for cancer recurrence, with 95% confidence intervals. **Results**: We identified 364 pts. Those managed without SNB were significantly older, more often with apocrine, mucinous or papillary histology and less likely to undergo mastectomy, with no significant differences in other characteristics. There were 5 recurrences (4 local, 1 axillary) in pts without SNB and 16 (11 local, 2 axillary, 3 distant) with SNB. CIF for recurrence at 5 years was 4.8% (CI, 2.6-8.0) for all pts, 6.6% (CI, 1.7-16.3) without SNB and 4.3% (CI, 2.1-7.8) with SNB, not significantly different ($P = .80$). Positive SNB (in 12%) was not prognostic for recurrence ($P = 0.94$). CIF for death from competing causes was twice as high in pts without SNB (24.6 *vs* 11.1%, $P = .0001$), resulting in lower overall survival (77.5 *vs* 89.3%). **Conclusions**: Overall recurrence rate was similar to prior clinical trials. Pts selected for management without SNB have a high risk of death from non-cancer causes, which reflects their advanced age and comorbidities, but they experience no significant increase in the risk of recurrence. Our results, if confirmed in a larger dataset, suggest that SNB does not provide useful prognostic information in older pts who are not planning multimodality adjuvant therapy, and could be omitted.

SNB	N	Median age	Low-risk histology	High grade	HER2-positive	LVI†	Mastectomy	Positive margin
Yes	283	73	7%	14%	6%	13%	39%	3%
No	81	82*	21%*	10%	3%	7%	7%*	5%

* $P < .001$; † Lymphovascular invasion

529 Poster Session (Board #17), Sat, 8:00 AM-11:30 AM

Role of pazopanib (PZ) in modulating hormone resistance in advanced breast cancer (ABC). *First Author: Melanie Catherine Majure, UC San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Hormone resistance develops in nearly all patients (pts) with hormone receptor positive (HR+) ABC. Preclinical data suggests that higher levels of vascular endothelial growth factor (VEGF) are associated with hormone resistance. We conducted a phase II trial to evaluate the clinical benefit (CB) from adding PZ, a VEGF receptor tyrosine kinase inhibitor (TKI) to a nonsteroidal aromatase inhibitor (NSAI) in pts with ABC progressing on NSAIs. **Methods:** Eligibility included postmenopausal women with HR+ ABC and evidence of progressive disease after at least one month of NSAI therapy. Treatment was PZ 800 mg/day plus either letrozole or anastrozole. The primary endpoint was CB rate (CBR) at 12 weeks (wks). Secondary endpoints were progression free survival (PFS) and safety. A CBR of 20% was considered a clinically meaningful comparison to the expected CBR of < 5% with continued therapy after progression on an NSAI. Using a 2 stage design, stable disease in at least one of the first 13 pts allowed continued enrollment to a planned 27. **Results:** Thirty pts were enrolled; 27 are evaluable for study endpoints. The median age was 58 years. Pts were heavily pre-treated with a mean of 2.6 lines of prior hormone therapy (range 1-6) and 1.6 lines of chemotherapy (range 0-8). Eight pts (30%) stopped treatment due to toxicity including hypertension (HTN), fever, transaminitis, and pulmonary embolism; 6 pts progressed prior to wk 12. The CBR at 12 wks was 44.4% (11 SD, 1 PR), and at 24 wks was 22.2% (4 SD, 2 PR). Median PFS for pts with CB at 12 wks was 30 wks (95% CI 20-40); 6 pts had PFS > 6 months (26, 32, 32, 36, 48, and 78 wks). Three pts remain on study at 20, 32 and 78 wks. The most common adverse events (AE) were nausea (52%), fatigue (41%), arthralgia (26%), back pain (26%), and HTN (26%). Grade 3/4 AE included HTN (11%), transaminitis (11%), and headache (7%). **Conclusions:** The addition of PZ to a NSAI resulted in a CBR of 44% at 12 wks, and 22.2% at 24 wks in pts with heavily pre-treated hormone resistant ABC, suggesting that the antiangiogenic TKI PZ can modulate resistance to hormone therapy. Expected toxicities resulted in early discontinuation in 30% of pts, which limited drug exposure. Evaluation of biomarkers and immune signatures is ongoing. Clinical trial information: NCT01466972.

530 Poster Session (Board #18), Sat, 8:00 AM-11:30 AM

Evaluation of possible linkage between everolimus benefit in estrogen receptor (ER)-positive breast cancer and genomic alterations of the PI3K/AKT/mTOR pathway. *First Author: Esther P. Black, University of Kentucky, Lexington, KY*

Background: Everolimus, which inhibits mTOR, is used to treat metastatic ER-positive breast cancer after aromatase inhibitor failure. Because not all patients benefit and toxicity can be prohibitive, it is critical to identify biomarkers of sensitivity to this treatment strategy. **Methods**: We studied 36 tumors from patients enrolled on protocol NCT00570921 using fulvestrant and everolimus for metastatic ER-positive breast cancer. There were 15 pretreatment tumors from 11 patients who experienced benefit and 14 from 10 patients who did not. DNA was extracted from FFPE tumor tissue and subjected to next-generation-based comprehensive genomic profiling using the FoundationOne assay and alterations were then compared. **Results:** 9 out of 11 responders (82%) had at least one genomic alteration in the PI3K/AKT/mTOR pathway vs. 7 out of 10 nonresponders (70%). Mutations detected in the responder group were 7 *PIK3CA* and 1 *AKT1*, and 1 *PTEN* truncation, while in nonresponders there were 5 *PIK3CA* and 2 *AKT1* mutations, and 1 *RICTOR* amplification (in association with a *PIK3CA* mutation). Interestingly, none of the responders had more than one alteration in individual components of this pathway, while 2 of the nonresponders had more than one alteration observed (one with a concomitant *PIK3CA* mutation and *AKT3* amplification, and one with a *PIK3CA* mutation and *RICTOR* amplification). Other notable alterations include mutations in *TP53* and *GATA3*, and amplification of CCND1, with no specific association with everolimus benefit. Additional analysis and frequency of other alterations will be presented in greater detail. **Conclusions:** In this small study, we did not identify predictors for lack of benefit from everolimus, although it appears that the presence of multiple aberrations in the PI3K/AKT/mTOR pathway may promote *de novo* resistance. It is possible that genomic alterations alone may not adequately explain breast cancer response to this strategy without functional signaling analysis. Alternatively, it is possible that everolimus benefit in endocrine resistance may be independent of PI3K/mTOR signaling altogether and its mechanism of action is yet to be fully determined.

531 Poster Session (Board #19), Sat, 8:00 AM-11:30 AM

Efficacy and safety of neoadjuvant docetaxel, carboplatin, trastuzumab/pertuzumab [TCH-P] in non-metastatic HER2+ breast cancer: The Cleveland Clinic experience. *First Author: Shruti Rakesh Tiwari, Cleveland Clinic Foundation, Shaker Heights, OH*

Background: Pertuzumab is FDA approved for use in combination with trastuzumab and chemotherapy as neoadjuvant therapy in women with non-metastatic HER2+ breast cancer. The TRYPHAENA trial reported a pathologic complete response rate (pCR), i.e. ypT0ypN0, of 52% in 77 patients (pts) treated with neoadjuvant TCH-P. Aside from this study, there is limited information regarding the overall safety and efficacy of neoadjuvant TCH-P at FDA approved doses. Our goal was to evaluate the safety and efficacy of neoadjuvant TCH-P in women with non-metastatic breast cancer in a non-clinical trial setting. **Methods:** After IRB approval, a cancer data registry was utilized to identify all pts with HER2+ non-metastatic breast cancer treated at Cleveland Clinic with neoadjuvant TCH-P. pCR was defined as the absence of invasive tumor in both breast and lymph nodes, i.e. ypT0ypN0. **Results:** 71 pts met our inclusion criteria, with a median age of 52 years. Clinical staging was as follows: stage I (8%); Stage II (69%); Stage III (22%). 60% of pts were also hormone receptor (HR) positive (42/71). 89% of pts (63/71) have received all 6 planned chemotherapy cycles without dose reductions, with only 11.2% (8/71) requiring a dose reduction for rash, diarrhea, neuropathy, or thrombocytopenia. Seven pts are currently receiving chemotherapy. No patients had symptomatic cardiac toxicity with TCH-P, with only 6.6% of patients having an asymptomatic reduction in LVEF > 10%. The overall observed pCR rate for neoadjuvant TCH-P was 53% in the 60 patients that have completed all planned chemotherapy, and definitive surgery. As expected, the pCR rate was higher in patients with HR negative breast cancer than in those with HR positive disease: 67% (16/24) vs. 42% (14/33), respectively. **Conclusions:** Neoadjuvant TCH-P was associated with a pCR rate of 53% in a non-clinical trial setting, which was similar to reported rates in the TRYPHAENA trial. Toxicity was manageable, with no patients experiencing symptomatic reductions in LVEF. Long term clinical outcomes are being prospectively followed in all patients being treated with pertuzumab based chemotherapy.

532 Poster Session (Board #20), Sat, 8:00 AM-11:30 AM

Effect of mutations in distinct components of the PI3K/AKT/mTOR pathway on sensitivity to endocrine therapy in estrogen receptor (ER)-positive breast cancer. *First Author: Suleiman Alfred Massarweh, University of Kentucky, Lexington, KY*

Background: Aberrations of the PI3K/AKT/mTOR pathway are common in ER-positive breast cancer and may be associated with endocrine-resistance. We hypothesized that, since the majority of ER-positive breast cancers are actually sensitive to endocrine therapy, the most prevalent aberration in this pathway will more likely be associated with endocrine-sensitivity rather than resistance. **Methods**: We studied 28 tumors from patients enrolled on protocol NCT00570921 using fulvestrant and everolimus after aromatase inhibitor failure; 19 from 13 patients with endocrine-sensitive disease and 9 from 8 patients with resistant tumors. Resistance was defined as relapse within 3 years of adjuvant use or progression within 6 months in the metastatic setting. DNA was extracted from FFPE tumor tissue and subjected to next-generation-based comprehensive genomic profiling using the FoundationOne assay and alterations were then compared. **Results:** 10 of 13 patients with endocrine-sensitive tumors (77%) had at least one alteration in the PI3K/AKT/mTOR pathway vs. 6 of 8 patients with resistant disease (75%). *PIK3CA* mutations were more frequent in the sensitive group; 9/13 (69%) vs. 2/8 (25%) in the resistant group ($p = 0.08$). Interestingly, aberrations of pathway components other than *PIK3CA* were present in only 1 of 13 patients (8%) with sensitive disease vs. 4 of 8 patients (50%) with resistant disease ($p = 0.0475$). These aberrations were 1 activating *AKT1* mutation in the sensitive group and 2 each of *AKT1* activating mutations and *PTEN* loss in the resistant group. Further analysis of additional alterations will be presented in greater detail. **Conclusions:** Alterations in the PI3K/AKT/mTOR pathway are common in both endocrine-sensitive as well as resistant breast cancer but mutations of specific pathway components may distinguish sensitive from disease that is more likely to be resistant. *PIK3CA* mutations, which are relatively common, may be associated with more estrogen-dependent tumor biology while non-*PIK3CA* mutations are potentially associated with endocrine-resistance in ER-positive breast cancer. Further investigation of these findings is warranted.

533 Poster Session (Board #21), Sat, 8:00 AM-11:30 AM

Recurrence score and clinicopathologic characteristics of TAILORx participants by race and ethnicity. *First Author: Maria M Zlobinsky Rubinstein, Montefiore Medical Center, Bronx, NY*

Background: Black race is associated with worse outcomes in localized breast cancer. We evaluated the characteristics of patients enrolled in the Trial Assigning Individualized Options for Treatment (TAILORx) by race and ethnicity. **Methods:** The analysis included 10,071 evaluable patients with Recurrence Score (RS) data. Eligibility criteria included: (1) T1-2, N0 disease, (2) estrogen receptor (ER) and/or progesterone receptor (PR) positive disease that was also HER2/neu negative, (3) age 75 years or younger and medically appropriate for adjuvant systemic chemotherapy. **Results:** The study population included 8,501 whites (84%), 722 blacks (7%), 423 Asians (4%), and the remainder other/unknown race. With regard to ethnicity, 7,916 were non-Hispanic (79%), 919 were Hispanic (9%), and 1,236 were of unreported ethnicity (12%). There was no significant difference in RS distribution ($p = 0.14$), median RS (17 vs. 17), and mean RS (19.6 vs. 18.4) in blacks compared with non-blacks. There was likewise no difference in Hispanic vs. non-Hispanic ethnicity for RS distribution ($p = 0.53$), median RS (17 vs. 17), and mean RS (18.6 vs. 18.4). Blacks were significantly more likely to be younger (39% vs. 30% $<$ 50 years), have larger tumors (37% vs. 31% $>$ 2 cm), poor histologic grade (25% vs. 17%), and PR-negative disease (14% vs. 10%) (Chi square test $p < 0.05$). Hispanic women were also significantly younger (39% vs. 30% $<$ 50 years), and demonstrated marginal but statistically significant differences in tumor size (34% vs. 31% $>$ 2 cm), histologic grade (20% vs. 18% poor), and PR expression (12% vs. 10% negative) (Chi square test < 0.05). In 974 patients with information on body mass index (BMI), there was no correlation between BMI and RS ($r = -0.04$). BMI was higher for blacks than whites (medians 31.6 vs. 28.9, $p = 0.02$, Wilcoxon test), but not in Hispanics. **Conclusions:** In patients selected for participation in TAILORx there were no significant differences in RS by race, ethnicity, and BMI. When compared to white patients, black and Hispanic patients were significantly younger, had tumors that were larger, and more likely to be associated with poor grade. Clinical trial information: NCT00310180.

534 Poster Session (Board #22), Sat, 8:00 AM-11:30 AM

The vitamin D receptor: A therapeutic target for the treatment of breast cancer? *First Author: Alyson M Murray, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland*

Background: Recent studies suggest vitamin D (VD) plays a role in cancer cell growth, with evidence indicating that a deficiency can lead to higher disease risk and a poorer outcome. Activation of the vitamin D receptor (VDR) by the active form of VD (calcitriol) leads to the regulation of anti-cancer genes. Therefore, we propose that VDR could be targeted as a potential therapeutic for treatment of breast cancer. **Methods:** The effects of calcitriol and inecalcitol (Hybrigenics, Paris) on breast cancer (BC) cell growth were investigated in 16 cell lines (TN = 7, Her2+ = 5, luminal = 4) and 7 cell lines (TN = 3, Her2+ = 2, luminal = 2), respectively. Cytotoxicity was determined by MTT assays and cell proliferation by colony formation assays (CFA). VDR expression was measured by ELISA (USCN Life Science Inc.). **Results:** IC_{50} concentrations for treatment with calcitriol, across the 16 cell lines ranged from 0.12 μM to $>$ 100 μM, using the MTT assay. These IC_{50} values were validated by CFA with a significant correlation between the 2 assays ($p = 0.0046$, $r = 0.898$). Sensitivity to calcitriol was higher in ER+ compared to ER- cell lines ($p = 0.0454$) but was independent of HER2 status ($p = 0.8181$). VDR expression in the cell lines varied from undetectable to 10 pg/mg. A significant correlation was found between VDR levels and IC_{50} value ($p = 0.0076$, $r = -0.6401$). IC_{50} concentrations for treatment with the low calcemic-inducing VD analogue inecalcitol ranged from 4.2 nM to 54.4 nM across 7 cell lines. Sensitivity to inecalcitol was higher in ER+ compared to ER- cell lines ($p = 0.0092$), but like with calcitriol, was independent of HER2 status ($p = 0.4745$). A significant correlation was found between IC_{50} values for inecalcitol and calcitriol ($p = 0.0231$, $r = 0.8571$). However, depending on the cell line, inecalcitol was approximately 14 to $>$ 50 fold more sensitive than calcitriol ($p = 0.0006$). **Conclusions:** These preclinical results suggest that calcitriol and inecalcitol can inhibit breast cancer cell line growth. Since inecalcitol, is considerably more potent than calcitriol and has low calcemic potential, it should be further investigated as a treatment for breast cancers expressing VDR.

535 Poster Session (Board #23), Sat, 8:00 AM-11:30 AM

Significance of prospective multicenter decision impact WSG-BCIST Study in postmenopausal ER+ HER2- N0 early breast cancer (EBC) for molecular testing for intrinsic subtype definition. *First Author: Rachel Wuerstlein, University of Munich, Munich, Germany*

Background: Prosigna is a standardized test measuring expression levels of 50 classifier genes (PAM50) in formalin-fixed, paraffin-embedded (FFPE) breast tumor tissue using nCounter Technology (NanoString Technologies, Inc., Seattle, WA). It provides intrinsic subtype and risk of recurrence (ROR) score predicting 10y recurrence probability. It was retrospectively validated by ABCSG 8 and TransATAC. WSG BCIST evaluates its impact on systemic therapy decisions in EBC. **Methods:** 201 consecutive postmenopausal pts. with ER+ HER2- N0 were recruited (11 centers; 10/2013-10/2014). Primary objective was to assess impact of Prosigna vs. standard immunohistochemistry (IHC) on adjuvant chemotherapy recommendations and actual therapy received. Secondary objectives include physicians' confidence in recommendations, patients' decisional conflict, and rate of chemotherapy-related adverse events. Prosigna testing was performed centrally (university) and repeated de-centrally (community-based pathology) for quality control. **Results:** Intrinsic subtypes were highly concordant (95.5%) between the two pathologies. Risk group differed in only 1/9 discordant cases; underlying tumor heterogeneity is being evaluated. In the total cohort (198 patients evaluated), 58.1% of tumors were classified by PAM50 as Luminal A, 39.9% as Luminal B, 1.5% Basal, 0.5% HER2-E. Local IHC classified 18.3% of PAM50 Luminal A as Luminal B, and 39.2% PAM50 Luminal B as luminal A (overall 26.9% discordance). Prosigna results led to a reported change in chemotherapy (CT) indication in 19.2% overall, including 39.2% of PAM50 luminal B patients. Actual CT use and morbidity will be evaluated after scheduled 6-month follow-up. **Conclusions:** In the WSG BCIST prospective decision impact study, Prosigna results led to a 19% change in chemotherapy indication. The 27% discordance in intrinsic subtyping between PAM50 and IHC underlines the importance of molecular testing for optimal systemic therapy indications in EBC. As a pre-planned pooled analysis, WSG BCIST can later be evaluated together with two similar studies currently ongoing in Europe. Clinical trial information: NCT01974856.

536 Poster Session (Board #24), Sat, 8:00 AM-11:30 AM

Incidence and survival for young women with operable breast cancer: SEER 1992-2011. *First Author: Mary Chen Schroeder, University of Iowa, Iowa City, IA*

Background: Recent work has shown an increasing incidence of Stage IV breast cancer (bc) in young women (wm). We examined the incidence and survival of young wm with operable bc. **Methods:** Wm ages 20-39 diagnosed with stages 1-3 bc from 1992-2011 were identified from SEER data and categorized by hormone receptor (HR) status and grade (low = well/moderately differentiated, high = poor/undifferentiated). Those with missing information were excluded. Annual percent change (APC) in age-adjusted incidence rates for the SEER 13 registries were calculated. Kaplan Meier survival curves were estimated by HR and grade. **Results:** We identified 3,566 wm aged 20-29 and 34,508 wm 30-39. For wm 20-29, stages 1, 2, 3 comprised 25.2, 50.5, and 24.3% of the sample versus 30.6, 47.1, and 22.3% for wm 30-39 (all $p < 0.001$). HR status and grade also differed significantly by age. Wm 20-29 were more likely to have HR- disease (40.4 v 34.2%), less likely to have HR+ low grade disease (25.7 v 35.6%) and more likely to have HR+ high grade disease (33.9 v 30.2%) than wm 30-39 (all $p < 0.001$). APC in incidence along with 5- and 10-yr survival is reported in the table. In HR+ disease, regardless of grade, survival decreased more rapidly beyond 5 years from diagnosis for 20-29 than 30-39. This was not seen for HR- disease. **Conclusions:** Wm age 20-39 presented more frequently with Stage II bc. Wm 20-29, unlike wm 30-39, have not seen a decline in Stage III disease. Low and high grade HR+ disease in wm 20-29 also increased with the highest APC in incidence. 10-year survival for 20-39 year old wm with HR+ disease showed continued late deaths. This was most pronounced for wm 20-29.

	20-29 yrs	30-39 yrs	p
APC in incidence			
Full cohort	0.9*	0.7*	< 0.001
Stage 1	.2	-.3	< 0.001
Stage 2	1.5*	1.8*	< 0.001
Stage 3	.4	-.1*	< 0.001
HR-	-.4	.6	< 0.001
HR+ low grade	6.6*	4.1*	< 0.001
HR+ high grade	3.4*	2.3*	< 0.001
Survival at 5(10) yrs			**
Full cohort	0.82 (0.71)	0.86 (0.76)	< 0.001
Stage 1	.94 (.87)	.96 (.90)	0.020
Stage 2	.87 (.76)	.88 (.79)	0.041
Stage 3	.59 (.42)	.67 (.50)	< 0.001
HR-	.78 (.72)	.79 (.72)	0.822
HR+ low grade	.92 (.76)	.94 (.84)	< 0.001
HR+ high grade	.79 (.62)	.86 (.72)	< 0.001

* APC significantly different from zero ($p < 0.05$); ** p-value compares 10-yr survival of the two age groups

537 Poster Session (Board #25), Sat, 8:00 AM-11:30 AM

An indirect evaluation of bone saturation with zoledronic acid after long-term Q4 week dosing using plasma and urine pharmacokinetics. *First Author: Gabriel N. Hortobagyi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Zoledronic acid (ZA) has a high binding affinity for human bone. This post-hoc analysis from the OPTIMIZE-2 trial evaluated whether there is evidence for bone saturation of ZA following long-term dosing at the standard q 4wk dosing. We hypothesized that if bone saturation of ZA would occur, then 1. Plasma and urinary levels of ZA would increase with prolonged dosing, and 2. Switching to a reduced dosing frequency of q12 weeks would reduce plasma and urinary ZA levels. **Methods:** OPTIMIZE-2 was a randomized, double-blind, multicenter trial in female pts with bone metastases from breast cancer who previously received long term ZA treatment (1 to 7 yrs) with standard q4 wk (infusion time of 15 min). Pts were randomized (1:1) to receive ZA 4 mg IV q4 wk or q12 wk for 1 year. ZA levels were analyzed in plasma and urine during 0-6h after thefirst dose (week 1) and after the week 36 dose in ZA-pretreated (1-7 yrs) pts with evaluable ZA levels (n=38). **Results:** Baseline creatinine clearances were comparable between the ZA q4 wk (N=21) and q12 wk (N=17) groups. Pre-infusion urine and plasma concentrations (ng/mL) at either time point (week 1 and 36) were in most cases near or below the lower limit of quantification. The table shows mean (SE) of ZA excreted in urine (in % of dose) and AUC (in h x mg/L) of ZA plasma concentrations, after the first and week 36 dose of ZA in OPTIMIZE-2. The plasma level s in the two dosing frequency groups (q4 wk and q12 wk) and both time points were similar. Urine ZA level s were also similar between the 2 dosing frequencies at both time points. These plasma and urine levels were also similar to levels from newly dosed patients receiving q 4wk ZA dosing for the first time (Chen et al. J Clin Pharmacol 2002;Skerjanec et al. J Clin Pharmacol 2003). Switching ZA dosing frequency from q4 wk to q12 wk did not reduce plasma and urinary ZA levels. **Conclusions:** Based on plasma and urinary ZA levels with standard and reduced dosing frequencies, our data does not suggest that prolonged treatment with ZA q4 wk results in bone saturation of ZA. Clinical trial information: NCT00320710.

	First dose; q4 wk	Week 36; q4 wk	First dose; q12 wk	Week 36; q 12wk
Plasma AUC 0-6h	0.37 (0.03)	0.43 (0.06)	0.40 (0.02)	0.43 (0.05)
Urine 0-6h	26.0 (4.4)	36.6 (6.6)	23.7 (5.6)	30.8 (4.7)

538 Poster Session (Board #26), Sat, 8:00 AM-11:30 AM

Prospective study of the decision-making impact of the Breast Cancer Index in the selection of patients with ER+ breast cancer for extended endocrine therapy. *First Author: Tara Beth Sanft, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: The Breast Cancer Index (BCI) has been validated to quantify an individualized risk of late recurrence and to predict likelihood of benefit from extended endocrine therapy in ER+ early stage breast cancer.The purpose of this study was to prospectively assess the impact of BCI i) to change treatment recommendations regarding extended endocrine therapy, and ii) to examine its effects on patient anxiety and decision conflict. **Methods:** Patients with stage I-III, ER+ breast cancer treated at the Yale Cancer Center who completed at least 3.5 yrs of adjuvant endocrine therapy were prospectively enrolled over 6 months in 2014. BCI was performed on FFPE samples from the original biopsy (bioTheranostics Inc.). Patients and physicians completed pre- and post-test questionnaires. Patients completed the Traditional Decisional Conflict Scale (DCS) and State Trait Anxiety Inventory Form Y (STAI) pre- and post-test. **Results:** 100 patients[mean age 61y (45-88), 80% postmenopausal, 57% stage I] were included in this study. Integration of BCI resulted in a change in treatment recommendation for 27% of patients. A majority of changes were based on identification of patients with low risk of late recurrence and low likelihood to benefit from extended endocrine therapy. Extended therapy was recommended for 75% patients pre- and for 55% post-testing. No extended therapy was recommended for 25% patients pre-and for 45% post-testing. Satisfaction increased in 38% of patients. After receiving results, 52% of patients changed their treatment decision. Patients experienced less anxiety (53%) and decisional conflict (50%) after receiving results. The STAI ($p = 0.03$) and DCS ($p < 0.001$) scores decreased significantly post testing (mean difference of -2 and -9, respectively) compared to baseline scores (31 and 20, respectively). **Conclusions:** The Breast Cancer Index led to changes in treatment recommendations regarding extended adjuvant endocrine therapy in 27% of cases and resulted in significantly less decision conflict and anxiety for patients. Overall, knowledge of BCI resulted in fewer recommendations for extended therapy and improved patient satisfaction. Clinical trial information: NCT02057029.

539 Poster Session (Board #27), Sat, 8:00 AM-11:30 AM

Case-control study of hormone receptor expression in benign breast and cancer risk. *First Author: Caroline Fenger Healy, Northwestern University, Chicago, IL*

Background: Previous studies have shown that hormone receptor expression in non-proliferative epithelium (NPE) indicates increased breast cancer risk, whereas other studies have been null. We assessed estrogen receptor (ER), progesterone receptor (PR) and Ki67 expression in NPE of newly diagnosed breast cancer cases and benign disease controls using contemporary immunohistochemical (IHC) methods and digital image analysis. **Methods**: Formalin-fixed paraffin-embedded breast samples (171 cases and 169 age-matched controls) were collected from women treated between 1994-1999. 4-μm sections were stained for ER (ThermoScientific/SP1, 1:200-pH6), PR (Dako/M3569, 1:1600-pH6) and Ki67 (Dako/MIB-1, 1:100-pH6) on Leica Bond Max and Dako automated stainers. The NPE portions of the digitized slides were sampled in random fashion and evaluated blindly with Aperio Spectrum software. % positive cells were scored for ER, PR and Ki67 and categorized into quartiles. Wilcoxon rank-sum test and logistic regression with age adjustment were used for pairwise comparison. Spearman's rank correlation test and one-way ANOVA test with Sidak adjustment were used for the correlation and comparison among multiple markers and subgroups. **Results**: The mean age was 49 years for cases and 48 years for controls. Overall, there was no significant difference between the cases and controls for ER, PR or Ki67 expression. In analyses stratified by menopausal (M) status, post-M ER % positivity was significantly higher in cases than controls (34.0 vs 29.8, OR = 1.49, $p = 0.007$). ER was significantly higher in post-M than in pre-M cases ($p < 0.0001$). ER and PR were positively correlated among cases ($R = 0.433$, $p < 0.0001$) and controls ($R = 0.547$, $p < 0.0001$). Ki67 was significantly lower in post-M than in pre-M controls ($p = 0.004$). **Conclusions**: ER expression in benign non-proliferative breast epithelium is significantly higher in postmenopausal cases, suggesting increased ER expression may indicate increased breast cancer risk in older women.

ER % logistic regression on quartile (age-adjusted).

	Premenopausal		Postmenopausal	
	Control	Case	Control	Case
N	83	82	84	81
Median	27.5	26.4	29.8	34.0
95% CI	0.68-1.20		1.12-1.98	
OR	0.90		1.49	
P	0.49		0.007	

540 Poster Session (Board #28), Sat, 8:00 AM-11:30 AM

Relationship of germline polymorphisms to docetaxel toxicity in the ROSE/TRIO-012 trial. *First Author: Sambasivarao Damaraju, University of Alberta/Cross Cancer Institute, Edmonton, AB, Canada*

Background: TRIO-012 is a double blinded, multinational trial that randomized 1,144 patients with advanced breast cancer to receive first-line docetaxel (Doc) in combination with ramucirumab or placebo. Our objective is to address genetic predisposition to Doc toxicity. In this independent validation study, we selected single nucleotide polymorphisms (SNPs) previously associated with taxane-induced adverse events (AEs; fatigue, myalgia, peripheral neuropathy), including CYP3A5*3 reported by our group to be strongly associated with Doc toxicity. **Methods:** Germline SNPs were studied in participants who gave prospective consent for peripheral blood DNA genotyping. All subjects received Doc until unacceptable toxicity or progressive disease. From these, 399 subjects predominantly of Caucasian origin were analysed here. Toxicity grades 0-1 (controls; low toxicity) vs. grade $>$ 2 (cases, high toxicity) were compared. Dominant genotypic model was assumed; Chi-square test with 10000 permutations were employed using SVS v8.3 and $p < 0.05$ considered statistically significant. **Results:** Each reported variant conferred risk. CYP3A5*3 allele (rs776746; OR 2.16 [1.18-3.96]), TNF-alpha (rs1800629), NAV1 (rs478472), NOS3 (rs1799983) were associated with fatigue. SNPs associated with myalgia were FACND2 (rs7637888), HIF1-alpha (rs11549465) and NDRG1 (rs2233335). XKR4 (rs4737264) showed association with peripheral neuropathy. SNPs in ABCC2, SLCO1B3 and VEGF-R1 genes showed associations with all three individual AEs tested. In a combined analysis of all the AEs, CYP3A5*3 allele retained significance (OR 1.9 [1.08-3.37]; as did IL1-beta (rs16944) and CYP2C8 (rs11572080). **Conclusions:** We confirm our previous finding that CYP3A5*3 genotype determines toxicity by its influence on Doc metabolism (EurJCancer 8(7),175,2010). NDRG1, FACND2 and XKR4, SNPs previously associated with paclitaxel-induced neuropathy, were now associated with Doc-induced myalgia or neuropathy. In conclusion, we report a subset of variants analysed conferring genetic predisposition to both paclitaxel and Doc AEs. The pleotropic drug effects on multiple genes/pathways appear to contribute to the overall phenotype of taxane toxicity.

541 Poster Session (Board #29), Sat, 8:00 AM-11:30 AM

Oncotype DX scores in BRCA1 and BRCA2 associated breast cancer. *First Author: Nicholas Patrick McAndrew, Basser Research Center for BRCA, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: The Oncotype DX score is widely used to evaluate recurrence risk and potential benefit of chemotherapy in stage 1, estrogen receptor (ER) positive, Her2 negative tumors. Oncotype DX was developed and validated in sporadic breast cancer patients. No data are available regarding Oncotype DX results in BRCA1/2 mutation carriers. The purpose of this study is to determine the distribution of Oncotype DX scores in patients with BRCA1/2 associated cancers, as well as subsequent therapy and disease course for this population. **Methods:** 18 patients were identified between 2006-2013 who had deleterious BRCA1/2 mutations and stage 1, ER positive, Her2 negative, node negative invasive breast cancer. Data regarding Oncotype DX scores, subsequent therapy (including local, prophylactic, hormonal, and chemotherapy), and length of follow-up was collected. **Results:** The distribution of Oncotype DX scores was similar in this population as compared to prior published data on patients with sporadic tumors, with approximately 41% of patients having a "low" score, 47% having an "intermediate" score, and 12% having a "high" score. While none of the patients with "low" risk scores had a recurrence of disease at an average of 44.1 months in follow-up, one patient with "intermediate" risk disease had a recurrence 48 months after initial diagnosis. Further molecular analysis of one of the "low" risk tumors failed to demonstrate loss of heterozygosity. **Conclusions:** These findings are suggestive that the Oncotype DX assay is a reliable and applicable clinical decision making tool in patients with certain BRCA 1/2 associated tumors.

Family-Ego #	BRCA Mutation	Age at Diagnosis	Oncotype Score	Risk Category	Follow Up (mo)
3099-1	BRCA1	40	Not Sent	N/A	67.9
3343-1	BRCA1	44	8	Low	46.5
2500-1	BRCA1	59	11	Low	78.2
3944-1	BRCA1	43	16	Low	5.3
3557-1	BRCA1	36	17	Low	27.7
3336-1	BRCA1	38	19	Intermediate	29.4
4074-1	BRCA1	54	22	Intermediate	14.5
3389-1	BRCA1	64	28	Intermediate	55.8
3761-1	BRCA1	52	28	Intermediate	74.6
3827-1	BRCA1	51	55	High	12.6
2862-10	BRCA2	70	10	Low	22.6
3402-1	BRCA2	33	15	Low	40.5
4062-1	BRCA2	40	16	Low	5
3873-1	BRCA2	30	21	Intermediate	13.9
3041-1	BRCA2	49	22	Intermediate	69.8
3276-1	BRCA2	43	28	Intermediate	56.2
2951-1	BRCA2	33	29	Intermediate	17.9
3760-1	BRCA2	43	60	High	14.5

542 Poster Session (Board #30), Sat, 8:00 AM-11:30 AM

There is more to the picture than meets the eye: Population-based study on biopsy verification of suspected breast cancer recurrences. *First Author: Ulla Wilking, Department of Oncology and Pathology - Karolinska Institutet and Cancer Center Karolinska, Stockholm, Sweden*

Background: Core biopsy/Fine needle aspiration (Bx) is recommended to confirm the diagnosis of Recurrent Breast Cancer (RBC). Up to 10% of all Bx are not RBC but benign or other malignancy. Hormone Receptor (HR)/HER2 status is known to change impacting management of RBC. The objective was to study the proportion of benign/other malignancies in suspected RBC, as well as to study the change in subgroup (see Methods) between PBC/RBC and consecutive RBCs from the same patient. **Methods:** In a population-based cohort in Stockholm, Sweden, of women with a diagnosis of RBC during 2007 until 2012 (and PBC before 2007), we reviewed all Bx-reports after PBC diagnosis. Exclusion criteria: stage IV disease, bilateral breast cancer. The trigroup was defined as three subgroups, HR+/HER2-, HER2+ and triple negative (TNBC), and compared between PBC/RBC and multiple RBCs from the same patient. **Results:** Only 60 patients did not undergo Bx and there were a total of 1034 Bx samples in 453 women with RBC. Sites of sample: bone, ascites, lung/pleura, CNS, liver, spleen, GI, gyn, etc. Results of Bx show that suspected RBC may be other malignancy (3%), benign (35%) or inconclusive (6%). Of the 52 lung/pleura samples were 2 lung cancers, 10 were cancers of unknown primary (CUP) and 6 showed inflammation. Of the 56 liver biopsies one was hemangioma and one showed inflammation. Also, one of the 185 local biopsies showed to be a neuroendocrine tumor. Tumor trigroup changed between PBC and RBC in almost one out of three patients as well as between consecutive RBCs (see table). **Conclusions:** For correct clinical management of patients with RBC it is essential to take Bx of any suspected site, since up to 55% of suspected RBC lesions are not RBC. Furthermore, biology changed in around 30% of patients, also between consecutive relapses.

	RBC			
PBC	**HR+ and HER2- Number (%)**	**HER2+ Number (%)**	**TNBC Number (%)**	**Total**
HR+ and HER2-	38 (36.2)	7 (6.7)	8 (7.6)	
HER2+	3 (2.9)	13 (12.4)	2 (1.9)	
TNBC	7 (6.7)	3 (2.9)	24 (22.9)	
Total number	48 (45.7)	23 (21.9)	34 (32.4)	105
FIRST RBC		CONSECUTIVE RBC		
HR+ and HER2-	23 (50)	3 (6.5)	2 (4.3)	
HER2+	1 (2.2)	5 (10.9)	0	
TNBC	3 (6.5)	3 (6.5)	6 (13)	
Total number	27 (58.7)	11 (23.9)	8 (17.4)	46

543 Poster Session (Board #31), Sat, 8:00 AM-11:30 AM

21-gene recurrence score assay (RS) and impact on adjuvant chemotherapy (CTx) use among lobular (L) and ductal (D) histology hormone receptor positive (HR+) early breast cancers (EBC). *First Author: Simon Daniel Baxter, BC Cancer Agency, Vancouver, BC, Canada*

Background: RS identifies lower risk HR+ EBCs that may avoid adjuvant CTx. L histology may influence CTx use in intermediate RS cancers given its association with high HR+ expression and hormone therapy benefit. We examined RS and its utility in clinical decisions among L relative to D EBCs. **Methods:** We identified BC Cancer Agency referred pts with a RS performed on their HR+ EBC between 2007 and 2014, as part of routine care (node negative only) or in clinical trials. Multifocal tumors and mixed L-D histology were excluded. Demographic and histopathological variables and rates of CTx were compared for D and L using univariate and multivariate analyses. **Results:** After exclusions, 577 cases (89% D, 11% L) were identified. Compared with D tumors, L tumors were larger, lower grade, had a lower mean RS (20 vs 16 $p = 0.0002$), and fewer had high RS (Table 1). These differences were not significant after adjustment for age, degree of HR+ expression, size, grade, nodal status, LVI. Among 289 pts (256 D, 33 L) with treatment not mandated in a trial based on RS, 82 (28.4%) had CTx, including 5 (15.2%) L and 77 (30.1%) D ($p = 0.10$). Of the 97 with intermediate RS cancers, CTx was given in 3/12 (25%) L and 26/85 (30.6%) D cases. **Conclusions:** The observed frequency of L and D histology in this series mirrors the incidence distribution described in EBC. The overall lower use of CTx in L cancers can be accounted for by lower RS and more favourable histopathological variables. Among intermediate RS cancers, histology did not appear to impact CTx use. In the absence of prospective data, L histology should not influence CTx use for intermediate RS cancers.

Comparison of ductal and lobular cancers.

	Ductal	Lobular	P-value
Pts, n (%)	512 (89)	65 (11)	
Age, mean (range)	55 (23-78)	58.5 (42-77)	0.008
Premenopausal, n (%)	232 (45)	19 (29)	0.01
Grade, n (%)			
1	82 (16)	6 (9)	< 0.0001
2	282 (55)	54 (83)	
3	148 (29)	5 (8)	
Size, n (%)			
T1	328 (64)	24 (37)	< 0.0001
T2	180 (35)	38 (58)	
T3	4 (1)	3 (5)	
Node negative, n (%)	375 (73)	50 (77)	0.53
LVI present	106 (20)	4 (6)	0.01
RS, mean (range)	20 (0-73)	16.4 (4-33)	0.0002
High, n (%)	82 (16)	3 (5)	0.047
Intermediate, n (%)	170 (33)	23 (35)	
Low, n (%)	260 (51)	39 (60)	

544 Poster Session (Board #32), Sat, 8:00 AM-11:30 AM

Prediction of late distant recurrence (DR) using the Prosigna (PAM50) test in a Danish Breast Cancer Cooperative Group (DBCG) cohort of postmenopausal women diagnosed with hormone receptor-positive (HR+) early breast cancer (EBC) allocated to 5yr of endocrine therapy (ET). *First Author: Anne-Vibeke Lænkholm, Department of Pathology, Region Zealand, Denmark*

Background: Accurate assessment of the risk of late DR (5-10 yr after surgery) may be used to tailor the duration of ET for patients with HR+ EBC. The Prosigna (PAM50) risk of recurrence (ROR) score was shown to predict late DR for EBC patients treated with 5yr of ET in two randomized clinical trials. Here we assess the ability of PAM50 to predict late DR in a comprehensive nationwide cohort from Denmark consisting of postmenopausal women diagnosed with HR+ EBC allocated to 5yr of ET alone. **Methods:** Using the population based DBCG database FFPE primary tumor blocks and follow-up data were collected from all HR+ EBC patients diagnosed from 2000-2003 who by nationwide guidelines were allocated to 5yr of ET alone (N = 2749). The PAM50 test was run on the NanoString nCounter Analysis System. Multivariate analyses tested the ability of PAM50 to predict late DR. Patients were categorized as Low, Intermediate, or High risk based upon prespecified ROR cutoffs varied by number of positive nodes. **Results:** From 2722 included patients, 2164 were disease free at 5yr and analyzed for risk of late DR. Median follow-up was 4.58 years from completion of ET. High risk patients (N = 870) had a late DR risk of 10.2% [95%CI: 8.0-12.7], compared to 6.1% [4.2–8.6] for Intermediate (N = 650) and 2.4% [1.3–4.1] for Low risk patients (N = 644). When ROR was added to a multivariable model including standard clinical and pathological variables it improved the prediction of late DR (likelihood ratio: $p < 0.0001$; HR for a 20-point change = 1.5 [1.2–1.9]). Luminal B (N = 733, late DR risk = 10.3% [7.8–13.1]) and Her2-enriched patients (N = 132, late DR risk = 8.8% [4.4–15.0]) had a significantly worse outcome than Luminal A (N = 1281, late DR risk = 4.5% [3.3–5.9]), $p < 0.0001$ for LumB and = 0.034 for Her2e. **Conclusions:** We have confirmed the ability of Prosigna (PAM50) to predict late DR for HR+ EBC patients regardless of nodal status in a real world cohort devoid of physician selection bias. PAM50 can reliably be utilized to identify patients who need, or most importantly may be safely spared, extended ET beyond 5yr.

545 Poster Session (Board #33), Sat, 8:00 AM-11:30 AM

Predictive testing for selection of patients for extended endocrine therapy: Clinical utilization of Breast Cancer Index (BCI) in early-stage, ER+, LN- breast cancer. *First Author: Stephen C. Malamud, Beth Israel MedcI Ctr, New York, NY*

Background: Randomized trials have demonstrated significant but modest (3-5%) benefit from extended (10y) endocrine therapy (EET) vs 5y in pts with early stage ER+ breast cancer. Clinical practice guidelines have speculated on the risk vs benefit of EET in pts with a low clinicopathologic risk profile. Breast Cancer Index (BCI) is a gene expression-based test that that is prognostic for risk of late (> 5y) recurrence and predictive of EET benefit. This study examined the clinical utility and utilization of BCI in clinical practice, and its ability to identify pts likely to benefit from EET in an otherwise low risk population. **Methods:** Consecutive cases (N = 853) from LN- pts submitted for BCI prognostic and BCI predictive [HoxB13/IL17BR (H/I) ratio] analyses were investigated. Patient characteristics, clinician testing patterns, and clinical results were analyzed descriptively. **Results:** Patient characteristics are shown in the top table. BCI identified 54% and 46% as having low and high risk of late recurrence, respectively. Predictive testing identified 42% of pts with a high likelihood vs. 58% with a low likelihood of benefit from EET. The bottom table shows the integrated prognostic and predictive results. In the subset of pts with a low clinicopathologic risk profile (LN-, T1, Grade 1-2, HER2-neg; n = 321), BCI identified 23% of pts with both a high risk of late recurrence (mean, 7.1% DRR) and likely to benefit from EET. Physicians utilized BCI across a range of intervals from time of diagnosis: 11% < 2y; 14% ≥ 2 to < 4y; 57% ≥ 4 to < 6y; and 18% ≥ 6y. **Conclusions:** Data from this large retrospective analysis further define BCI clinical utility in selection of which early-stage, ER+ pts are at risk of late recurrence and likely to benefit from EET vs those that may be adequately treated with 5y of endocrine therapy.

Characteristics (N = 853)

Mean Age	57y
> 65y	27%
Size	%
≤ 1cm	26
> 1 - ≤ 2cm	49
> 2 - ≤ 5 cm	23
>5 cm	2%
Grade	%
1	29
2	52
3	19
HER2	%
Neg	89
Pos	19

Stratification by BCI prognostic (risk of late recurrence) and BCI predictive (H/I)

All pts (N=853)		
	Likelihood of Benefit	
Risk Group	Low	High
Low	43%	11%
High	15%	31%
LN-, T1, Grade 1-2, HER2- (n = 321)		
	Low	High
Low	54%	12%
High	11%	23%

546 Poster Session (Board #34), Sat, 8:00 AM-11:30 AM

Prediction of 10yr distant recurrence (DR) using the Prosigna (PAM50) assay in a Danish Breast Cancer Cooperative Group (DBCG) cohort of postmenopausal Danish women with hormone receptor-positive (HR+) early breast cancer (EBC) allocated to 5yr of endocrine therapy (ET) alone. *First Author: Anne-Vibeke Lænkholm, Department of Pathology, Region Zealand, Denmark*

Background: The Prosigna (PAM50) risk of recurrence (ROR) score has been validated in two randomized clinical trials to predict 10yr DR in EBC patients treated with ET alone. Here we examine the value of PAM50 for predicting risk of DR in a comprehensive nationwide cohort from Denmark consisting of all postmenopausal women diagnosed with HR+ EBC allocated to 5yr of ET alone. **Methods:** Using the population based DBCG database FFPE primary tumor blocks and follow-up data were collected from all patients diagnosed from 2000-2003 (N = 2749) who by nationwide guidelines were allocated to 5yr of ET alone. PAM50 was conducted using the NanoString nCounter Analysis System. Univariate and multivariate analyses tested the ability of PAM50 to predict DR. Patients were categorized as Low, Intermediate, or High risk based upon pre-specified ROR cutoffs varied by number of positive nodes. **Results:** Blocks from 2749 patients were identified and data from 2722 samples (1256 N0, 1466 N1) were included in the analysis (99%). Median follow-up was 9.25yr. High risk patients (n = 1200) had a DR risk of 20.8% [95%CI: 18.3-23.4] at 10 years, compared to 4.3% [2.9-6.2] for Low risk patients (n = 733). These figures were consistent across nodal status. Adding ROR to a Fine and Gray's proportional sub-hazards model containing clinical and pathological variables significantly improved the model (likelihood ratio: $p < 0.0001$; HR for a 20-point change in ROR = 1.7 [1.5-1.9]. Luminal B tumors (N = 977, DR risk = 18.0% [15.4-20.9]) and Her2-enriched tumors (N = 203, DR risk = 27.7% [21.5-34.3]) had a significantly worse outcome than Luminal A (N = 1515, DR risk = 7.7% [6.2-9.3]), both $p < 0.0001$. **Conclusions:** To our knowledge, this is the first genomic study of breast cancer on a comprehensive nationwide population. Prosigna (PAM50) improved the prediction of outcome over and above standard clinical and pathological variables in this DBCG cohort devoid of physician selection bias. PAM50 can reliably identify patients in a real world setting who may be spared overtreatment with chemotherapy.

547 Poster Session (Board #35), Sat, 8:00 AM-11:30 AM

Genetics of ramucirumab-associated hypertension in the ROSE/TRIO-012 breast cancer trial. *First Author: John Robert Mackey, Cross Cancer Institute, Edmonton, AB, Canada*

Background: TRIO-012 is a double-blinded multinational phase III trial that randomized 1,144 patients with advanced breast cancer to receive first-line docetaxel in combination with ramucirumab (anti-VEGFR2) or placebo. We investigated the association of genotype (single nucleotide polymorphisms, SNPs) with the phenotype (hypertension, HT as a treatment-emergent adverse event) to seek genetic predispositions to ramucirumab toxicity. **Methods:** In this study, 220 SNPs were selected from literature related to anti-angiogenic pathways, drug metabolism/transport, immune regulation, and hypertension. SNPs were genotyped using germline DNA on the platforms, Sequenom iPLEX Gold and Pyrosequencing. Genotype data was filtered for deviations from Hardy Weinberg Equilibrium and minor allele frequency of > 0.05. Study subjects provided ethics-committee approved prospective consent for this genetic study. 257 Caucasian subjects were analysed here from the docetaxel-ramucirumab arm. Toxicity grades 0-1 (n = 208 controls; low toxicity) vs. grade > 2 (n = 49 cases, high toxicity) were tested for genetic associations. Dominant genotypic model was assumed; Chi-square test with 10000 permutations were employed (Golden Helix-SVS v8.3) and $p < 0.05$ considered statistically significant. **Results:** VEGF-R2 (rs17709898) conferred protection (OR 0.51 [0.26-0.96]) and rs7691507 conferred risk (OR 2.01 [1.07-3.77]). Polymorphism in ABCB1 (MDR1), rs2235067 conferred risk (OR 2.37[1.21-4.64]). SNPs (rs9508033, rs722503 and rs3794405) in VEGF-R1 and NR1I3 (rs2307418 and rs5085) showed association (risk and protection, respectively). **Conclusions:** The association of VEGF- R2 rs17709898 with HT is consistent with the known mechanism of ramucirumab VEGF-R2–directed antibody. rs17709898 is in linkage disequilibrium with rs1870377, a variant previously shown to be associated with HT. Similarly, the association of VEGF-R1 with HT suggests compensatory pathways may have a role in anti-angiogenic toxicity. None of the polymorphisms in the VEGF ligand (21tagSNPs) were associated with hypertension. Confirmation of these findings in ongoing ramucirumab studies may permit risk stratification of ramucirumab therapy.

548 Poster Session (Board #36), Sat, 8:00 AM-11:30 AM

Impact of combining PgR score and original preoperative endocrine prognostic index (PEPI) score as a prognostic factor of neoadjuvant endocrine therapy using exemestane in postmenopausal ER-positive/HER2-negative breast cancer. *First Author: Sasagu Kurozumi, Division of Breast Surgery, Saitama Cancer Center, Saitama, Japan*

Background: Neoadjuvant endocrine therapies (NAE) using aromatase inhibitors effectively reduce tumor size in postmenopausal ER-positive breast cancer (BC). The utility of PEPI scoring in predicting of the recurrence-free survival (RFS) after NAE is well-known. On the other hand, PgR can be a prognostic factor of ER-positive BC. We compared original PEPI score with PgR status alone, and modified PEPI score including PgR status, as prognostic factors of NAE in postmenopausal ER-positive/HER2-negative BC. **Methods:** Our study included 107 Japanese women with invasive ER-positive/HER2-negative BC who were received NAE with exemestane (25 mg/day) for at least 4 months (median follow-up: 47 months). *Analysis 1:* PEPI score (0-12 points) of each patient was determined using ypT, ypN, Ki67 and ER (Allred score), and patients were divided into 3 risk groups: low (0), moderate (1-3), and high ($\geq$ 4). RFS and cancer-specific survival (CSS) were compared between groups. *Analysis 2:* Cutoff values of PgR were tentatively defined as, 0, 1, 10, 20, 33, 50 or 66%; an effective cutoff value was determined by analysis of RFS and CSS. *Analysis 3:* PgR score (3 to low; 0 to high, using cutoff value determined by analysis 2) and original PEPI score were combined, and RFS and CSS of 3 risk groups were analyzed. **Results:** The PgR staining of 50% was the most significant cutoff value for predicting differences of RFS and CSS (RFS: P = 0.005, CSS: P = 0.003). PEPI score was also significant prognostic factor for CSS and RFS (RFS: P = 0.0009, CSS: P = 0.043). The hazard-ratio (HR) of PEPI score was greater than that of PgR in RFS (PEPI: 13.99 vs. PgR: 7.76), but lower than for CSS (PEPI: 6.28 vs. PgR: 8.74). However, combining PgR score to original PEPI score was the most potent prognostic indicator for both RFS and CSS (RFS: HR 20.35, P = 0.000001 and CSS: HR 18.48, P = 0.000097). **Conclusions:** PgR alone using 50% of cutoff value and original PEPI score might be a significant prognostic indicator for NAE using exemestane. However, combining PgR score and original PEPI score might be more potent prognostic indicator in both RFS and CSS.

549 Poster Session (Board #37), Sat, 8:00 AM-11:30 AM

Bevacizumab maintenance (BM) in first line treatment for metastatic breast cancer (MBC): A multicenter retrospective observational study. *First Author: Lucia Mentuccia, Medical Oncology Unit, Frosinone, Italy*

Background: Bevacizumab (B) combined with paclitaxel (P) is a treatment option in MBC patients (pts). This multicenter observational study was performed in order to evaluate activity of both B-P association and BM after P discontinuation in real world MBC pts. **Methods:** 280 MBC pts treated with weekly dose of P with B, with or without BM after P discontinuation were enrolled from 11 Italian cancer centres and retrospectively evaluated. Firstly, the RR for B-P was calculated, and secondly the PFS and OS were evaluated for all pts and separately for pts with/without BM. Chi-square and Fisher Exact tests were used to evaluate possible associations. OS and PFS were calculated by the Kaplan-Meier product-limit method. Log-rank and Tarone-Ware tests were used to assess differences between subgroups. **Results:** pts median age was 56 yrs (range 27-82), PS 0/1-2 66/44%, ER/PgR positive 83%, TNBC 17%, prior neo/adjuvant taxanes 73%, visceral involvement 60% and bone metastasis alone 11.4%. The median administrations of P and B per pts were respectively 18 (1–39) and 14 (1-52). 14.6% of pts are still receiving B-P and 16.8% pts having PD during B-P are not evaluable for BM. Of the remaining 192 pts, 51.7% received BM after P interruption (withBM). At a median follow-up of 20 mo (range 2-90) 10% pts achieved CR, 54% PR, 18% SD and 12% PD. Disease control rate (CR+PR+SD $\geq$ 6 m) occurred in 74% pts. The RR was significantly different between ER/PgR pos and TNBC (p = 0.03), which had RR respectively of 71% and 52%. No significant difference was found between pts with or without P pretreatment, nor between different P schedules. Overall, median PFS was 14 mo (95% CI, 12-16) and median OS was 41mo (95% CI 30-51). The median duration of BM was 6 mo (range 2-40). A significant difference was highlighted when comparing median PFS among pts withBM (18 mo, 95%CI 16-20) and withoutBM (13 mo 95% CI 7-18). The median OS was 55mo (95% CI 41-69) in pts withBM and 40 mo (95% CI 29-51) in pts withoutBM: the two groups did not differ significantly. **Conclusions:** Our analysis showed that the pts withBM after B-P combination had statistically and clinical significant improvement in PFS. Data collection is ongoing and update results will be presented.

550 Poster Session (Board #38), Sat, 8:00 AM-11:30 AM

Could any pT1a,bN0M0 hormone-responsive, invasive breast carcinomas be safely treated without endocrine therapy? *First Author: Christophe Perrin, Centre Eugène Marquis, Rennes, France*

Background: Overtreatment is a daily concern in the adjuvant setting for breast carcinoma. Most of Hormone Responsive (HR+) pT1a,bN0 breast cancers have an excellent prognosis. The aim of this study was to identify a subset of patients in whom abstention of adjuvant endocrine therapy would be safe. **Methods:** In this bicentric retrospective study, we analysed the prognosis of consecutive patients treated for HR+ pT1a,bN0M0 breast cancer, focusing on the population without adjuvant endocrine therapy. Log rank test was used for univariate analysis and a cox model was used for multivariate analysis. **Results:** 885 patients with HR+ pT1a,bN0M0 breast carcinoma were treated between 1997 and 2007. Local treatment involved either mastectomy or breast conserving surgery followed by breast radiotherapy. 227 patients (25.6%) did not receive any adjuvant endocrine therapy. Comparatively to the group treated with endocrine therapy, these patients were significantly younger (< 50 years old patients), with less grade II or III and less ductal histology. After a median follow-up of 6.4 years, 5 years-invasive disease free survival (IDFS) was significantly lower (89.8%) in the no endocrine therapy group than in the endocrine therapy group (94.6%) with log-rank p = 0.005. Distant Disease Free Survival (DDFS) and Overall Survival (OS) were not significantly different with numerically better results in the no-endocrine therapy group. In multivariate analysis, avoidance of endocrine therapy, grade II-III and young age (under 50 years old) were independent adverse prognostic factors for IDFS. **Conclusions:** In pT1a,bN0 HR+ patients, avoiding adjuvant endocrine therapy was slightly deleterious for IDFS but DDFS and OS were not affected. Discussion about risk/benefit ratio is crucial before proposing adjuvant endocrine therapy in this setting.

551 Poster Session (Board #39), Sat, 8:00 AM-11:30 AM

Influence of immunohistological detection of intratumoral urokinase-type plasminogen activator (uPA) on disease outcome in endocrine-treated postmenopausal patients with hormone receptor-positive early breast cancer. *First Author: Christian F. Singer, Medical University of Vienna, Vienna, Austria*

Background: Elevated intratumoral levels of uPA and PAI-1 in ELISA-based measurements are associated with a high recurrence risk and allow to select patients who might particularly benefit from adjuvant chemotherapy. The clinical utility of ELISA-based uPA/PAI-1 analysis is, however, greatly limited by the requirement of fresh tissue. We have therefore evaluated whether immunohistochemical uPA analysis from formalin-fixed paraffin-embedded (FFPE) tumor samples is also suited to identify women with poor clinical outcome. **Methods:** 547 postmenopausal patients with hormone receptor positive, early breast cancer who had received 5 years of endocrine therapy in the prospective randomized ABCSG-06 trial, and from whom FFPE tumor tissue was available, were included in this analysis. uPA protein expression was evaluated by immunohistochemistry, and was correlated with distant-disease free (DDFS) and overall survival (OS). **Results:** uPA protein was expressed in 296 of 547 (54%) tumors and was associated with size (p = 0.016, Chi Square test) but not with nodal status, grading, age, or receptor status. After a median follow-up of 11.5 years, patients with uPA-positive tumors experienced a significantly shorter DDFS (p = 0.005 log rank test) and OS (p = 0.022). Women with uPA-positive tumors were more likely to experience a shorter DDFS (adjusted HR for distant relapse 1.642; 95% CI 1.046-2.576; p = 0.031 Cox regression analysis) and OS (adjusted HR for death 1.348; CI 0.984-1.846; p = 0.063) than women without uPA expression. **Conclusions:** When measured by immunohistochemistry, intratumoral uPA protein expression predicts poor DDFS and OS in postmenopausal women with hormone receptor positive early-stage breast cancer who receive endocrine therapy. Clinical trial information: NCT00309491.

552 Poster Session (Board #40), Sat, 8:00 AM-11:30 AM

Prognostic significance of Focal Adhesion Kinase (FAK) in node-negative breast cancer. *First Author: Marcus Schmidt, University Hospital Mainz, Mainz, Germany*

Background: Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase playing an important role as a key mediator for signal transduction. We examined the subtype specific prognostic significance of FAK in node-negative breast cancer. **Methods:** Using microarray based gene-expression data, we analysed the prognostic significance of FAK (208820_at). The subtype specific prognostic role of FAK was analysed in four previously published cohorts (Mainz, Rotterdam, Transbig, Yu) of node-negative breast cancer patients not treated with adjuvant therapy (n = 824). A meta-analysis of previously published cohorts was performed using a random effects model. Prognostic significance of FAK for metastasis-free survival (MFS) was examined in the whole cohort of patients as well as in different molecular subtypes: luminal A (ER^+/$HER2^-$/aurora kinase A [AURKA]^{low}, luminal B (ER^+/$HER2^-$/$AURKA^{high}$), basal-like (ER^-/$HER2^-$), and $HER2^+$. **Results:** Prognostic significance of FAK was seen in the whole cohort of patients (HR 1.48, 95% CI 1.16-1.87, P = 0.001). Considering the different molecular subtypes, the prognostic effect was most pronounced in luminal B carcinomas (HR 1.67, 95% CI 1.07-2.62, P = 0.0233). FAK expression was neither significantly associated with MFS in luminal A (HR 1.69, 95% CI 0.96-2.98, P = 0.0692), basal-like (HR 0.98, 95% CI 0.64-1.50, P = 0.9400) nor $HER2^+$ (HR 1.63, 95% CI 0.49-5.46, P = 0.8512) carcinomas of the breast. **Conclusions:** A higher expression of FAK was associated with worse MFS in node-negative breast cancer. The prognostic significance was confined to luminal B carcinomas.

553 Poster Session (Board #41), Sat, 8:00 AM-11:30 AM

Medication use trajectories of postmenopausal breast cancer survivors and matched cancer-free controls. *First Author: Kathy Pan, Harbor-UCLA Medical Center, Torrance, CA*

Background: While distinct health issues are associated with breast cancer and related therapies, comprehensive assessment of medication use before and after breast cancer diagnosis compared to age-matched, cancer-free controls has not been reported. **Methods:** From the 93,338 postmenopausal participants in the Women's Health Initiative trials, medication inventories by pill container review were serially obtained before and > 3 years (mean 5.3 + 2.1 SD) after early stage breast cancer in 1730 cases matched with 1730 controls on age, dates of initial and follow-up medication inventories, body mass index, and smoking. Number of medications and medication classes (excluding tamoxifen and aromatase inhibitors [AI]) in cases and controls were compared. **Results:** Medication use (n) was comparable at baseline in both groups and significantly increased at follow-up in both cases (4.12 + 2.73 vs 6.47 + 3.29, P< .0001) and controls (3.92 + 2.59 vs 5.94 + 3.37, P < .0001), with clinically marginal but statistically significant additional medication use 0.53 ± 3.93 by breast cancer survivors (P < .0001). More breast cancer survivors used antidepressants (15.3% vs 12.2%, P = .006) and bisphosphonates and/or calcium/vitamin D (62.2% vs 54.8%, P < 0.001). Use of the following classes did not differ: anti-diabetic, cardiovascular, anti-anxiety, and narcotic and non-narcotic analgesics. Medication use at follow-up inventory by adjuvant endocrine therapy are outlined below. Medication use in breast cancer survivors on tamoxifen was lower than controls while those on AIs used more medications. **Conclusions:** Reflecting age-related co-morbidities, medication use significantly increases over time in both breast cancer survivors and controls. Overall, breast cancer impact on medication use is limited.

	Breast Cancer Cases (n=1730)				Controls (n=1730)
Selected medication classes (non-endocrine treatment) mean ± SD	*All*	*Current Tamoxifen (n=426)*	*Current AI (n=331)*	No Current Endocrine (n=975)	3.95 ± 2.13 (min=0, max=11)
	4.15 ± 2.13 (min=0, max=11)	3.40 ± 1.89 (min=0, max=10), P=.05*	4.85 ± 2.10 (min=0, max=10). P=.002*	4.23 ± 2.14 (min=0, max=11)	

*Adjusted Poisson regression used for test of case-control differences.

554 Poster Session (Board #42), Sat, 8:00 AM-11:30 AM

Detection and functional analysis of estrogen receptor mutations (ESR1-mut) in patients with metastatic breast cancer (MBC). *First Author: Shannon Puhalla, University of Pittsburgh Medical Center, Women's Cancer Program at Magee-Womens Hospital of UMPC, Pittsburgh, PA*

Background: Mutations in ESR1 (ESR1-mut) are a potential resistance mechanism to endocrine therapy, especially aromatase inhibitors (AI). Although these mutations are rare in untreated patients with early breast cancer, they have been observed to develop after exposure to hormonal therapy, suggesting a critical functional role for ER signaling in MBC and the potential to use ESR1-mut as a predictive marker and novel treatment target. **Methods:** Primary (44 patients) and metastatic breast cancers (brain, 38 patients; bone, 15 patients), and plasma (30 patients) samples collected from patients with MBC were examined for the presence of ESR1-mut D538G , K303R, Y537C, Y537N, S463P and Y537S using digital droplet (dd)PCR and Sanger Sequencing. Ten mL of plasma were collected in 4 Streck tubes for the isolation of circulating free DNA (cfDNA). Matched plasma and tissue samples were correlated when both were available. ER overexpression and physiological relevant models through genome editing were used to characterize phenotypes of ESR1-mut breast cancer cells. **Results:** ESR1-mut were found in 7% of ER+ primary cancers, 18% of ER+ brain metastases, 8% of ER+ bone metastases, and 40% of cfDNA collected from patients with ER+ MBC. D538G was the most common mutation found, followed by Y537C. K303R and S463P ESR1-mut were not demonstrated in these samples. We identified tumor and cfDNA that contained more than one distinct ESR1 mutation. The allele frequency ranged from 0.01% to 37%. The lowest allele frequency was in the primary cancers (0.01-0.4%) and likely a reflection of the high sensitivity of ddPCR. All patients with mutations had undergone prior treatment with tamoxifen and/or aromatase inhibitor prior to ESR1-mut analysis. In vitro, ESR1-mut cells were characterized by estrogen-independent signaling, and partial resistance to endocrine therapy. **Conclusions:** There is a high prevalence of ESR1-mut in patients with ER+ MBC acquired following hormonal treatment, particularly in cfDNA, suggesting both an ER signaling dependency for tumor survival and an important mechanism driving endocrine resistance.

555 Poster Session (Board #43), Sat, 8:00 AM-11:30 AM

Adjuvant aromatase inhibitor adherence based on the Morisky Medication Adherence Scale and identification of predictors to adherence. *First Author: Paula Rosenblatt, University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD*

Background: Aromatase inhibitors (AI) improve outcomes in hormone receptor positive breast cancer. Unfortunately, adherence to these oral agents remains difficult for many patients. The Morisky Medication Adherence Scale (MMAS) is a validated eight item questionnaire that measures adherence to medication in many chronic conditions. However, the MMAS has not been studied in the oncology setting. The purpose of this study was to identify the level of AI adherence in breast cancer patients based on the MMAS. Secondary objectives were to identify predictors of adherence. **Methods:** Patients were eligible if they had stage 1-3 hormone receptor positive breast cancer and were being treated at the University of Maryland Marlene and Stewart Greenebaum Cancer Center with AI therapy. Consecutive eligible patients were offered participation on an IRB approved protocol and informed consent was obtained. Participants completed the study questionnaires consisting of the MMAS and demographics. Participants were stratified by duration of AI therapy ≤ 2 years and > 2 years. **Results:** Between March 2011 and November 2014,100 women were accrued. Median age was 59, 37% were African American, and 62% received chemotherapy. Total adherence was 13% low (MMAS < 6), 37% medium (MMAS 6-7), and 50% high (MMAS = 8). There was no association of duration of AI treatment ≤ 2 yrs vs > 2 yrs and adherence level. The cumulative logit model revealed that possibly race and use of chemotherapy have some predictive ability for adherence, however p-values were only of marginal statistical significance. No association was found between adherence level and age, stage, tumor size, lymph node positivity, type of surgery, use of radiation, education level, marital status, insurance status, or comorbid conditions. **Conclusions:** Our study shows that only 50% of our patients on adjuvant AI therapy have high adherence based on the MMAS scale. There is a possible association of improved adherence to AI therapy in white patients and those who received adjuvant chemotherapy. Further research is needed to identify predictors to AI adherence in order to develop effective interventions to optimize compliance.

556 Poster Session (Board #44), Sat, 8:00 AM-11:30 AM

Effect of tumor infiltrating lymphocytes (TILs) and stromal CD68 on trastuzumab (T) benefit in early stage HER2 positive breast cancer (BC). *First Author: Jacques Raphael, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada*

Background: The presence of high TILs has been implicated as a predictor of pathologic complete response (pCR) and decreased recurrence rates in BC patients. However, there is conflicting data for the benefit of T in the adjuvant setting for HER2 positive (HER2+) BC patients with high TILs. In addition, greater numbers of CD68 (+) cells (macrophage marker) in tumor stroma has been shown to be an independent prognosticator for reduced BC specific survival. **Methods:** Core biopsies from52 Her2+ BC patients treated with neoadjuvant (NAT) chemotherapy with or without T were identified. Two pathologists independently quantified stromal TILs and CD68 ratio (inside the TILs population) using Hematoxylin/Eosin and immunohistochemistry respectively. The association of TILs and CD68 with pCR rates was determined by Mann-Whitney U, Chi-square or Fisher's exact test. Prognostic significance of TILs and CD68 ratio on pCR rates, disease free survival and overall survival (OS) was assessed by Kaplan-Meier analysis and log-rank test. **Results:** The median age and follow up for the cohort were 52 and 2.8 years, respectively. In the NAT setting, 40 patients received conventional chemotherapy and T (77%) and 12 patients were treated with chemotherapy alone (23%). Overall the pCR rate in the studied population was 40%. Eight patients (15%) had high levels of TILs ($\geq$ 60%) and 20 patients (38%) had low CD68 ratio ($\leq$ 60%). A high percentage of TILs was significantly correlated to low CD68 ratio ($p < 0.0001$). High levels of TILs and low CD68 ratio were each associated with greater pCR rates for the cohort of patients who received NAT T, respectively ($p = 0.05$, $p = 0.03$). Furthermore, pCR was predictive of better OS ($p = 0.02$) for the patients treated with NAT T. However, these associations were no longer significant when we performed the analysis on the whole population ($p = 0.09$, $p = 0.32$). **Conclusions:** Our results show that high levels of TILs are associated with low CD68 ratio, and both are predictors of pCR in patients with HER2+ BC receiving NAT T. Importantly, pCR as determined by CD68 and TILs translated into an OS benefit. TILs and CD68 ratio represent potential prognostic and predictive markers in patients with HER2+ BC.

557 Poster Session (Board #45), Sat, 8:00 AM-11:30 AM

Tamoxifen (TAM)-induced severe hot flashes (HF): Is dose reduction (DR) a safe and effective strategy? *First Author: Clara Inkyung Lee, Westmead Hospital, Sydney, Australia*

Background: It is recognized that severe HF toxicity due to TAM can compromise compliance. We previously established that HF do not correlate with endoxifen level or *CYP2D6*genotype, though prior reports are varied on this subject. In this pilot study, we reduced TAM dose in patients with severe HF and determined whether HF were ameliorated whilst maintaining a purported therapeutic endoxifen level of $>$ 15nM. **Methods:** Eighteen patients with severe HF on 20mg TAM were enrolled. *CYP2D6*genotype, trough level TAM and metabolites were measured. Loprinzi HF diaries were filled out before and after DR to 10mg TAM, and hot flash scores (HFS) derived. Other data collected included demographics, smoking and alcohol history, breast cancer history, previous chemotherapies, concurrent medications, menstrual history, body mass index (BMI) and other toxicities recognized to be associated with TAM. **Results:** At 20mg dose of TAM, baseline endoxifen levels were 24.5, 27.9, 0-91.9 nM (median, mean, range), consistent with the high variability seen in our previous 122 patient cohort. HFS at baseline were 108, 188, 4-1482 (median, mean, range). Upon dose reduction to 10mg, endoxifen levels fell to 13.2, 18.6, 0.6-71.9 nM (difference in means $p = 0.056$, two-tailed T test). HFS at 10mg fell to 38, 101, 5-864 (difference in means $p = 0.36$, two-tailed T test). Despite this lack of statistical significance, 78% of patients reported subjective improvement of hot flashes with DR. However after DR, the proportion of patients with an endoxifen level below a suggested therapeutic target of 15nM increased from 22% to 50%. HFS did not correlate with several patient characteristics including menopausal state, duration since last menstrual period and BMI (Spearman's rank correlation coefficient). **Conclusions:** In this group of women selected for having significant HF, DR of TAM from 20mg to 10mg daily resulted in halving of endoxifen levels and subjective improvement of HF, however half were below a potential therapeutic level of endoxifen at the reduced dose. Therefore routine DR to ameliorate HF toxicity may not be safe unless therapeutic drug level monitoring is performed.

558 Poster Session (Board #46), Sat, 8:00 AM-11:30 AM

Molecular profiling to identify genetic heterogeneity in synchronous and asynchronous breast cancers. *First Author: Windy Marie Dean-Colomb, Lafayette General Health, New Orleans, LA*

Background: Histologic heterogeneity of tumors is well documented; however, the molecular heterogeneity is not well understood, especially relative to driver mutations within clonal populations and their prognostic and predictive value. **Methods:** Molecular profiling of breast cancers (BCs) at a single institution were analyzed for differences in clonal populations within the same breast, bilateral synchronous BCs, and/or within primary and paired locally recurrent or metastatic tumors. Gene alterations (GAs) were identified by next generation sequencing (NGS). GAs were compared in 9 synchronous BCs and 48 primary/recurrent paired BCs. Estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), were evaluated by immunohistochemistry (IHC). HER2 was evaluated by IHC and in situ hybridization (ISH). **Results:** We identified GAs in 11 of 57 cases (19%); 2 were bilateral and 9 were paired primary/recurrent BCs. The 11 cases included 1 primary, 1 primary/locally recurrent, and 9 primary/metastatic pairs. ER, PR, and HER2 status differed in 9 cases (16%), while AR status differed only in 3 (5%).16% 13/57 were negative for ER, PR, and HER2 (triple negative [TN]); of 9 TN BCs with GAs in paired primary/recurrent BCs, 6 of 9 (67%) were TN on both primary and recurrent disease ($p = 0.0135$). *TP53* GAs were identified in 5 of the 11 cases (including the 2 synchronous), *PIK3CA* GAs were identified in 4 (1 synchronous), and *PTEN* GAs were identified in 3 (1 synchronous) cases. Other genes in which GAs appeared in only one of the pairs included *CDH1* (synchronous), *cMET* and *KRAS* (Primary/recurrent pair). Of the 2 synchronously profiled cases, 1 had 2 and 1 had 3 different GAs in the bilateral BCs, and 2 GAs in both BCs. In the primary/metastatic pairs, all discordant GAs were wild type in the primary and pathogenic in the metastasis. **Conclusions:** We identified that common GAs differ in both synchronous primary BCs and in paired primary/metastatic tissues. Such discordance could influence treatment recommendations. These findings highlight the molecular evolution of BC and the importance of evaluating predictive markers of treatment benefit both in synchronous and metastatic BCs.

559 Poster Session (Board #47), Sat, 8:00 AM-11:30 AM

P95HER2 as a predictive marker in the phase III randomized HERNATA trial of trastuzumab and chemotherapy as first-line therapy to metastatic or locally advanced HER2-positive breast cancer. *First Author: Ann S. Knoop, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

Background: HER2+ tumours express a series of carboxy-terminal HER2 fragments (CTFs or p95HER2) lacking the receptor extracellular domain that have been investigated as a potential trastuzumab resistance marker. Utilizing patients with locally-advanced or metastatic HER2+ breast cancer enrolled in the randomized HERNATA study, we assessed the expression of p95HER2 and its association with time to progression (TTP). **Methods:** Immunohistochemical (IHC) staining for p95HER2 was performed using a monoclonal antibody that specifically recognizes 611-CTF variant, blinded to clinical outcome (bioTheranostics Inc.). All slides were scored in consensus with a pre-defined cut-point (10% cells of strong staining) to define positive P95HER status. Additionally, an H-score (0-300) based on IHC staining was calculated with a preselected cut-point, that ensured 30% of the patient to be classified p95HER2 positive. TTP was analysed by Cox proportional hazards models. The model assumption of proportional hazards was investigated by Schoenfeld residuals and was used to evaluate if re-parameterization of p95HER2 by time-dependent variables (cut-point: 1.5 year after randomization) affects the association of p95HER2 status with TTP. **Results:** P95HER2 staining was available from 207 (73%) patients within the HERNATA intention to treat population of 284 patients. 36% of the patients were p95HER2 positive ($\geq$ 10 % strong staining). Kaplan-Meier analysis showed no significant association between p95HER2 status and TTP ($p = 0.68$). However, Cox unadjusted analysis showed a marginally significant association between p95HER2 status and TTP 1.5 year after randomization ($P = 0.04$; HR 0-1.5 year after randomization: 1.04, 95% CI: 0.74-1.46; HR $>$ 1.5-year after randomization: 2.60, 95% CI: 1.23-5.51) – which were confirmed in the adjusted analyses, as seen by similar HR estimates although not significant ($P = 0.07$). Results based on H-score are similar. **Conclusions:** No evidence of p95HER2 as a resistance biomarker for trastuzumab was found in this cohort of HER2+ metastatic breast cancer patients from the randomized HERNATA trial.

560 Poster Session (Board #48), Sat, 8:00 AM-11:30 AM

Long-term rates of ipsilateral breast tumor recurrence (IBTR) for women with ductal carcinoma in situ (DCIS) meeting LORIS trial eligibility criteria undergoing standard therapy. *First Author: Melissa Louise Pilewskie, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Identification of DCIS patients at low risk for progression to invasive carcinoma could obviate the need for standard surgery and radiation therapy (RT). The "Surgery versus Active Monitoring for LOw RISk DCIS [LORIS]" trial is studying the safety of monitoring low-risk DCIS without excision, although IBTR rates in this population undergoing standard therapy are unknown. **Methods:** Women with DCIS treated with breast-conserving surgery (BCS) with or without RT from 1996-2010 were included from a prospectively maintained database. IBTR rates were compared between those who did and did not meet LORIS eligibility criteria (age ≥46yrs, screen-detected calcifications, non-high grade DCIS diagnosed on needle biopsy, absence of nipple discharge, minimal family history). **Results:** 2,537 women were identified; 405 met LORIS criteria. LORIS cohort median age was 60yrs (range 46-86yrs); 210 (52%) underwent RT, 81 (20%) received endocrine therapy. Median follow-up was 5.8yrs (range 0-18yrs). 24 experienced an IBTR (14 DCIS, 10 invasive) (see table for overall IBTR rates). 5 and 10yr invasive-IBTR rates for women meeting LORIS criteria by treatment group were: 1.7% and 5.3% BCS with or without RT; 3.0% and 6.0% no RT; 0.55% and 4.6% with RT, respectively. **Conclusions:** LORIS eligibility criteria identify women with DCIS at somewhat lower risk for IBTR, yet among such women treated with BCS alone, the 10yr overall IBTR rate was 12% and invasive-IBTR rate was 6%. Given that approximately 20% of women with core biopsy proven non-high grade DCIS have invasive cancer at excision, women managed with observation alone would be expected to incur significantly higher rates of invasive cancer development. Additional risk predictors are needed to identify women who do not require intervention for DCIS.

	5 yr IBTR (%)	95% CI	10 yr IBTR	95% CI	P value
Entire cohort					0.083
LORIS (n=405)	4.5	2.7-5.4	10.2	6.4-16.3	
Non-LORIS (n=2132)	7.7	6.5-9	15.3	13.2-17.6	
No RT					0.099
LORIS (n=194)	6.9	3.8-12.2	12.0	7-20.3	
Non-LORIS (n=900)	11.2	9.1-13.7	20.5	17.1-24.4	
RT					0.28
LORIS (n=210)	2.3	0.9-6	8.7	3.7-19.9	
Non-LORIS (n=1212)	5.2	3.9-6.7	11.3	9-14.2	

561 Poster Session (Board #49), Sat, 8:00 AM-11:30 AM

Variation in the use of granulocyte-colony stimulating factor (G-CSF) for dose dense paclitaxel: A single institution retrospective study. *First Author: Flavia Rocha Paes, Oncoclinicas do Brasil, Belo Horizonte, Brazil*

Background: In randomized trials, administration of dose dense (dd) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with G-CSF support improved outcomes compared with every 3 week dosing in the adjuvant treatment of early breast cancer. However, the use of G-CSF in dd regimens is associated with increased cost and its utility for the T portion of this regimen is unclear. We studied patients (pts) treated with ddACT to investigate variation in the use of G-CSF among the medical oncologists at our NCI designated cancer center. **Methods:** Among 523 pts treated with adjuvant chemotherapy from 01/2011 to 12/2013, we identified pts who received ddACT. Descriptive analyses were used to analyze patterns of G-CSF use in the T portion of this regimen, and the impact of G-CSF use on delays, toxicity and treatment completion. **Results**: Overall, 155 pts (29.6%) were treated with ddACT by 26 providers during the study period. Variation in the use of G-CSF by provider and by patient was found. 21 (13.6%) pts did not receive any G-CSF support during the T portion of ddACT, with 11 providers choosing this approach in at least one pt. The majority of pts (134, 86%) received G-CSF support in at least one of the cycles, ranging from 17% of pts receiving G-CSF in one cycle to 48% of pts receiving G-CSF in all 4 cycles. Reasons for omitting of G-CSF included high baseline absolute neutrophil count and pain. Among the 21 pts who did not receive G-CSF with any cycle there were no treatment delays and no reports of febrile neutropenia; 90.4% (n = 19) completed treatment. Among the 134 pts treated with G-CSF during at least 1 cycle, 6 % had a treatment delay and 94.7% (n = 127) completed treatment. **Conclusions:** We identified variation in the use of G-CSF among medical oncologists in the administration of ddACT at our comprehensive cancer center. In addition, many physicians did not utilize G-CSF in a consistent fashion. Omitting of G-CSF was not associated with treatment delays or adverse events, though our sample size was small. To provide data to support uniform institutional practice, a prospective study formally evaluating the feasibility of delivering dd paclitaxel without routine G-CSF support is planned.

562 Poster Session (Board #50), Sat, 8:00 AM-11:30 AM

Tumor infiltrating lymphocytes (TIL) and Ki67 suppression after neoadjuvant therapy for HR+/HER2- breast cancer (BC): Results from two prospective trials. *First Author: Maria Vittoria Dieci, University of Padova, Padova, Italy*

Background: In BC, TIL predict for pCR after neoadjuvant chemotherapy. Since pCR is a suboptimal surrogate for treatment efficacy for HR+/HER2- patients (pts), we evaluate the association between TIL and molecular response after preoperative endocrine or cytotoxic treatment for HR+/HER2- BC. **Methods:** Stromal (Str) TIL were evaluated on H&E slides from diagnostic core-biopsies of 140 HR+/HER2- pts included in two prospective randomized trials. The LETLOB trial randomized 92 HR+/HER2- pts to neoadjuvant letrozole +/- lapatinib. The GIOB trial randomized 90 pts (n=48 HR+/HER2-) to primary anthracycline/taxane +/- gefitinib (Guarneri JCO 2012, BCRT 2008). Pre- and post-treatment Ki67 was centrally evaluated. **Results:** StrTIL were evaluable in 119 cases.Median StrTIL% was 2%. Pts with focal StrTIL or higher (StrTIL>=10%, n=28) were younger (p=0.034), had more frequently BC of ductal histology (p=0.04), high grade (p=0.025) and high Ki67 (p=0.012). After treatment, a significant Ki67 reduction from baseline (Wilcoxon p< 0.01) was observed overall and in each study (mean reduction similar in LETLOB and GIOB, T-test=ns). In the LETLOB trial a significant Ki67 suppression (Wilcoxon p< 0.01) was observed irrespectively of StrTIL, but mean Ki67 reduction was significantly greater in StrTIL>=10% vs < 10% (-13% vs -5%, T-test p=0.012). In the GIOB trial, a significant reduction in Ki67 was observed only for StrTIL< 10% pts (mean reduction -12% vs -0.9%, Wilcoxon p=0.001 and p=0.612 in StrTIL< 10% and >=10%, respectively). There was no difference according to arm in each study. The table reports the association of StrTIL with molecular response (proportional Ki67 reduction from baseline >50%). Test for interaction with treatment (cytotoxic or endocrine) was of borderline significance. **Conclusions:** The presence of TIL correlates with greater Ki67 suppression after neoadjuvant endocrine therapy but seems to prevent a molecular response after chemotherapy for HR+/HER2- pts.

		Ki67 reduction < 50% (%)	Ki67 reduction > 50% (%)	Chi2	Interaction p
All					
StrTIL< 10%		49	60	p=0.3	
>=10%	51		40		
LETLOB					
StrTIL< 10%		56	44	p=0.38	p=0.07
>=10%	44		56		
GIOB					
StrTIL< 10%		36	64	p=0.003	
>=10%	90		10		

563 Poster Session (Board #51), Sat, 8:00 AM-11:30 AM

Hormonal treatment (HT) and late recurrence in early-stage breast cancer (BC) patients. *First Author: Carlos Hernando Barcenas, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BC patients who are disease free after 5 years (Y) of diagnosis still remain at risk of developing a late recurrence. We assessed the effect of HT on the risk of late recurrence in early-stage BC patients with hormone-receptor-positive, HER2-negative disease from a large institutional database. **Methods:** We retrospectively identified a cohort of female early-stage (I to III) BC patients who had hormone-receptor-positive, HER2-negative (or not tested) disease, diagnosed between January 1997 and August 2008, who had received initial treatment at MD Anderson, and had remained disease free for ≥ 5 Y. We excluded patients who had incomplete HT data and those who received > 10 Y of HT. The primary endpoint was recurrence-free survival measured from the initial BC diagnosis to the first local-regional or distant recurrence. HT agents were categorized as aromatase inhibitors (AI), tamoxifen (T), sequential T and AI (T→AI), and other. The length of HT was categorized as " < 5 Y", "5 Y", " > 5- < 10 Y" and "10 Y". We used a multivariable Cox proportional hazard model to calculate hazard ratios (HR) and 95% confidence intervals (CI) for recurrence-free survival adjusted for patient demographics, tumor characteristics and treatments received. **Results:** We identified 2,839 patients; 155 (5.5%) developed late recurrence (median follow-up of 8.8 Y, range 5-16 Y). Compared to patients who received 5 Y of HT (72%), those who received 10 Y (4.4%) had a 79% reduced risk of late recurrence (HR = 0.21, 95% CI = 0.05, 0.88), while patients who received < 5 Y (14%) had an increased risk (HR = 1.88, 95% CI = 1.23, 2.89), with no difference in the HT length category " > 5- < 10 Y". Compared to patients who received T alone (32%), those who received T→AI (26%) had a significantly lower risk of late recurrence (HR = 0.52, 95% CI = 0.32, 0.85), with no difference for patients who received AI alone or other. **Conclusions:** In this retrospective cohort, HT duration of 10 Y, and the sequential use of T→AI were both factors independently associated with a significantly lower risk of late recurrence, after adjusting for several other known prognostic factors.

564 Poster Session (Board #52), Sat, 8:00 AM-11:30 AM

Oncotype-DX recurrence score distribution among breast cancer patients harboring a germline mutation in the BRCA1/2 genes. *First Author: Ron Lewin, Davidoff Cancer Center, Rabin Medical Center, Petach-Tikva, Israel*

Background: In about 10% of breast cancer (BC) cases, a genetic mutation in the BRCA1/2 genes can be found. BCs associated with BRCA2 mutations present with positive estrogen receptor (ER) status in about 50% of all cases, whereas BCs associated with BRCA1 mutation are more aggressive and more likely to be ER-negative. Oncotype genetic profiling has become a standard of care to predict recurrence and the benefit from chemotherapy in ER positive BC. The role of Oncotype-DX in BRCA mutation-carriers is not clear. Our primary end-point is to compare the RS distribution of BRCA carriers to that of the General Population (GP). **Methods:** Two different data bases were crossed: the list of BRCA mutation-carriers at Rabin Medical Center (n=1,191) with the list of all the oncotype-DX tests which were performed through Kupat Holim Clalit, our HMO (n=5,491), between 2003 and 2015. **Results:** Patients and tumor characteristics, including Oncotype RS are shown in the Table. **Conclusions:** Our study indicates that among BC patients with mutations in the BRCA1/2 genes, the distribution of the RS is different from that of the GP. In these patients a larger portion of the population was shifted toward the intermediate- and high- risk groups. This was more pronounced in the BRCA1 carriers. To our knowledge this is the largest BRCA cohort in which the oncotype-Dx RS has been reported.

	*Non-BRCA n=1,031	BRCA1 n=16	P-value	BRCA2 n=27	P-value
Age (years)	60	54.1	0.015	58.3	0.37
ER index	2.59/3	2.2/3	0.013	2.5/3	0.45
PR index	1.65/3	0.98/3	0.017	1.03/3	0.004
Grade (%):					
I	16.7	0	< 0.0001	8.7	0.09
II	66.2	37.5		56.5	
III	16.9	62.5		34.7	
KI67 (%)	14.5	35.9	< 0.0001	19.2	0.13
Tumor size (cm)	1.64	1.62	0.91	1.44	0.18
Oncotype RS (%):					
Low	52.7	6.2	< 0.0001	25.9	0.0016
Intermediate	37.8	37.5		44.4	
High	9.4	56.2		29.6	

*All Oncotype tests which were performed for patients at our institute. **The BRCA groups were compared to the non-BRCA group.

566 Poster Session (Board #54), Sat, 8:00 AM-11:30 AM

Steps in developing Watson for Oncology, a decision support system to assist physicians choosing first-line metastatic breast cancer (MBC) therapies: Improved performance with machine learning. *First Author: Julia Fu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: IBM Watson for Oncology (WFO), trained by Memorial Sloan Kettering (MSK), is a cognitive computing system designed to apply machine learning, informed by MSK expertise, to enhance clinical decision making. We expanded the initial adjuvant therapy prototype to include MBC. Patients with MBC share many common attributes (e.g. age, performance status, receptor status, prior therapy) but receive widely varying therapies. Accuracy of WFO treatment recommendations for similar cases can be improved with machine learning features built on highly influential attributes. **Methods:** 101 manufactured MBC training cases were grouped by biologic characteristics and then analyzed for variation. A set of clinical attributes characterizing disease burden was posited to be influential in selecting the initial systemic therapy for MBC recommended by MSK breast medical oncologists (e.g. endocrine therapy vs chemotherapy for a patient with hormone receptor (HR)+MBC). WFO learned weights characterizing each attribute's importance (e.g. site(s), extent, and size of metastatic lesions, degree of symptoms) through iterative experiments on training cases, and incorporated them into a "disease burden score"). Model performance as quantified by a combination of precision and recall (F1 Score) defined as (2 * true positives) / [(2 * true positives) + (false positives) + (false negatives)], was measured with and without the use of the disease burden score. **Results:** Activation of the disease burden score feature yielded a relative improvement in F1 Score of 11.5% across all cases (n = 101) from 73.6% to 82.1%; 28.8% among HR+ HER2+ cases (n = 32); 9.6% among HR+ HER2- cases (n = 29); 2.8% among HR- HER2+ cases (n = 17) and -1.4% among HR- HER2- cases (n = 23). **Conclusions:** Using training data and medical logic, WFO's machine learning model can assign weights to attributes and features to select therapy for patients that better align with the nuanced decision-making of MSK breast medical oncologists than rules alone. WFO's machine-learned disease burden score is a useful driver of treatment recommendations for HR+ and/or HER2+ MBC.

567 Poster Session (Board #55), Sat, 8:00 AM-11:30 AM

Variations in measured ER, PR, and HER2 status in synchronous and asynchronous paired breast cancer (BC) tumors. *First Author: Clayton Yates, Tuskegee University, Tuskegee, AL*

Background: That tumor heterogeneity exists and evolves over time is well appreciated but how often to biopsy patients' metastatic BC is not well established. **Methods:** Immunohistochemical (IHC) and in situ hybridization (ISH) analysis of estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and HER2 in 337 cases with > 1 asynchronous primary/metastatic BC molecular profiles and in 40 cases with > 1 synchronous molecular profiles was performed at a single institution. We evaluated differences in ER, PR and HER2 status in same or contralateral breast, and in primary vs. locally recurrent or metastatic BC's. **Results:** We identified a change in ER or HER2 status in 8 (31%) synchronous BCs and in 55 (16%) primary/recurrent BCs, including in biopsies of distinct tumor foci within the same breast or metastatic organ site. Of the 8 synchronous bilateral primary BC's, 4 (50%) had discordant ER results (ER, PR, and HER2 negative [TN] vs. ER+); 5 of 18 (28%) with two or more metastatic foci tested within the same organ had discordant ER results; 23% of BCs with biopsies of different organ sites had discordant ER results. Of the 55 paired primary/metastatic BCs, 15% of the discordant findings were in cases with biopsies from two different metastatic sites, 19% were in cases with one metastatic and one primary or local recurrent biopsy, and 23% were from 2 primary biopsies or from primary and locally recurrent disease. Discordance was bidirectional from either TN to ER+ or ER+ to TN, and independent of discordance in HER2. **Conclusions:** Standard systemic treatment of BC relies on reliable assessment by IHC analysis of ER, PR, and HER2. Within a patient, ER and HER2 status are not always concordant between lesions within the same breast, between bilateral BCs, and between distinct foci in a metastatic organ site. Patients are at risk of not being treated for the most clinically important foci of BC if the biopsy(s) obtained are not representative of the more aggressive areas of disease. Profiling should be performed on multiple BC samples both at diagnosis and at each time of recurrence/progression in the cancer continuum, to more accurately reflect the tumor profile at the time of treatment.

568 Poster Session (Board #56), Sat, 8:00 AM-11:30 AM

Meta-analysis of clinical outcomes to second-line endocrine therapy for visceral and non-visceral metastases. *First Author: John Forsyth Russell Robertson, School of Medicine, University of Nottingham, Derby, United Kingdom*

Background: A previous meta-analysis reported that patients with hormone receptor-positive visceral metastases (VMs) who respond to 1st-line endocrine therapy (ET) benefit for as long as those with only non-VMs. Here, we assess outcomes in the 2nd-line setting. **Methods:** We meta-analyzed five phase 3 RCTs of 2nd-line ETs for hormone receptor-positive breast cancer (anastrozole, exemestane and fulvestrant 500 and 250 mg; Table). All reported objective response rate (ORR), CBR, time to progression (TTP) and duration of clinical benefit (DoCB). **Results:** Combined ORR was similar for non-VMs (10%) vs VMs (9.2%) (Peto method p=0.485); only CONFIRM was an exception (ORR: 5.4% [non-VMs] vs 13.2% [VMs]); Tarone's test for heterogeneity: p=0.0014). CBR for non-VMs (38.8%) vs VMs (31.9%) was significantly different (Peto method p< 0.001); Tarone's test: p=0.068. Combined median DoCB was 420 days (non-VMs) vs 338 days (VMs) (odds ratio, 0.79; 95% CI, 0.68-0.91; Yusuf-Peto method p=0.001); Tarone's test: p=0.028. The odds ratio of TTP (non-VMs vs VMs) was 0.71 (0.65-0.77) (Yusuf-Peto method p=0.001); Tarone's test: p=0.022. **Conclusions:** VMs and non-VMs had similar ORRs. Approximately a third of patients with VMs (31.9%) achieve clinical benefit, 7% less than non-VMs (38.8%). VMs which achieve clinical benefit have prolonged periods of disease control, the median being almost 1 year. ET remains the well-tolerated treatment of choice for hormone responsive disease in the 2nd-line setting until newer agents, alone or in combination with ET, exhibit better efficacy than ET monotherapy.

	0020	0021	EFECT	CONFIRM	SOFEA	Combined
Total, N	343	345	681	736	723	2828
Non-visceral	202	181	292	333	297	1305 (46.1%)
CBR, n (%)	95 (47.0)	75 (41.4)	69 (23.6)	165 (49.6)	102 (34.3)	506 (38.8)
ORR, n (%)	38 (18.8)	34 (18.8)	18 (6.2)	18 (5.4)	23 (7.7)	131 (10.0)
Median TTP, d	174	210	147	253	162	173
Median DoCB, d	418	446	254	459	430	420
Visceral	141	164	389	403	426	1523 (53.9%)
CBR, n (%)	54 (38.3)	61 (37.2)	103 (26.5)	148 (36.7)	120 (28.2)	486 (31.9)
ORR, n (%)	19 (13.5)	27 (16.5)	21 (5.4)	53 (13.2)	20 (4.7)	140 (9.2)
Median TTP, d	91	87	85	139	104	101
Median DoCB, d	306	272	273	491	362	338

d, days. ET Treatment groups are combined for all studies.

569 Poster Session (Board #57), Sat, 8:00 AM-11:30 AM

Blinded independent validation of the PAM50-based Chemo-Endocrine Sensitivity Predictor (CESP) in hormone receptor (HR)-positive/HER2-negative (HR+/HER2-) breast cancer following neoadjuvant chemotherapy (NAC). *First Author: Aleix Prat, Medical Oncology Department. Hospital Clinic, Barcelona, Spain*

Background: Pathological complete response following NAC is associated with improved survival. CESP is a novel algorithm derived from the GEICAM 2006-03 clinical trial which is based on the association of treatment response with correlation to each PAM50 subtype centroid. CESP has been validated in two datasets consisting of patients with HR+/HER2- disease treated with either NAC or neoadjuvant endocrine therapy (unpublished data). Here, we examined whether CESP score is associated with chemosensitivity in another independent dataset. **Methods:** 216 pre-/post-menopausal patients from a multi-center Spanish cohort, with banked and centrally-confirmed FFPE HR+/HER2- pre-treatment breast tumor samples, were re-consented. All patients were treated with anthracycline/taxane-based NAC between years 2003-2014. The Prosigna assay was performed on the NanoString nCounter Dx Analysis System at Hospital Universitario Virgen de la Victoria de Málaga and CESP score and cutoffs were determined from those results at Hospital Clínic of Barcelona (blinded from clinical data). Univariate and multivariable analyses were used to evaluate the association of CESP score with centrally determined Residual Cancer Burden (RCB). **Results:** 207 core-needle pre-treatment biopsy samples yielded passing results (95.8%) of which 180 had clinical data including an RCB classification. The overall proportion of RCB-0/I in this patient population was 18.9%. In univariate and multivariate (adjusted for tumor size, age at diagnosis and grade) analyses, CESP as a continuous variable was significantly associated with response ($p < 0.001$ and $p = 0.003$). The rates of response in CESP-high, -med and -low groups were 10.3%, 15.2% and 30.4%, respectively ($p = 0.006$). The odds ratio of the CESP-low group for achieving a RCB-0/I was 3.80 (95% Confidence Interval 1.57-9.18) compared with the CESP-high group. Similar results were obtained after excluding PAM50 non-Luminal disease ($n = 23$). **Conclusions:** CESP is a strong and independent predictor of pathological response in patients with HR+/HER2- disease treated with NAC.

570 Poster Session (Board #58), Sat, 8:00 AM-11:30 AM

Long-term safety profile of palbociclib (P) in combination with letrozole (L) as first-line treatment for postmenopausal patients with ER+ and HER2- advanced breast cancer (ABC) (PALOMA-1/TRIO-18). *First Author: Dennis J. Slamon, School of Medicine/Translational Oncology Research Laboratory, University of California, Los Angeles, Los Angeles, CA*

Background: P is a selective and reversible oral CDK4/6 inhibitor. In a randomized phase (ph) I/II trial comparing P plus L (P + L) to L alone in patients (pts) with ER+ and HER2– ABC who had not received any prior systemic therapy for their ABC (Study 1003), P + L demonstrated significantly longer progression-free survival (PFS) vs L (20 vs 10 m; HR = 0.488, *P*=0.0004). **Methods:** We analyzed reported Adverse Events (AE) from Study 1003 by time interval (0-6m, 6-12m, 12-24, and >24m), cumulatively (12 m, 24 m time points) and assessed latency (event onset) of pertinent Adverse Drug Reactions (ADRs). **Results:** As of Nov 2013, 95 pts received P + L. The median duration of treatment for P was 374 d (range: 63-1682) for Ph1 (n=12) and 420 d (range: 7-1242) for ph2 (n=83). The 6 m interval analysis of the most common (>15%) ADRs (Table 1) indicated that ADRs tend to occur with greater frequency within the first 6 m with some decrease in incidence over time. Comparison of the cumulative incidences between the end of the 2nd year and 1st year shows that the cumulative event rates of the most common ADRs such as neutropenia (76% vs. 76%), fatigue (45% vs 40%), leucopenia (45% vs. 39%) and anemia (34% vs. 30%) were stable. The cumulative event rates for Grade 3/4 events were also stable except for a slight increase in fatigue (5% vs. 3%). The median time to onset of neutropenia was (20d), leucopenia (36d), anemia (168d), and thrombocytopenia (140d). **Conclusions:** Long term safety analysis suggests no evidence of any specific cumulative or late onset of toxicity with the prolonged treatment with P + L as first-line treatment for ER+ and HER2- ABC. Clinical trial information: NCT00721409.

Summary of treatment emergent all causality ADRs by 6-m intervals (>15%).

	P + L Treatment Duration (M)				
Adverse Events	0-< 6 N = 95 %	6-< 12 N = 77 %	12-< 18 N = 59 %	18-< 24 N = 40 %	≥24 N = 29 %
Any AE	97.9	88.3	81.4	72.5	79.3
Neutropenia	69.5	54.5	44.1	40.0	51.7
Leucopenia	33.7	27.3	16.9	20.0	13.8
Fatigue	33.7	14.3	13.6	10.0	10.3
Nausea	23.2	6.5	5.1	2.5	6.9
Anemia	22.1	19.5	15.3	15.0	13.8
Diarrhea	18.9	0	5.1	2.5	10.3
Alopecia	16.8	2.6	1.7	0	3.4

571 Poster Session (Board #59), Sat, 8:00 AM-11:30 AM

Efficacy and safety of first-line palbociclib plus letrozole compared with letrozole alone in patients aged ≥ 65 years with estrogen receptor-positive, HER2-negative advanced breast cancer: A subgroup analysis by age of the PALOMA-1/TRIO-18 trial. *First Author: John Crown, Irish Cooperative Oncology Research Group, Dublin, Ireland*

Background: Of the estimated 232,670 new cases of breast cancer (BC) diagnosed in the U.S. in 2014, 40% will have occurred in women ≥ 65 years. In this population, the most common type of BC is estrogen receptor-positive (ER+), HER2-negative (HER2-) for which endocrine treatment (ET) is currently the treatment of choice. When tumors become refractory to ET, chemotherapy is often initiated; palliative measures might also be suitable. Palbociclib (P) is an oral small-molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6). In a randomized phase 2 trial (PALOMA-1/TRIO-18; NCT00721409), first-line P plus letrozole (L) showed median progression-free survival (PFS) benefit that was double that shown by L alone in patients (pts) with ER+ and HER2- advanced BC (Finn et al, Lancet Oncol, 2015; 16: 25-35). In the present subgroup analysis, we evaluated the effect of P + L versus L alone in pts aged ≥ 65 years. **Methods:** Postmenopausal women (N = 165) with advanced ER+, HER2-BC were randomized 1:1 to receive P (125 mg/day for 3 weeks, 1 week off) plus L (2.5 mg/day) or L alone (2.5 mg/day). Of the 76 pts aged ≥ 65 years, 37 were assigned to P + L and 39 were assigned L alone. The primary endpoint was investigator-assessed progression-free survival (PFS). **Results:** In pts ≥ 65 years, the median PFS was 26.6 months (95% CI 12.6 – NR) for the P + L arm and 7.7 months (95% CI 3.7 – 10.9) for the L arm (HR 0.505, 95% CI 0.269 – 0.948; one-sided p = 0.0155). In pts eligible for safety analysis, grade 3-4 neutropenia was reported in 56.8% in the P+L arm vs 2.7% in the L arm, leucopenia in 29.7% vs none, and fatigue in 10.8% vs none. In general, neutropenia associated with P+L was short-lived and did not require management with hematopoietic growth factors. **Conclusions:** The median PFS was > 3 times longer in the P+L arm than in the L alone arm for the subgroup of pts ≥ 65 years. The toxicity profile was consistent with that of entire study population. A phase III study evaluating P+L is ongoing; P+L is an important treatment option for elderly, as well as non-elderly, patients with ER+, HER2- advanced BC. Clinical trial information: NCT00721409.

572 Poster Session (Board #60), Sat, 8:00 AM-11:30 AM

The effect of palbociclib (P) in combination with letrozole (L) on bone metastases in women with ER+/ HER2- metastatic breast cancer (MBC): Subanalysis from a randomized phase II study. *First Author: Richard S. Finn, University of California, Los Angeles Medical Center, Los Angeles, CA*

Background: Bone metastases (BM) are common in MBC. They are often the first and only site of distance disease. Patients with BM only usually have a protracted clinical course though increased bone pain and fractures can be debilitating. PALOMA-1/TRIO-18 was a randomized Phase II study, comparing P plus L (P+L) vs L alone as first-line treatment of advanced ER+ / HER2- BC. At final analysis, P+L doubled progression-free survival (Finn et al. Lancet Oncol 2015). In this sub-analysis, we evaluated the effects of P+L on bone metastases. **Methods:** 165 ER+ and HER2- postmenopausal women who were untreated for their ABC were randomized to receive L (2.5 mg/day) (N = 81) or L (2.5 mg/day) plus P (125 mg/day for 3 weeks on/1 week off) (N = 84). The primary endpoint was investigator-assessed PFS. Tumor assessments were performed every 8 weeks and bone scans every 12 weeks. PFS analysis was performed for those patients (pts) with objective progression determined based on the appearance of new bone lesion(s) and/or progression of existing bone non-target lesion(s). Patient reported outcomes (PRO) on pain severity (PS) and pain interference (PI) were assessed with Modified Brief Pain Inventory-Short Form (mBPI-sf). **Results:** 75% of patients had bone disease at baseline (73% P+L vs. 77% L) and 18% had bone only disease (20% P+L vs. 15% L). Median PFS among pts who had objective PD due to the appearance of new BM and/or objective PD in bone as non-target lesion were 18 m (95% CI 9, 28) for P+L (n = 8) vs. 4 m (95% CI 2, 35) for L (n = 16). Among those patients with bone-only disease at baseline, significant prolongation of PFS (NR P+ L vs 13.3 m L, HR = 0.294, 95% CI 0.092-0.945). Numerical differences in PI and PS scores in favor of P + L over L were observed from the PRO data collected from all randomized pts. **Conclusions:** Theaddition of P to L demonstrated a significant improvement in PFS. P+L leads to clinically meaningful delays in progression in the bone. Clinical trial information: NCT00721409.

573 Poster Session (Board #61), Sat, 8:00 AM-11:30 AM

Impact of locoregional therapy among women 70 years or older with early stage hormone receptor positive breast cancer: A population based study. *First Author: Shaheenah S. Dawood, Dubai Hosp, Dubai, United Arab Emirates*

Background: In 2004 the CALGB 9343 trial determined that omission of radiation therapy after lumpectomy in women ≥ 70 years with ER+ T1N0 breast cancer did not significantly impact outcome. This retrospective study aimed to determine trends in locoregional therapy practice in this cohort and to determine its impact on outcome. **Methods:** Using SEER registry we identified 27852 pts who were ≥ 70 years with pT1N0M0 ER+ breast cancer diagnosed between 1990 and 2005. A cutoff of 2005 was chosen to ensure a minimum of 5 years of follow up. Pts were divided into 3 groups based on locoregional therapy received: a) mastectomy, b) lumpectomy plus radiation, c) lumpectomy without radiation. Breast cancer specific survival (BCSS) was computed and Cox models were then fitted to evaluate the association between type of locoregional therapy and BCSS, adjusted for various pt and tumor characteristics. We expanded the cohort to include pts diagnosed until 2010 to look at practice trends in locoregional therapy. **Results:** 11533 (41.4%) pts had mastectomy, 13035 (56.8%) pts had lumpectomy plus radiation therapy and 3284 (11.8%) pts had lumpectomy alone. At a median follow-up of 92 months, 5- year BCSS was 97%, 98% and 97% among pts who had undergone mastectomy, lumpectomy plus radiation and lumpectomy alone, respectively ($p < 0.0001$). Compared to those who underwent mastectomy, there was no significant difference in breast cancer deaths among those who underwent lumpectomy plus radiation (HR 0.89, 95% CI 0.7-1.003, $p = 0.056$) or lumpectomy alone (HR 1.13, 95% CI 0.94-1.36, $p = 0.18$). Comparing 1990, 2005 and 2010, the proportion of pts undergoing mastectomy steadily decreased (74.2%, 27.4% and 25% respectively) while proportion undergoing lumpectomy plus radiation steadily increased (21.1%, 51.5% and 52.7% respectively) as did proportion undergoing lumpectomy alone (4.7%, 21.1% and 22.4% respectively). **Conclusions:** Omission of radiation therapy after lumpectomy in older women did not seem to significantly impact BCSS in this population based analysis. Although the use of lumpectomy without radiation increased over time, post-lumpectomy radiation is still the more favored treatment practice.

574 Poster Session (Board #62), Sat, 8:00 AM-11:30 AM

A combined screening approach of Fracture (Fx) Risk Algorithm (FRAX) and Trabecular Bone Score (TBS) to identify osteoporotic-range fracture risk (ORFR) in breast cancer (BC) patients treated with adjuvant aromatase inhibitor (AI). *First Author: David B. Page, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The NCCN recommends serial bone mineral density (BMD) measurement with dual energy x-ray absorptiometry (DXA) to diagnose and treat AI-associated osteoporosis. The FRAX algorithm identifies additional patients with ORFR who may benefit from anti-resorptive therapy (ART). The TBS, which measures bone microstructure by DXA, is an independent indicator of ORFR. Here, we retrospectively evaluate the utility of a combined screening approach (BMD+FRAX+TBS) in identifying ORFR at baseline and following AI. **Methods:** Breast cancer patients > 60 years, treated with AI and no ART between 2006-12, who had serial DXA at Memorial Sloan Kettering Cancer Center were identified (n= 74). BMD, FRAX, and TBS were evaluated at baseline (< 3 months from AI initiation) and at 12-24 months, and various screening strategies for identifying ORFR were assessed. Based on National Osteoporosis Foundation criteria and Manitoba TBS study fracture rates, ORFR was defined as: BMD T-score≤-2.5; ≥3% hip or ≥20% osteoporosis-associated 10-year fracture risk by FRAX; or TBS score≤1.2 with BMD T-score< -1.0. **Results:** Following AI, lumbar spine (LS)-BMD declined in 75% of patients (median: -2.9%; SD: 4.3%) and TBS declined in 58% of patients (median: -1.0%, SD: 7.7%). Declines in LS-BMD and TBS were not correlated (Spearman r=-.16, p=NS) and were not influenced by age, BMI, ethnicity, or chemotherapy (by Wilcoxon rank-sum). Compared to BMD alone, a combined screening approach (BMD+FRAX+TBS) identified an additional 15% of patients with ORFR at baseline. (table) Following AI, an additional 2% developed ORFR by BMD alone, versus 7% by BMD+FRAX+TBS. **Conclusions:** AIs caused bone loss, leading to ORFR as measured by BMD, FRAX, and TBS. Because FRAX and TBS are derived from DXA and patient history, a combined screening approach may efficiently and cost-effectively identify additional BC patients with ORFR who may benefit from ART.

	Pts with ORFR (%)	
Screening Method	**Before AI**	**After AI**
BMD alone	3/74 (5%)	5/74 (7%)
BMD+FRAX	7/74 (9%)	11/74 (15%)
BMD+TBS	12/74 (16%)	16/74 (22%)
BMD+FRAX+TBS	15/74 (20%)	20/74 (27%)

575 Poster Session (Board #63), Sat, 8:00 AM-11:30 AM

Clinical efficacy and safety profile of palbociclib (P) in combination with letrozole (L) as first-line treatment in patients (pts) with ER+ and HER2- advanced breast cancer (ABC) who have not received any systemic treatment (ST): A subgroup analysis of PALOMA-1/TRIO-18. *First Author: Richard S. Finn, University of California, Los Angeles Medical Center, Los Angeles, CA*

Background: P is an orally active inhibitor of CDK4/6. In a randomized phase II study, P + L significantly prolonged progression-free survival (PFS) vs L alone (20 vs 10 mo; HR = 0.488, $P = 0.0004$; Finn et al, Lancet Oncol, 2015) in ER+/HER2- ABC as first-line treatment. Given that pts who did not receive any systemic treatment (ST) may have different disease biology/course from those treated and relapsed from early stage disease and many pts may initiate endocrine therapy (ET) alone, we investigated the benefit of P + L in this subgroup in the PALOMA-1/TRIO-18 study. **Methods:** 165 ER+ and HER2- postmenopausal pts who are treatment naïve for their ABC were randomized to receive L (N = 81) or P+L (N = 84). A subset of pts did not receive any ST in the adjuvant setting prior to randomization (P+L n = 44, L n = 37). The primary endpoint was investigator-assessed PFS. Tumor assessment was performed every 8 weeks. Tumor tissues were collected for correlative biomarkers. **Results:** Clinical characteristics at baseline were well balanced on median age (P+L vs. L: 63 vs 62), ECOG PS (0/1 59%/41% vs. 49%/51%) and site of disease (visceral/bone only/other: 55%/14%/32% vs. 51%/14%/35%). Observed mPFS was 24 m (95% CI 13, 35) for P+ L vs. 8 m for L (95% CI 6, 13) with HR = 0.315 (95% CI 0.175-0.566) ($p < 0.0001$). Overall response rate (ORR) was 48% (95% CI 33%, 63%) vs. 41% (25%, 58%); clinical benefit rate (PR+SD ≥ 24 wks) was 84% (70%, 93%) vs. 70% (53%, 84%). The most common treatment emerged adverse events (all grades) for P + L arm were neutropenia (67%), fatigue (49%), leucopenia (49%), and anemia (35%), consistent with the overall safety profile. Tissue samples were available in 73 pts. Loss of RB expression by immunohistochemistry was rare (5.4%). Ki67 baseline did not predict response. **Conclusions:** The addition of P to L increased by > 2 the PFS in pts who did not receive ST for their ER+ MBC. The most common AEs are manageable. Favorable risk benefit profile suggests P+L be considered for this group of pts. Clinical trial information: NCT00721409.

576 Poster Session (Board #64), Sat, 8:00 AM-11:30 AM

GHRH-receptor as a new targetable biomarker in breast cancer and its correlation with ER/PR/HER2 status. *First Author: Mehrdad Nadji, University of Miami Jackson Memorial Hospital, Miami, FL*

Background: In addition to its nominative function as a neurohormone acting on the pituitary, growth hormone-releasing hormone (GHRH) has been shown to modify the growth behavior of numerous cancers, including breast. GHRH is produced by tumor cells, acts in an autocrine/paracrine manner, and requires the presence of the GHRH receptor (GHRH-R) on the tumor cells to exert its effects. The aim of this study was to evaluate the relationship of GHRH-R expression in different subtypes of breast cancer (triple negative, HER2-positive and hormone receptor-positive subsets). **Methods:** The cohort consisted of 96 primary breast cancers. Immunohistochemistry for GHRH-R was performed on paraffin sections and the staining results were assessed semi-quantitatively from 0 (negative) to 3+ (strongly positive). Patients with 0 or 1+ GHRH-receptor expression were classified as having low expression, and 2+ or 3+ as high expression. The ER/PR/HER2 levels of each tumor were correlated with the GHRH-R IHC results. **Results:** 62/96 (65%) patients had hormone receptor (HR) positive (ER- and / or PR-positive), 12/84 (14%) had HER2-positive, and25/84 (30%) had triple negative breast cancers (TNBC). 92% of HER2-positive, 68% of HR-positive, and 44% of TNBC had high expression of GHRH-R. HER2-positive primaries had a significantly increased frequency of high (11/12, 92%) vs. low (1/12, 8%) GHRH-R expression compared to HER2-negative primaries ($p = 0.018$). There was no difference in GHRH-R expression by HR status ($p = 0.38$). TNBC had a significantly decreased frequency of high (11/25, 44%) vs. low (14/25, 56%) GHRH-R expression compared to non-TNBC ($p = 0.041$). **Conclusions:** GHRH-R is expressed by the majority of primary mammary carcinomas regardless of their hormone receptor status. HER2-positive tumors were more likely to express high levels of GHRH-R; TNBC expressed lower levels. This finding could potentially serve as a basis for therapeutic approaches using synthetic peptide GHRH-R antagonists that have already shown significant efficacy combined with minimal pharmacologic side effects in experimental models.

577 Poster Session (Board #65), Sat, 8:00 AM-11:30 AM

Activation of PI3K/AKT/mTOR pathway in ER+ breast cancer: Analysis of paired primary and metastatic tumor samples. *First Author: Teresa R. Pacheco, Oncology Division, Hospital de Santa Maria - CHLN and Instituto de Medicina Molecular, Lisboa, Portugal*

Background: The activation of the mammalian target of rapamycin (mTOR) pathway is associated with resistance to endocrine therapy in breast cancer. Our aim was to evaluate changes in activation of the PIK3/AKT/mTOR pathway between primary and corresponding metastatic tumor samples in estrogen receptor (ER) positive breast cancer patients and to test whether phosphorylated protein levels are predictive of overall survival (OS). **Methods**: Phosphorylated forms of AKT (p-AKT) and S6 (p-S6) were assessed by immunohistochemistry on archival paraffin embedded samples of primary breast tumors and distant metastases collected from 132 breast cancer patients in two centers. A semi-quantitative scoring system (H-score) was used, combining the intensity of staining and the percentage of stained cells. The difference between expression of p-AKT and p-S6 in primary and metastatic tumor samples was analyzed using the Wilcoxon signed-rank test and the correlation of expression of p-S6 with OS using the Cox's proportional hazards model. **Results**: Overall, 93 cases ER and/or PR positive were analyzed. The median age was 55 years; 66 patients were treated with endocrine therapy in adjuvant and/or palliative setting. The median time to relapse was 42.7 mo and the median follow-up was 73.4 mo. The median OS from time of metastatic sample collection was 26.2 mo. The p-AKT H-score index was higher in primary tumor samples when compared to metastases ($p = 0.0003$). The p-S6 H-score index at the primary tumor and metastatic samples was not significantly different ($p = 0.26$); concordance between paired samples was 60% using median as cut-off; only metastatic p-S6 H-score index associated with OS ($p = 0.022$) and the association was also significant when analyzed by quartiles ($p = 0.001$). **Conclusions:** Expression levels of p-AKT are significantly lower in metastatic tumor samples. Metastatic p-S6 higher expression might predict worse prognosis in ER+ breast cancer patients, and deserves further study as a novel predictive breast cancer biomarker.

578 Poster Session (Board #66), Sat, 8:00 AM-11:30 AM

A prospective comparison of ER, PR, Ki67 and gene expression in paired sequential core biopsies of primary, untreated breast cancer. *First Author: Alastair Mark Thompson, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Sequential biopsy of breast cancer is increasingly favoured to assess biomarker effects and drug efficacy. The "window of opportunity" in the preoperative setting is recognised as advantageous to test biomarker changes in response to therapeutic agents in previously untreated cancers. However, tissue sampling over time could confound biomarker effects. This study tested the consistency over time of paired, sequential biomarker measurements on primary, operable breast cancer in the absence of drug therapy. **Methods:** Immunohistochemistry was performed for ER, PR and Ki67 on paired preoperative/operative tumor samples taken from untreated patients within 2 weeks of each other. Additionally, microarray analysis on mRNA extracted from formalin fixed paraffin embedded cores was performed using Affymetrix based arrays on paired core biopsies analysed using Ingenuity Pathway Analysis (IPA) and Gene Set Analysis (GSA). **Results:** In 41 *core/resection* pairs, the recognised trend to lower ER, PR and Ki67 score on resected material was confirmed: concordance for ER, PR and Ki67 without switch in status by Allred or Quickscore was 90%, 74% and 80% respectively. However, in 23 paired *core* samples (diagnostic core v on table core), Ki67 using a cut off of 13.25% was concordant in 22/23 (96%) and differences in ER and PR immunohistochemistry by Allred or Quickscore between the pairs did not impact hormone receptor status. IPA and GSA demonstrated substantial gene expression changes between paired *cores* at the mRNA level, including under expression of ER pathway analysis, despite the absence of drug intervention. **Conclusions:** This study addresses the potential impact of sampling effects over time in the context of preoperative (window of opportunity) trials. Sequential core biopsy of primary breast cancer (but not core versus resection) was consistent and may be appropriate to assess the effects of drug therapy in vivo on ER, PR and Ki67 using immunohistochemistry. Conversely, studies including mRNA expression may require non-treatment controls to distinguish therapeutic from biopsy differences.

579 Poster Session (Board #67), Sat, 8:00 AM-11:30 AM

The pattern of somatic mutations and chromosomal copy number variations (CNV) in young breast cancer (BC) patients (pts). *First Author: Hatem Abdel Azim, Institut Jules Bordet, Brussels, Belgium*

Background: Young age at diagnosis is associated with poor prognosis, different distribution of BC subtypes and unique gene expression patterns. Yet, it is unknown whether young pts have different prevalence of somatic mutations or CNV. **Methods:** This analysis was performed on The Cancer Genome Atlas dataset. We divided pts according to their age into; young (< 45 years) and old (≥ 45 years). We evaluated the association between age as a continuous variable and number of somatic mutations, CNV (amplification, gain, or deletions) using the chi-square test. We examined the genes showing somatic mutations or CNV in young pts and compared it to older pts using t-test. **Results:** 959 (138 $<$ 45y) and 788 (124 $\geq$ 45y) pts were included in the somatic mutation and CNV analyses, respectively. Young age at diagnosis was associated with less number of somatic mutations, mainly in ER- BC ($r = 0.21$, $p = 0.002$). Within young ER+ pts, mutations in *PIK3CA* (32.6%), *GATA3* (16.8%) and *TP53* (16.8%) were the most common with prevalence highly comparable in older pts. Of relevance, higher rates of mutations in *NTRK2* (5% vs.0%, $p < 0.0001$) and *ARID1A* (7% vs.2%, $p = 0.03$) were observed in young compared to old ER+ patients. No major differences were observed in the pattern of somatic mutations in ER- BC according to age, with mutations in *TP53* (67.5%), *RYR2* (13.5%) and *CSMD2* (10.8%) being the most common in young pts. We found more chromosomal amplifications in young pts with amplification events decreasing as a function of age, but only in ER+ BC ($r = -0.13$, $p = 0.007$). 22% of young pts showed *AXIN2* amplification vs. 4% in older patients ($p < 0.0001$). No other relevant associations were observed between CNV and age at diagnosis. **Conclusions:** This is the first analysis to interrogate the impact of young age at BC diagnosis on the pattern of somatic mutations and CNV. We observed that young age at diagnosis is associated with 1) less number of somatic mutations, and 2) more chromosomal amplifications, the latter observed only in ER+ disease. *AXIN2*, which regulates the Wnt/B-catenin pathway appear to be more amplified in young pts and if further validated could represent a potential treatment target in these women.

580 Poster Session (Board #69), Sat, 8:00 AM-11:30 AM

Impact on relapse free survival (RFS) of time to hormone therapy (HTx) after diagnosis (Dx) of low risk hormone receptor positive (HR+) early breast cancer (BC). *First Author: Wen Yee Chay, BC Cancer Agency, Vancouver, BC, Canada*

Background: Retrospective series show worse RFS for adjuvant chemotherapy (CTx) delay. We hypothesized the same effect for delays to HTx in low risk HR+ BC, for which CTx benefit is low. **Methods:** Histopathologic and demographic data were collected for all patients referred to the British Columbia Cancer Agency with a new dx of stage I or II, grade 1 or 2, HR+, HER2 negative BC from 01/2005 to 12/2009. Neoadjuvant-treated, prior or synchronous bilateral BC, no HTx prior to relapse, or $>$ 53 weeks (w) to HTx start were excluded. RFS was calculated for three pre and postmenopausal cohorts (C), defined as 1) 0- $<$ 20 w; 2) 20- $<$ 34 w; 3) 34-53 w from dx to HTx, based on first prescription. Multivariable (M) analysis identified factors significant for RFS. **Results:** Median follow up for the 3737 cases was 6.4 years (y). 80% were stage I: 28% of C1 and 69% of C3 were stage II. 90% were strongly estrogen receptor (ER) positive. Median age was 64, 58, and 51y in C 1, 2, and 3. Most were menopausal (71%) and 23% had CTx ($<$ 1%, 27%, and 76% of C 1, 2, 3). HTx was started $<$ 20 w and $>$ 34 w after dx in 57% and 15%, respectively. Five year RFS was 97.3%, 96.4%, and 95.5% for C1, 2, and 3 (p0.018). The table below shows univariate (U) and M results, M hazard ratios (Hz) and 95% confidence intervals. **Conclusions:** While unnecessary delays to HTx should be avoided, we did not detect a significant impact on RFS of up to 1 year delay in low stage and grade, population-based HR+ HER2 negative BCs. RFS was influenced by stage, PR level (all); grade and ER level (menopausal); and age at dx (premenopausal). If there is an impact on early RFS of HTx delay, it is likely subtle and only in premenopausal women. Our results do not exclude an impact on late RFS or in higher risk disease, or explore impact of longer delays.

	Menopausal			Premenopausal		
p-value	**U**	**M**	**Hz**	**U**	**M**	**Hz**
Time cohort	0.007	0.51		0.07	0.055	$<$ 20 v 34+ w 0.90 (0.32, 2.54) pNS
Stage I vs II	$<$ 0.0001	$<$ 0.0001	0.24 (0.16,0.38)	0.005	0.001	0.32 (0.16,0.63)
Progesterone receptor (PR)	0.003	0.0014	High vs zero 0.58 (0.35,0.99) p0.046	0.02	0.007	high vs zero 0.24 (0.10,0.58) p0.001
ER	$<$ 0.0001	0.016	high vs Low 0.21 (0.07,0.61) P0.004	0.88		
Grade 1 vs 2	0.0003	0.0088	0.54 (0.34,0.86)	0.06	0.09	
Age	0.77			0.04	0.022	0.94 (0.90,0.99)

581 Poster Session (Board #70), Sat, 8:00 AM-11:30 AM

Correlation between the DCIS Score and traditional clinicopathologic features in the prospectively-designed Ontario population-based validation study. *First Author: Eileen Rakovitch, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: In the Ontario population based study, the DCIS Score was significantly associated with 10 year risk of an ipsilateral local recurrence (LR - in situ or invasive carcinoma) in women treated with breast conserving surgery (BCS) without radiation (RT) ($P < 0.001$). Here we evaluate correlation between DCIS Score and clinicopathologic (CP) features in the same cohort, and whether DCIS Score provides independent recurrence risk information. **Methods:** The study population included 571 women diagnosed with DCIS in the province of Ontario from 1994 – 2003 prospectively selected for treatment with BCS without RT. CP variables examined included age at diagnosis, DCIS tumor size, DCIS nuclear grade, comedo necrosis (absent, focal, or extensive), histologic type, multifocality, and surgical margin width. The association between DCIS Score and CP variables was examined by spearman rank correlation, and proportional hazards regression models were used to determine variables significantly associated with LR. **Results:** Tumor size ($p = 0.002$), multifocality ($p < 0.001$), histologic type ($p = 0.005$), and nuclear grade ($p = 0.04$) were significantly associated with LR. In a multivariable analysis, including significant CP covariates, the DCIS Score was statistically significantly associated with LR ($p = 0.02$). DCIS Score was moderately correlated with grade ($r_s = 0.47$; 95% CI 0.41,0.54), comedo necrosis ($r_s = 0.43$; CI 0.36,0.50), tumor size ($r_s = 0.24$; CI 0.13,0.35), and multifocality ($r_s = 0.11$; CI 0.03,0.19) but not other features. All CP subgroups showed a wide range of DCIS Scores in each subgroup. **Conclusions:** DCIS Score is only moderately correlated with grade, comedo necrosis, tumor size, and multifocality. DCIS Score provides recurrence risk information independent of CP features, and quantifies risk of local recurrence in individuals treated by BCS alone, validating previous findings from the E5194 clinical trial

582 Poster Session (Board #71), Sat, 8:00 AM-11:30 AM

Cyclin D1 as a biomarker of response to fulvestrant (F) in hormone receptor-positive (HR+) breast cancer (BC). *First Author: Krystal Pauline Cascetta, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Overexpression of cyclin D1 (CD1) occurs in up to 45% of BCs. High cyclin D1 expression (HCD1) has been shown to significantly increase overall survival yet the opposite is observed in HR+ BC patients (pts) with HCD1 who receive tamoxifen (TAM). TAM is the drug of choice for premenopausal pts with ER+ BC. Numerous studies report an association btwn CD1 overexpression & TAM resistance. Thus, a large fraction of pts who receive TAM may not benefit from it. F may serve as an alternative approach for these pts. We hypothesized that pts with HCD1 will have a better duration of response to F compared to those with low expression. In order to address the above, we retrospectively analyzed CD1 expression in HR+ metastatic BC (MBC) pts treated with F at our institution. **Methods:** 20 primary BCs were stained for CD1 expression. IHC was scored based on intensity as 0 (negative), 1+, 2+, 3+ & extent as 0 (< 10%), 1 (11-25%), 2 (26-50%), 3 (51-75%), 4 (76-90%) & 5 (> 90%). A total score was subgrouped as low (0 to 4) or high (5 to 8). A retrospective chart review extracted clinical data. The primary endpoint was duration of response to F as it relates to CD1 expression in HR+ MBC. **Results:** Of the 20 pts (median age 54 years), 40% had low cyclin D1 (LCD1) expression (n = 8) vs. 60% with HCD1 (n = 12). All but 1 pt in the LCD1 cohort had poorly differentiated (PD) invasive ductal carcinoma (IDC) (87.5%). The remaining pt had moderately differentiated (MD) invasive ductal & lobular carcinoma (mixed). 50% of HCD1 pts had PD tumors while 16.7% were MD. In the HCD1 cohort, 41.7% were IDC, 33% ILC and 25% mixed. Four pts were HER2-neu+, 2 in the LCD1 group & 2 in the HCD1 group. 75% in the LCD1 group were postmenopausal vs. 58% in the HCD1 cohort. TAM exposure was higher in the HCD1 group compared to the LCD1 group (58% vs. 25%). LN positivity was higher in the HCD1 group compared to the LCD1 group (58% vs. 37.5%). Median time to progression (TTP) with F was significantly increased in tumors with HCD1 expression compared to those with LCD1 (1149 days vs. 133 days, respectively; $p = 0.027$). **Conclusions:** TTP on F is significantly increased for HR+ HCD1 expressing BC compared to HR+ BC with LCD1 expression. Clinical trials exploring the use of F in BCs with HCD1 expression may be warranted.

583 Poster Session (Board #72), Sat, 8:00 AM-11:30 AM

Docetaxel, cyclophosphamide and trastuzumab as neoadjuvant chemotherapy in HER2-positive primary breast cancer. *First Author: Katsuhiko Nakatsukasa, Department of Endocrine and Breast Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan*

Background: The current standard treatment of primary systemic therapy (PST) in HER2+ breast cancer is anthracyclines and/or taxanes combined with trastuzumab which demonstrates high pathological complete response (pCR). The pCR is considered as a predictive marker of prognosis although results are slightly different depending on the hormone receptor status. The efficacy and tolerability of docetaxel, cyclophosphamide and trastuzumab (HER-TC) as neoadjuvant chemotherapy (NAC) remains unclear. We performed a prospective multicenter study of HER-TC NAC in HER2+ primary breast cancer. **Methods:** Eligible patients had HER2+ invasive breast cancer that measured more than 1cm, less than 7 cm and N0~N1 clinically between July 2011 and February 2014. Four cycles of HER-TC (6 mg/kg loading dose 8 mg/kg, 75 and 600 mg/m^2) were administered intravenously every 3 weeks as NAC. We investigated the pCR of primary breast tumors; pCR was defined as no histological evidence of invasive carcinoma, or the appearance of only ductal carcinoma in situ. Cardiac toxic effects, defined as a decrease in left ventricular ejection fraction (LVEF), were assessed by echo-cardiography at baseline, at the completion of NAC. **Results:** 42 patients were enrolled. The completion rate for 4 cycles of HER-TC was 97.6 % (41 of 42). Relative dose intensity was 98.0 % for HER-TC therapy. Overall pCR rate was 43.9 % (18 of 41). pCR rate for patients with luminal HER2 (ER+, HER2+), and HER2 enriched (ER-, HER2+) were 40.0 % (8 of 20), and 47.6 % (10 of 21), respectively. pCR was achived with about same probability in each subtype. Mean LVEF at baseline and, the completion of NAC were 66.1% and 64.8%, respectively. **Conclusions:** Four cycles of HER-TC might be one of the NAC options for HER2 positive breast cancer. There were no patients with decrease in LVEF during the treatment. Clinical trial information: UMIN000013263.

584 Poster Session (Board #73), Sat, 8:00 AM-11:30 AM

Phase I study of HER3 targeted antibody patritumab in combination with trastuzumab and paclitaxel in patients with HER2-overexpressing metastatic breast cancer (MBC). *First Author: Toshiaki Saeki, Saitama Medical University, Hidaka, Japan*

Background: It is considered that HER2-HER3 heterodimerization is mechanically important in HER2-overexpressing breast cancer. Patritumab is a fully human anti-HER3 monoclonal antibody, which inhibits ligand binding, receptor activation and induces HER3 down-regulation. This study aimed to assess recommended dose for subsequent studies as well as the safety, pharmacokinetics (PK), and preliminary efficacy of patritumab in combination with trastuzumab and paclitaxel in patients with HER2-overexpressing MBC. **Methods:** This study was an open-label, multicenter phase I study in patients with HER2-overexpressing MBC who had progressed after at least one prior chemotherapy regimen including trastuzumab. Patients received patritumab 9 mg/kg or 18 mg/kg i.v. Q3W, trastuzumab 8 mg/kg loading dose, followed by 6 mg/kg maintenance dose i.v. Q3W, and paclitaxel 175 mg/m^2 i.v. Q3W or 80 mg/m^{2}i.v. 2 weeks administration followed by 1 week rest (Q3W). **Results:** Eighteen patients were enrolled in total in this study. As of the October 10, 2014 cutoff, four patients were continuing treatment. All patients had received prior trastuzumab and 66.7% patients had received prior paclitaxel. No DLTs were observed. The most common ($\geq$ 50.0%) adverse events (AEs) were diarrhea (88.9%), alopecia (72.2%), leukopenia (72.2%), neutropenia (66.7%), and rash maculo-papular (50.0%). Some AEs including leukopenia and neutropenia were more frequent in patients received paclitaxel 175 mg/m^{2}i.v. Q3W. These AEs were generally mild and manageable. As a serious adverse event (SAE), cataract was reported in one patient and it was not related to study drugs. All patients were negative for anti-patritumab antibodies. The target trough serum concentration of patritumab was achieved in all patients at a dose of 18 mg/kg. The response rate was 38.9% (2 CR and 5 PR). The median progression-free survival was 274 days. **Conclusions:** Patritumab in combination with trastuzumab and paclitaxel was well tolerated up to 18 mg/kg and the preliminary efficacy was encouraging in patients with HER2-overexpressing MBC. Clinical trial information: JapicCTI-121772.

585 Poster Session (Board #74), Sat, 8:00 AM-11:30 AM

Total pathologic complete response (tpCR) and event-free survival (EFS) with subcutaneous (SC) or intravenous (IV) trastuzumab in HER2-positive early breast cancer (EBC). *First Author: Christian Jackisch, Sana Klinikum Offenbach GmbH, Offenbach, Germany*

Background: HannaH (NCT00950300) compared SC and IV trastuzumab (Herceptin SC [H SC] and IV [H IV]) as neoadjuvant–adjuvant therapy for HER2-positive EBC; the co-primary endpoints, pCR and serum trough concentration, were non-inferior between H SC and H IV. Prior studies have indicated that pCR is reasonably likely to predict for long-term efficacy outcomes in patients (pts) with EBC, and tpCR (absence of invasive neoplastic cells in ipsilateral lymph nodes and the breast) is considered more likely to be predictive than pCR. **Methods:** HannaH is a phase III, open-label, multicenter, randomized trial. Pts received 4 cycles of neoadjuvant docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide administered concurrently with 3-weekly H SC (600 mg fixed dose) or H IV (8 mg/kg loading, 6 mg/kg maintenance doses). Post-surgery, pts received 10 cycles of adjuvant H SC or H IV to complete 1 year of therapy. In an exploratory analysis, we used Cox regression to assess the correlation between the secondary endpoints tpCR and EFS (time from randomization to local, regional, or distant recurrence, contralateral breast cancer, or death). EFS rates per subgroup were estimated using the Kaplan–Meier (K–M) method. **Results:** In all, 297 pts were randomized to the H SC arm and 299 to the H IV arm; intent-to-treat (ITT) populations were 294 and 297 pts, respectively. At 40 months' median follow-up, Cox regression indicated that pts in the ITT population who achieved tpCR had a reduced risk of an EFS event compared with those who did not: H SC arm hazard ratio (HR) = 0.38 (95% CI, 0.22–0.65); H IV arm HR = 0.32 (95% CI, 0.18–0.60). Results were similar between arms: treatment-tpCR interaction $P = 0.67$. Three-year EFS rates according to tpCR are shown in the Table. Results were consistent for pCR and the efficacy per protocol population. **Conclusions:** In each of HannaH's two treatment arms, H SC or H IV, tpCR correlated with improved long-term efficacy outcomes (EFS) in pts who received neoadjuvant–adjuvant therapy for HER2-positive EBC. Clinical trial information: NCT00950300.

	H SC n = 294		H IV n = 297	
	tpCR n = 108	No tpCR n = 186	tpCR n = 94	No tpCR n = 203
K–M 3-year EFS rate, %	88	69	87	67
95% CI	82–94	62–76	80–94	61–74

586 Poster Session (Board #75), Sat, 8:00 AM-11:30 AM

The co-administration of pertuzumab (P) and trastuzumab (T) as a single infusion, followed by vinorelbine (V), in first-line (1L) treatment of HER2-positive locally advanced or metastatic breast cancer (MBC) patients (pts): VELVET study interim analysis. *First Author: Michael Andersson, Department of Oncology, Rigshospitalet,, Copenhagen, Denmark*

Background: The combination of P + T + chemotherapy has been shown to be more efficacious than T + chemotherapy in 1L HER2-positive MBC. P + T administration is normally undertaken sequentially. A single infusion would reduce treatment time and increase convenience for the patient. In the ongoing VELVET study (NCT01565083), the feasibility of co-administering P + T in the same infusion bag followed by V for 1L treatment of HER2-positive locally advanced BC or MBC is being examined. **Methods:** VELVET is a two-cohort, open-label, multicenter, phase II study; Cohort 1 pts receive P + T as separate IV infusions and Cohort 2 (C2) pts receive, after the first cycle, P + T in a single 250 ml IV infusion bag given over 60 mins. Pts had not received prior non-hormonal anticancer therapy in the metastatic setting. The initial dose of P was 840 mg followed by 420 mg q3w; the initial dose of T was 8 mg/kg followed by 6 mg/kg q3w; V was administered at 25 mg/m^2 in Cycle 1 followed by 30–35 mg/m^{2}on Days 1 and 8 of each subsequent cycle. The primary endpoint is investigator-assessed objective response rate (ORR) based on RECIST 1.1. Secondary endpoints include PFS, OS, and safety. Interim analyses for C2 are reported. **Results:** C2 was fully enrolled with 107 pts. At initial diagnosis, 25% of pts had de novo MBC. In (neo)adjuvant settings, 32% had received chemotherapy and 24% had prior T exposure. As of Jan 22, 2015, the median number of cycles received was 15 for P + T and 9 for V (range: 2–28). AEs were reported in 99% of pts. Grade ≥ 3 AEs were reported in 78% of pts. Grade ≥ 3 AEs in ≥ 5 pts were neutropenia (30.8%), hypertension (13.1%), diarrhea (5.6%), leukopenia (4.7%), increased gamma-glutamyl transferase (4.7%), and fatigue (4.7%). SAEs were reported in 41% of pts. Interim efficacy analyses (ORR and PFS) for C2 are ongoing and will be presented. **Conclusions:** Administration of P + T in a single IV infusion followed by V had an acceptable AE and SAE profile with no unexpected safety signals in this interim analysis. This approach is therefore feasible from a safety standpoint and may offer greater convenience for pts. Clinical trial information: NCT01565083.

587 Poster Session (Board #76), Sat, 8:00 AM-11:30 AM

Associations of HER2-specific immunity with survival during treatment with trastuzumab and chemotherapy in breast cancer. *First Author: Keith L. Knutson, Vaccine and Gene Thrpy Inst of Florida, Port St Lucie, FL*

Background: The addition of trastuzumab to chemotherapy improves response to therapy and extends survival among patients with HER2-positive (HER2+) breast cancer. Prior work showed that trastuzumab and chemotherapy also induces HER2 extracellular domain (ECD)-specific antibodies which correlate with tumor shrinkage. The present study investigates whether combination therapy induced immune responses to other tumor antigens and whether immune responses are associated with survival. **Methods:** Pretreatment and posttreatment sera were obtained from 54 women with metastatic HER2+ breast cancer on NCCTG (now Alliance for Clinical Trials in Oncology) studies N0337 and N983252. IgG to HER2, p53, IGFBP2, CEA and tetanus toxoid were examined using ELISAs. Sera from an age-matched group (25 patients) of controls and 26 HER2+ adjuvant patients were also examined. **Results:** Prior to therapy, some patients with metastatic disease had elevated IgG levels to IGFBP2, p53, HER2-ICD, HER2-ECD, and CEA, but not to tetanus toxin, relative to controls and adjuvant patients. Elevated preexisting immunity to HER2 was associated with significantly worse outcome ($p < 0.003$). Following therapy, increases in levels of IgG to IGFBP2, HER2-ICD, HER2-ECD, and p53 were observed in metastatic patients who did not have elevated preexisting immunity. Increased immunity to HER2 was associated with improved progression-free ($p < 0.003$) and overall survival ($p < 0.04$). **Conclusions:** Combination treatment results in induction of adaptive immunity to multiple antigens that contribute to disease outcome. If these results are validated, this could provide the basis for the development of biomarkers predictive of therapeutic benefit and the development of new therapeutic approaches with monoclonal antibodies.

588 Poster Session (Board #77), Sat, 8:00 AM-11:30 AM

Neoadjuvant chemotherapy in the real world: A study of 22,819 patients from the Japanese National Clinical Database-Breast Cancer Registry. *First Author: Naoki Niikura, Tokai School of Medicine, Isehara Kanagawa, Japan*

Background: Recently, neoadjuvant chemotherapy has become a treatment of choice in clinics. Estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) expressions may convert from positive to negative and vice versa after neoadjuvant chemotherapy. We investigate the pathological complete response (pCR) rate in each subtype and the discordance rate of ER, PgR, and HER2 before and after neoadjuvant chemotherapy using Japanese breast cancer registry data. **Methods:** Records for > 300,000 cases from 741 hospitals from 2004 onwards were retrieved from the Japanese National Clinical Database-Breast Cancer Registry. After data cleanup, 22,819 cases without distant metastases, where neoadjuvant chemotherapy was administered between January 1, 2004 and December 31, 2011, were selected. pCR was defined as no invasive tumor in the surgical specimen after neoadjuvant chemotherapy. HER2 overexpression was evaluated (i.e., immunohistochemically 3+ and/or fluorescence in situ hybridization-positive). **Results:** pCR was achieved in 6.2% of luminal-type (8,995 patients), 26.0% of HER2-type (4,654 patients), and 19.9% of triple-negative (3,786 patients) breast cancer cases. Among the HER2-type cases, pCR was achieved in 33.2% of ER-negative, 18.0% of ER-positive, 32.2% of trastuzumab-treated (as neoadjuvant chemotherapy), and 18.4% of trastuzumab-untreated cases. After neoadjuvant chemotherapy, HER2-negative tumors were found in 626 (21.5%) of the 2,913 patients with HER2-positive pretreatment tumors, and HER2-positive tumors were found in 343 (3.4%) of the 10,178 patients with HER2-negative pretreatment tumors. Furthermore, 536 (4.7%) of the 11,382 patients with ER-positive tumors had ER-negative tumors and 619 (9.6%) of the 5,870 patients with ER-negative tumors had ER-positive tumors after neoadjuvant chemotherapy. **Conclusions:** We confirmed that in the real world, pCR rates for each subtype follow the same trend in clinical trials. We confirmed that a loss of HER2-positive status in primary tumors could occur after neoadjuvant treatment in patients with primary HER2-positive breast cancer.

589 Poster Session (Board #78), Sat, 8:00 AM-11:30 AM

Graded prognostic assessment (GPA) of HER2 positive breast cancer patients with brain metastases. *First Author: Ming Chi, Cleveland Clinic, Cleveland, OH*

Background: Brain metastasis (BM) is a serious complication of HER2+ breast cancer (BC). We evaluated prognostic factors for overall survival (OS) in a contemporary cohort of patients (pts) with HER2+ BCBM treated at a tertiary care institution. **Methods:** The Cleveland Clinic's IRB approved BM database was used to identify HER2+ BCBM pts treated between 2000 and 2013. OS from the diagnosis of BM was the primary endpoint. Breast-specific GPA (Sperduto et al, 2012), based on age at BM (< 60 vs >60), KPS (90-100 vs 70-80 vs 60 vs < 60), and BC subtype (luminal B versus Her2), was correlated with OS. Cox proportional hazards models with and without stepwise variable selection were used for data analysis. Recursive partitioning was used to identify cut points. **Results:** Data from 205 pts were analyzed. Median age was 52 (23-86); 51% of pts had KPS 90-100, 23% KPS < 80; 52% of pts were ER and/or PR+, and 82% had extracranial metastases at BM diagnosis. BM were initially treated with WBRT +/- surgery (62%), or WBRT + stereotatctic radiosurgery + /-surgery (17%). Median OS was 16.9 months (95% C.I. 13.0-22.5). Using breast specific GPA, 63% of pts had the most favorable profile (scores of 3.5-4), 37% had the second most favorable profile (scores 2.5-3) while a single patient scored 1.5-2. In univariate analysis, breast GPA was associated with OS ($p = .004$) as were 2 of its components, KPS ($p < .0001$) and age ($p = .01$); breast subtype was marginally significant ($p = .09$). Multivariable analysis again identified KPS ($p < .0001$) and age ($p = .003$), as independent predictors (with difference categorizations). Bone/lung metastases ($p = .007$) rather than BC subtype were predictive of OS. An updated HER2+-specific GPA was thus defined by assigning "points" to each factor: KPS > 70 = 2 points; 1 point each for age < 50 and no lung or bone metastases. Based on the cumulative number of points, 3 prognostic groups were identified: favorable (3-4 points, 49% pts), intermediate (2 points, 30% pts) and unfavorable (0-1 point, 21% pts) with median OS of 25.7, 13.7 and 5.4 months, respectively. **Conclusions:** This study confirms the prognostic value of the breast GPA, and proposes a modified HER2+ specific version.

590 Poster Session (Board #79), Sat, 8:00 AM-11:30 AM

Phase I study of LJM716, BYL719, and trastuzumab in patients (pts) with HER2-amplified (HER2+) metastatic breast cancer (MBC). *First Author: Payal Deepak Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: HER2+ breast cancer is driven by HER2/HER3/PI3K signaling. Single agent targeted therapy (tx) is limited by redundant mechanisms of pathway activation and feedback loops; preclinical models support combinatorial tx. This phase I trial examined HER2, HER3 and PI3K inhibition in pts with HER2+ MBC (NCT02167854). **Methods:** Pts received weekly intravenous (IV) trastuzumab (T) at 2 mg/kg, LJM716 (L, HER3 inhibitor) at 20 mg/kg, and escalating dose cohorts of daily oral BYL719 (B, PI3Kα inhibitor) starting at 250 mg. Eligible pts had HER2+ MBC with a *PIK3CA* mutation and prior ado-trastuzumab emtansine and pertuzumab. Endpoints were: to define MTD (toxicity based on CTCAE 4.0) using the Continual Reassessment Method, to assess efficacy (RECIST v1.1), to evaluate genomics and proteomics of pre- and on-tx tumor biopsies, and to quantify cell-free DNA and *PIK3CA* mutant allele fraction (MAF). **Results:** 8 pts have been treated with a median (M) age 56y (range (R): 46-68), M ECOG of 1 (R: 0-1), and M of 6 (R: 3-10) prior tx. M duration on study was 10 weeks (R: 2-21.9). 7 pts were treated with B 250 mg. 1 pt was treated at 300 mg and had a DLT of supraventricular tachycardia in the setting of hypokalemia. A second pt had a DLT of G3 transaminitis at B 250 mg. Significant toxicities (and worst grades) included diarrhea (G3: 5 pts; G1/2: 2 pts); hyperglycemia (G3: 2 pts; G1/2: 6 pts); hypokalemia (G3: 2 pts; G1: 4 pts); mucositis: (G3: 1 patient; G1/2: 4 pts); and transaminitis: (G3: 2 pts), with no G4 toxicity. Despite prophylactic antidiarrheals, diarrhea led to dose reduction in 1 (13%) and tx interruptions in 5 (63%) pts. Overall, toxicities limited drug delivery, with only 72%/83% of total planned B/L doses given. In addition, B was dose-reduced in 2 (25%) and L in 4 (50%) of pts. Best response was SD in 5 of 6 evaluable pts. Pre-tx genomics and *PIK3CA* MAF will be correlated with response. **Conclusions:** The combination of T, L, and B has antitumor activity in these pre-treated HER2+ pts with MBC with *PIK3CA* mutations. Clinically significant gastrointestinal and metabolic toxicities limit drug delivery and dose escalation of B/L. Based on preclinical modeling, exploration of intermittent dosing schedules is warranted. Clinical trial information: NCT02167854.

591 Poster Session (Board #80), Sat, 8:00 AM-11:30 AM

Effectiveness of targeting HER2 in heavily pretreated patients with occult HER2-positive (tissue-negative, serum-positive and/or HER2-positive circulating tumor cells) metastatic breast cancer in the clinical routine. *First Author: Christian M. Kurbacher, Gynecologic Center Bonn-Friedensplatz, Bonn, Germany*

Background: A considerable proportion of patients (pts) with HER2-negative (HER2-) metastatic breast cancer (MBC) present with elevated serum levels of the HER2 extracellular domain (sHER2) and/or HER2-overexpressing circulating tumor cells (CTCs) during their further clinical course. These "occult" HER2-positive (HER2+) pts may be candidates for anti-HER2 therapy (Tx) albeit normally not subjected to such treatment. This retrospective study was undertaken to gain more insights into the feasibility of HER2-directed Tx in occult HER2+ MBC pts in the clinical routine. **Methods:** From our database, we identified 26 pts with heavily pretreated HER2- MBC (ER+, 21 pts) showing sHER2 values > 15 ng/mL (6 pts), HER2+ CTCs (6 pts), or both (14 pts) having failed 2-16 prior systemic treatments (median: 7) who did not qualify for recruitment onto a prospective clinical trial. All pts received anti-HER2 Tx with trastuzumab (H: 14 pts), lapatinib (L: 4 pts), H+L (2 pts), or H+pertuzumab (H+P: 6 pts). HER2-targeting Tx was given alone (4 pts), or in combination with endocrine agents (4 pts), cytotoxics (16 pts), or other targeted drugs (2 pts). Responses were scored according to RECIST 1.1, OS was calculated from the start of HER2-directed Ctx until death from any reason or loss to follow-up by using Kaplan-Meier statistics. **Results:** Anti-HER2 Tx was generally well tolerated. Median treatment duration was 16.1 wks (range 1.0-56.1 wks). In 2 pts with L and 1 pt with H+L, Tx was prematurely stopped due to toxicity (diarrhea, fatigue). 10 PR, 10 SD, 5 PD, and 1 non-evaluable (NE) pt accounted for an objective response rate (ORR) of 38.5% and a clinical benefit rate (CBR) of 76.9%. Median OS was 62.9 wks. **Conclusions:** Our findings indicate that anti-HER2 Tx may be a valid option in pts with heavily pretreated HER2- MBC with pathological sHER2 values and/or HER2+ CTCs in the clinical routine. Thus, results of ongoing randomized trials in this setting are eagerly awaited.

592 Poster Session (Board #81), Sat, 8:00 AM-11:30 AM

Implications of high tumor infiltrating lymphocytes (TIL) in HER2-positive and triple-negative breast cancer (TNBC). *First Author: Vassiliki Kotoula, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece*

Background: High TIL may confer better prognosis to TNBC patients and may interfere with trastuzumab (T) benefit in HER2-positive breast cancer (BC) patients. Here, we investigated the effect of TIL on BC patient outcome with respect to immunohistochemical subtypes and treatment. **Methods:** Intratumoral mononuclear infiltrates were assessed as % of stromal area under low magnification on whole routine sections of 2613 breast carcinomas. Three different cut-offs (c/o) for high/low TIL were used (50%, 35% and 25%). Subtyping revealed 948 Luminal A, 615 Luminal B, 477 Luminal-HER2, 246 HER2-enriched, and 327 TNBC tumors. Patients had been treated in the frame of 4 prospective trials with adjuvant anthracycline-based chemotherapy in the pre- and post-T era. T was administered sequentially for 1 year. **Results:** High TILs were present in 3.5%, 6.5% and 11.5% of all tumors, using the 50%, 35% and 25% c/o, respectively, and were subtype specific. Using the 35% c/o, high TIL were significantly more frequent in TNBC (13.8%), HER2-enriched (11.8%) and Luminal-HER2 (9.2%) than in Luminal B (5.7%) and Luminal A (1.8%) tumors ($p < 0.0001$). No significant TIL effect was observed on the outcome of patients with Luminal A and B tumors. High TIL, at all c/o, conferred decreased risk for relapse in patients with TNBC (e.g. 35% c/o, HR = 0.37, 95% CI 0.15-0.90, Wald's $p = 0.030$) and Luminal-HER2 (e.g. 25% c/o, HR = 0.41, 95% CI 0.21-0.82, $p = 0.011$), but not with HER2-enriched tumors. Among all HER2-positive patients, a significant T benefit was noticed for those with low TIL (35% c/o, HR = 0.61, 95% CI 0.44-0.85, $p = 0.003$), but not for those with high TIL tumors; non-T treated patients with high TIL performed better than those with low TIL (HR = 0.56, 95% CI 0.36-0.87, $p = 0.009$), but this effect was insignificant among T treated patients. No interaction between T and TIL was found. Similar results were obtained for all TIL c/o, in distinct test and validation sets within the entire cohort. **Conclusions:** In the context of operable BC, high TIL is a favorable prognosticator in patients with TNBC and HER2-positive tumors. In the latter, high TIL does not seem to specifically predict for T benefit upon sequential T administration.

593 Poster Session (Board #82), Sat, 8:00 AM-11:30 AM

Correlation of trastuzumab treatment benefit with quantitative HER2 expression levels in HER2 positive metastatic breast cancer. *First Author: Beatrice Bachmeier, Institute of laboratory medicine, Ludwig-Maximilians-University, Munich, Germany*

Background: The HERmark Breast Cancer Assay (Monogram Biosciences) is used as an adjunct to HER2 immunohistochemistry (IHC) and HER2 fluorescence in-situ hybridization (FISH) to determine the HER2 status of breast cancer (BC). Based on the high degree of concordance of HERmark with centrally determined HER2 status by IHC/FISH, it is expected that HERmark positive BC patients would realize greater benefit from trastuzumab treatment than HERmark negative BC patients. In the current study, this hypothesis was confirmed using a cohort comprised of: (1) HER2 positive BC patients treated before the availability of trastuzumab, (2) trastuzumab-treated HER2 positive BC patients and (3) HER2 negative BC patients. **Methods:** HERmark was performed retrospectively on formalin-fixed, paraffin-embedded tumors derived from 305 metastatic breast cancer patients in the Munich Cancer Registry with a median follow up of 10 years. Cases were evenly divided between trastuzumab-untreated HER2 positive (n = 91), trastuzumab-treated HER2 positive (n = 115) and HER2 negative (n = 99) tumors. Cutoffs for HERmark positive and negative status were pre-specified (Huang, Am J Clin Pathol, 134:303 2010). **Results:** HER2 positive patients treated with trastuzumab had longer overall survival (OS) than those not treated with trastuzumab, as expected (HR = 0.35; p < 0.0001). As reassessed by HERmark, HER2 positive patients treated with trastuzumab experienced longer OS (HR = 0.33; p = 0.0005). In contrast, the benefit of trastuzumab treatment in HERmark negative patients was not statistically significant (HR = 0.55; p = 0.13). Additionally, there was a statistically significant interaction between the degree of trastuzumab benefit and quantitative levels of HER2 expression within the HERmark positive subset (interaction p = 0.032). Potential correlations between additional markers, including p95HER2 and HER3, and treatment outcome are currently being assessed. **Conclusions:** The HERmark assay identified breast cancer patients who benefited from trastuzumab treatment. Within this group, increased levels of quantitative HER2 expression correlated with increased degree of benefit from trastuzumab therapy.

594 Poster Session (Board #83), Sat, 8:00 AM-11:30 AM

Prognostic impact of HER2 overexpression/amplification in women with pT1a N0 M0 breast cancer with known screening status: First results from a multicenter population-based cancer registry study. *First Author: Antonino Musolino, Medical Oncology Unit, University Hospital of Parma, Parma, Italy*

Background: Outcomes for women with pT1aN0M0 breast cancers (BC) may vary by biologic subtype. A higher proportion of HER2-positive BCs diagnosed in the interval between scheduled screening rounds has been proposed to account for the more aggressive behaviour of interval cancers (IC) compared with screen-detected (SD) tumors. No data are available on the prognostic role of HER2-positive status in a general population of pT1aN0M0 breast tumors with known screening status. **Methods:** All incident pT1aN0M0 BCs (n = 874), systematically collected by the Cancer Registries of Emilia Romagna Region (northern Italy) and diagnosed in women aged 50-69 from 2003 to 2009 were evaluated. Screening status was ascertained by reference to the Emilia Romagna Breast Cancer Screening Program (ERBSP) database. Patients unexposed to screening, with HER2 unknownprimary tumor and/or who received adjuvant chemotherapy or trastuzumab were excluded from analysis. **Results:** Twelve percent of patients had HER2-positive tumors. Fifty-three percent of the entire study population were SD cancers, while 18% were ICs. Tumors with high histologic grade, high proliferative rate, negative estrogen receptor status, or HER2-positive status were more likely to be diagnosed in the interval between screening. At a median follow-up of 84 months, there were 39 recurrences. The 5-year disease-free survival (DFS) rates were 89% and 95% in patients with HER2-positive and HER2-negative tumors, respectively ($P = 0.025$). In multivariate analysis, patients with HER2-positive tumors had higher risks of recurrence (hazard ratio [HR], 2.58; 95% CI, 1.38 to 5.3; $P = 0.01$) than those with HER2-negative tumors. **Conclusions:** In a general population of pT1aN0M0early BCs with known screening status, HER2-positive tumors account for a substantial proportion of screening failure and have a significant risk of relapse. Final analysis of this study will evaluate if IC detection may identify patients with HER2-positive pT1aN0M0 tumors in whom the rate of recurrence justifies consideration for systemic, anti-HER2, adjuvant therapy.

595 Poster Session (Board #84), Sat, 8:00 AM-11:30 AM

Evaluation of the Breast Cancer Index in patients with HER2+/HR+ breast cancer for risk of late recurrence and potential extended endocrine benefit. *First Author: Ruth O'Regan, Emory Univ, Atlanta, GA*

Background: Hormone-receptor positive (HR+), early stage breast cancer patients (pts) are at risk for late (> 5 year) distant recurrence (DR) and are now considered for extended (10 year) endocrine therapy (EET) to prevent late disease relapse. Approximately 50% of all HER2+ breast cancer pts are also HR+. Clinical trials investigating the benefit of EET to reduce late DR have included HER2+/HR+ pts, but subset analyses in comparison to HER2-/HR+ have been limited. Breast Cancer Index (BCI) is a gene expression based assay validated to 1) assess risk of late DR, and 2) predict benefit from EET using the endocrine response biomarker HoxB13/IL17BR (H/I). This study compared BCI results and clinicopathologic factors in HER2+/HR+ vs HER2-/HR+ breast cancer. **Methods:** Consecutive cases with known HER2 status (N = 1182) submitted for BCI clinical testing were analyzed for pt characteristics and BCI reporting rates according to HER2 status. Fisher's test was used to compare results between subgroups. **Results:** 12% of BCI testing was conducted on HER2+/HR+ pts. Tumor size distribution was similar for HER2+ and HER2- cohorts (P = 0.9). In converse, the HER2+ cohort was comprised of a higher proportion of grade 3 (51% vs 17%; P < 0.001) and ER+/PR- tumors (24% vs 7%; P < 0.001). In regards to risk of late DR, 3 times more tumors were classified as BCI High-Risk in the HER2+ cohort compared to the HER2- cohort (59% vs 19%, P < 0.001; Table 1). Twice as many HER2+ were predicted to benefit from EET compared to the HER2- cohort (High H/I; 69% vs 38%, P < 0.001; Table 1). **Conclusions:** BCI classifies a higher proportion of HER2+/HR+ tumors into a high-risk group compared to those that are HER2-/HR+, yet a subset of HER2+ tumors are classified as low-risk. Additionally, a significant proportion of the HER2+ cohort was predicted to benefit from ETT. Further studies to validate the ability of BCI to predict benefit of EET in HER2+/HR+ pts are warranted.

BCI and H/I categorizations by HER2 status.

BCI Risk Classification	HER2+ Cohort (N=140)	HER2- Cohort (N=1042)
Low	18 (13%)	564 (54%)
Intermediate	40 (29%)	283 (27%)
High	82 (59%)	195 (19%)
H/I Categorization		
Low	45 (32%)	646 (62%)
High	95 (69%)	396 (38%)

596 Poster Session (Board #85), Sat, 8:00 AM-11:30 AM

Determining whether functional subtyping with BluePrint 80-gene profile could potentially identify two distinct triple positive subtypes with and without trastuzumab/chemo-sensitivity. *First Author: Pat W. Whitworth, NRG Oncology/NSABP, ALLIANCE/ACOSOG, and Nashville Breast Center, Nashville, TN*

Background: Classification by molecular subtype can aid in the selection of therapy for patients with breast cancer. However at present, the methodology for molecular subtyping is not standardized. The aim of the prospective NBRST study is to compare chemosensitivity as defined by pathological Complete Response (pCR) using the 80-gene BluePrint (BP) functional subtype profile vs. conventional IHC/FISH subtyping. **Methods:** The study includes women aged 18–90 with histologically proven breast cancer, written informed consent, no excision biopsy or axillary dissection, and no prior therapy for breast cancer. Neo-adjuvant Chemotherapy (NCT) was at the discretion of the physician adhering to NCCN approved or other peer-reviewed regimens. BP in combination with MammaPrint classifies patients into 4 molecular subgroups: Luminal A, Luminal B, HER2 and Basal. **Results:** 721 patients had definitive surgery. 58/335 (17%) IHC/FISH HR+/HER2- patients were re-classified by BP as Basal (57) or HER2 (1). 92/222 (41%) IHC/FISH HER2+ patients were re-classified as BP Luminal (67) or BP Basal (25). 7/164 (4%) IHC/FISH triple negative (TN) patients were re-classified as BP Luminal (5) or BP HER2 (2). NCT pCR rates were 3% in Luminal A and 9% in Luminal B patients versus 10% pCR in IHC/FISH luminal patients. The NCT pCR rate was 54% in BP HER2 patients. This is significantly superior (p = 0.02) to the pCR rate in IHC/FISH HER2+ patients (40%). BP Basal and IHC/FISH TN had a pCR rate of 35%. Functional BP subtyping divided the 137 IHC/FISH triple positive patients into two major subgroups: BP Luminal (n = 66, pCR = 11%) and BP HER2 (n = 60, pCR = 45%).11 patients were re-classified as BP Basal with pCR = 45%. **Conclusions:** Molecular subtyping using BP leads to a reclassification of 23% of tumors. The re-classification is most prominent in classically assessed triple positive patients where 48% of patients are re-assigned to the less responsive BP Luminal-type group vs. 44% of patients assigned to the responsive BP HER2-type group. These findings confirm the more accurate identification of molecular subgroups for treatment decision by BluePrint functional subtype classifier. Clinical trial information: NCT01479101.

597 Poster Session (Board #86), Sat, 8:00 AM-11:30 AM

Effect of ranolazine administered after trastuzumab treatment on cardiotoxicity in mice. *First Author: Nicola Maurea, Istituto Nazionale per lo Studio e la Cura dei Tumori Fondazione Giovanni Pascale- IRCCS, Naples, Division of Cardiology, Naples, Italy*

Background: Trastuzumab (T), a monoclonal antibody against ErbB2, has improved the prognosis of breast cancer patients, but ErbB2 blockade in cardiomyocytes can produce asymptomatic left ventricular dysfunction and heart failure, whose mechanism has not been elucidated and can include changes in Ca2+ regulation. We aim at assessing whether Ranolazine (R), an inhibitor of the late sodium current, administered after T treatment, blunts T cardiotoxicity in vivo and in vitro. **Methods:** In vitro, rat H9C2 cardiomyoblasts were treated with T (0.2μM) for 3 days and then treated in the absence or presence of R (1μM or 10μM) for 3 days. In vivo, fractional shortening (FS) and ejection fraction (EF) were measured by M-mode echocardiography and radial and longitudinal strain (RS and LS) were measured using 2D speckle-tracking, in C57/BL6 mice, at 0, 2 and after 7 days of daily administration of T (2.25 mg/kg/day). These measurements were repeated after 5 days of R treatment (305 mg/Kg/day) initiated at the end of T treatment. We have divided mice in 4 groups. The first group (G1) was treated with T for 7 days. The second group (G2) was treated with T for 7 days and then treated with R for 5 days. The other 2 were control groups: CG1 (sham) and CG2 (no R). We have evaluated tissue expression of BNP (brain natriuretic peptide) by PCR analysis on heart tissue. **Results:** R reduced T toxicity in H9C2 cardiomyoblasts as evidenced by higher percentage of viable cells treated with T+ R with respect to cells treated with T alone ($p< 0.01$). In vivo, after 7 days with T, FS decreased to 48.7 $\pm$ 4.1%, $p< 0.01$ vs 62.3 $\pm$ 0.8% (sham), EF to 81.8 $\pm$ 3.5%, $p < 0.01$ versus 91.7 $\pm$ 0.5% (sham), RS to 21 $\pm$ 8.1%, $p < 0.01$ versus 43.2 $\pm$ 4% (sham), and LS to -11 $\pm$ 3.7%, $p < 0.01$ versus -38.8 $\pm$ 6% (sham). In mice treated with R for 5 days after T treatment, the indices of cardiac function recovered: FS was 61 $\pm$ 1.2%, EF was 91 $\pm$ 0.7%, $p < 0.01$; RS was 35$\pm$1.8%, $p < 0.05$ versus T. However the alteration of LS persisted after treatment with R (-15.4 $\pm$ 5.1%, $p = 0.3$ vs. T). R prevents the increased expression of BNP ($p < 0.05$) on heart tissue **Conclusions:** R post-treatment blunts cardiotoxic effects due to T both in vitro and in vivo in a mouse model, as demonstrated by the normalization of the values of FS, EF and RS. LS is the first to impair and may be the last to recover.

598 Poster Session (Board #87), Sat, 8:00 AM-11:30 AM

Skin and subcutaneous tissue disorders (SSTDs) in patients (pts) with HER2-positive metastatic breast cancer (MBC) in the phase III trial CLEOPATRA of pertuzumab or placebo with trastuzumab and docetaxel. *First Author: David Miles, Mt Vernon Cancer Centre, London, United Kingdom*

Background: CLEOPATRA established pertuzumab (P), trastuzumab (T), and docetaxel (D) as the first-line standard of care for pts with HER2-positive MBC. SSTDs were often observed in CLEOPATRA. We report detailed analyses of SSTDs from this phase III study. **Methods:** The safety population in this analysis included 396 pts in the placebo (Pla) arm (Pla+T+D) and 408 pts in the pertuzumab arm (P+T+D). SSTDs included rash (group term), pruritus, dry skin, alopecia, and nail disorders; incidence, severity (NCI-CTCAE v3.0), management, and outcome were analyzed in both treatment (tx) arms. **Results:** See table. The most common grade $\geq$ 3 SSTD in both arms of the study was rash before and after D discontinuation. Median time to onset of SSTDs was 22 days (Pla+T+D) and 20 days (P+T+D). Median duration of SSTDs was 121 days (Pla+T+D) and 96 days (P+T+D). SSTDs required medical tx in 33.8% (Pla+T+D) and 45.9% (P+T+D) of pts. Steroids were frequently used for tx of rash, antibiotics for nail disorders, and antihistamines for pruritus. Repeated episodes of any SSTD occurred in 17% (Pla+T+D) and 26% (P+T+D) of pts. SSTDs led to discontinuation of all study tx in 0.3% (Pla+T+D) and 0.2% (P+T+D) of pts; and discontinuation of D alone in 1.0% (Pla +T+D) and 3.7% (P+T+D) of pts. **Conclusions:** SSTDs were common in both Pla+T+D and P+T+D arms, although more frequent during D therapy. SSTDs were mostly low-grade, manageable, and rarely resulting in tx discontinuation. There is no specific tx for SSTDs and tx should be empirical, depending on the nature of the SSTD. These results will further inform clinicians on the nature and management of SSTDs for pts who receive P+T+D for the tx of HER2-positive MBC. Clinical trial information: NCT00567190.

Incidence of SSTDs.

All grades and most common ($\geq$ 10 or 5%) and grade $\geq$ 3 (total) SSTDs					
	Overall Exposure to Study Tx $\geq$ 10%			After D Discontinuation $\geq$ 5%	
AE n(%)	Pla+T+D n = 396	P+T+D n = 408	AE n(%)	Pla+T+D n = 267	P+T+D n = 311
Alopecia	240 (60.6)	248 (60.8)	Rash	21 (7.9)	56 (18.0)
Rash	95 (24.0)	153 (37.5)	Pruritus	15 (5.6)	42 (13.5)
Nail disorder	93 (23.5)	96 (23.5)	Nail disorder	13 (5.0)	13 (4.2)
Pruritus	40 (10.1)	72 (17.6)			
Dry skin	24 (6.1)	46 (11.3)			
Grade $\geq$ 3 SSTDs	8 (2.0)	18 (4.4)		1 (0.4)	2 (0.6)

599 Poster Session (Board #88), Sat, 8:00 AM-11:30 AM

Biologic characteristics of breast cancer in male compared to female: SEER analysis. *First Author: Mohammed Shaik, Michigan State University, East Lansing, MI*

Background: Male (Ma) breast cancer (BC) is a rare disease and information about tumor biomarkers(ER,PR and HER2) is lacking. Since HER2 status was not routinely collected in the population-based cancer registries for patients (pts) before 2010,in this study we aim to evaluate the expression of tumor biomarkers in MaBC compared to female (F) BC. **Methods:** Using SEER database we analyzed 917(0.84%) MaBC and 108,669 (99.16%) FBC (2010-2011). Data including age, sex, grade, stage, ER/PR status(HR), and HER2 status was used in analysis. These variables were compared between MaBC and FBC. Chi-square and t-test were used for categorical and numerical variables, respectively. **Results:** The median age for MaBC and FBC was 68 and 61, respectively. Majority were whites followed by blacks and others(81%, 14%, and 5% vs. 80%, 11% and 9%, respectively) in both MaBC and FBC. Stages(0, I, II, III and IV) in MaBC vs. FBC were 2.6%, 35.1%, 38.1% ,17.5% and 6.4% vs. 3%, 47%, 33.6%, 11.5%, and 4.7%, respectively. Tumor biomarkers in MaBC vs. FBC were HR+ 96.7%, HER2+ 12.5% and triple negative(TN) 2% vs. HR+ 83%, HER2+ 15% and TN 12%, respectively (Table). **Conclusions:** Overall prevalence of MaBC was 0.84%, diagnosed at older age and the most were of luminal subtype. Prevalence of HER2+ve in MaBC was slightly lower compared to FBC(12.5% vs 15%, $p = 0.03$). TN phenotype in MaBC was uncommon (2%). More favorable tumor biomarker profile was seen in MaBC as compared with FBC. However, HER2 +ve BC represented a significant proportion of MaBC in our study. MaBC should be included in future studies to evaluate HER2 targeted therapies.

Comparison of MaBC and FBC.

Variable	MaBC(%)	FBC(%)	p-value
Median Age (yrs)	68	61	< 0.0001*
Race			
White	742 (81%)	87037 (80%)	0.01
Black	128 (14%)	11635 (10.7%)	
Others	47 (5%)	9997 (9.3%)	
Receptor status			
HR+/HER2+	105 (11.4%)	11285 (10.3%)	< 0.0001**
HR-/HER2+	10 (1.09%)	5133 (4.7%)	
HR+/HER2-	783 (85.3%)	79145 (72.8%)	
HR-/HER2-	19 (2.07%)	13105 (12%)	
HER2 Status			
HER2+ve	115 (12.5%)	16418 (15%)	0.03***
HER2-ve	802 (87.5%)	92250 (85%)	
Stage ***			
0	23 (2.6%)	3212 (3%)	< 0.0001**
I	310 (35.2%)	49548 (47%)	
II	336 (38%)	35455 (33.6%)	
III	155 (17.5%)	12169 (11.5%)	
IV	57 (6.4%)	4961 (4.7%)	

* t test; ** chi-square test; *** data missing for 3307 pts.

600 Poster Session (Board #89), Sat, 8:00 AM-11:30 AM

Effect of high MMP2 and low MMP9 baseline serum levels on outcome in patients with HER2-positive inflammatory breast cancer (IBC) treated with bevacizumab (BEV)- and trastuzumab (TRA)-based neoadjuvant chemotherapy (NAC) in the BEVERLY 2 study. *First Author: Emeline Tabouret, Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France*

Background: Addition of BEV to TRA-based NAC in HER2-positive IBC has been associated with high pathological complete response (pCR) rate and favorable outcome in the BEVERLY 2 phase II trial (Pierga, Lancet Oncol, 2012; Viens, SABCS, 2013). Matrix metalloproteinase (MMP) 2 and 9 are matrix-degrading enzymes involved in tumor growth, invasion and angiogenesis. The plasma levels of which were recently associated with response to BEV in high-grade glioma (Tabouret, Neuro-Oncology, 2014). We examined the prognostic impact of MMP2 and MMP9 serum levels in Beverly 2 patients (pts). **Methods:** Serum levels of MMP2 and MMP9 were analyzed, using ELISA, in 45/52 samples from pts included in the BEVERLY 2 trial. Serums were analyzed at baseline and before surgical resection, and correlated to pCR, disease-free survival (DFS) and overall survival (OS). **Results:** Baseline (b) MMP2 and MMP9 serum levels were independent from pts characteristics including age, hormone receptor status, SBR grade, circulating tumor cells and endothelial cells, and were not correlated to pCR. As continuous variables (ROC curves), bMMP2 was significantly associated with relapse ($p = 0.002$) and death ($p = 0.049$) risks, while bMMP9 was only associated with death risks ($p = 0.035$). Using median value as cutoff, univariate analyses identified high bMMP2 as correlated to better DFS ($p = 0.001$) and OS ($p = 0.032$), while low bMMP9 was correlated to better OS ($p = 0.022$) and tended to be associated to longer DFS ($p = 0.071$). In multivariate analyses (DFS only, same cutoff), both bMMP2 ($p = 0.003$, Hazard Ratio [HR]: 10.614) and bMMP9 ($p = 0.041$, HR: 3.534) remained correlated to DFS. Between baseline and pre-surgery time points, significant increase in MMP2 and decrease in MMP9 levels ($p < 0.001$ for both) were observed in 100% and 87% of pts, respectively but did not correlate with outcome. **Conclusions:** High bMMP2 and low bMMP9 serum levels were associated with a better outcome in HER2-positive IBC pts treated with BEV- and TRA-based NAC. Their predictive value should be evaluated in randomized trial.

601 Poster Session (Board #90), Sat, 8:00 AM-11:30 AM

Expression levels of PARP1 and phospho-p65 protein in human HER2-positive breast cancers. *First Author: Jennifer Anne Stanley, University of Alabama at Birmingham, Birmingham, AL*

Background: Previous studies have shown that basal breast cancers, which may have an inherent "BRCAness" phenotype and sensitivity to inhibitors of poly (ADP-Ribose) polymerase (PARP), express elevated levels of PARP1. Our lab previously reported that HER2+ breast cancers are exquisitely sensitive to PARP inhibitors (PARPi) thru alteration of the NF-kB pathway. In this study, we assessed levels of PARP1 and phospho-p65, a marker of activated NF-kB, in human breast cancer tissues. **Methods:** PARP1 and PARP2 copy number, mRNA, and protein expression were assessed by interrogating the PAM-50 defined breast cancer patient set from the TCGA using the cBioPortal. PARP1 and phospho-p65 immunohistochemistry and correlation to clinical parameters were conducted using 307 primary breast cancer specimens (132 basal, 82 luminal, 93 HER2+) through univariate and multivariable analyses. **Results:** In the PAM50 breast cancer data set, PARP1 and 2 expression was altered in 24/58 (41%) HER2+, 32/81 (40%) basal, and 75/324 (23%) luminal A/B breast cancer patients. This correlated with a statistically significant increase in PARP1 protein levels in HER2+ and basal but not luminal breast cancers ($p = 0.003$, $p = 0.027$, $p = 0.289$, respectively). No change in PARP2 protein level was observed. Interestingly, using breast cancer specimens from 307 patients, HER2 positivity correlated with elevated PARP1 expression ($p < 0.0001$) and was three times more likely than HER2 negative breast cancers to exhibit high PARP1 levels. No significant differences were noted between race, ER status, or PR status for PARP1 expression. Additionally, we found a significant correlation between HER2 status and phospho-p65 expression ($p < 0.0001$). Lastly, a direct correlation between PARP1 and phospho-p65 ($p < 0.0001$) was noted. **Conclusions:** These results indicate a potential connection between HER2, PARP1, and phospho-p65 in human breast tumors. Additionally, these data suggest that the PARPi sensitivity we previously observed in HER2+ breast cancer cells may be due to elevated PARP1 expression. Future testing of PARPi in HER2+ breast cancer patients is warranted.

602 Poster Session (Board #91), Sat, 8:00 AM-11:30 AM

Phase 1b study of ONT-380, an oral HER2-specific inhibitor, in combination with capecitabine (C) and trastuzumab (T) in third line + treatment of HER2+ metastatic breast cancer (MBC). *First Author: Erika Paige Hamilton, Sarah Cannon Research Institute, Brentwood, TN*

Background: ONT-380, a potent, highly selective, small molecule inhibitor of HER2, was associated with clinical benefit and minimal EGFR-type toxicities in a phase 1 single agent study in HER2+ MBC. Based on synergistic activity with chemotherapy and T in preclinical models, ONT-380 is being evaluated in combination with C and T in pts with HER2+ MBC following prior treatment with T and ado-trastuzumab emtansine (T-DM1). ONT-380 300 mg PO BID was well tolerated in combination with either C or T alone, and is now being studied in combination with both C and T as triplet therapy. **Methods:** Phase 1b 3+3 dose escalation study with expansion cohort for a total of 15 pts at a given dose. ONT-380 (300 mg PO BID), C (1000 mg/m^2 PO BID 14 days of a 21-day cycle), and T (8 mg/kg IV loading; then 6 mg/kg IV once every 21 days), are administered to HER2+ MBC pts previously treated with trastuzumab and T-DM1. Prior pertuzumab, lapatinib, or neratinib, and asymptomatic brain metastases (treated or untreated) are allowed. Assessments include safety, tumor response by RECIST 1.1, and PK. **Results:** 8 pts (# prior treatments for MBC 2-6) have completed 2–8 cycles of triplet therapy; 6 pts remain active. A dose-limiting toxicity (DLT) of reversible cerebral edema with Gr 3 dysarthria and visual field deficit was seen in a pt with known brain metastases. No additional DLTs were seen. Most toxicities have been Gr 1 or 2; the most common being nausea, vomiting, diarrhea, palmar-plantar erythrodysaesthesia, and fatigue. One additional Gr 3 treatment-related event of reversible increase in AST/ALT was reported. No Gr $\geq$ 3 diarrhea has been seen. To date, best responses in pts with at least 1 follow up scan have been: partial response (PR) n = 4, stable disease (SD) n = 2, and progressive disease n = 2. Two pts with PR and 2 pts with SD also had received prior pertuzumab. **Conclusions:** ONT-380 in combination with C and T exhibits an acceptable safety profile without Gr 3 diarrhea. The combination shows preliminary evidence of disease control in heavily pre-treated HER2+ MBC pts with prior exposure to trastuzumab, pertuzumab, and T-DM1. Enrollment in an expansion cohort is ongoing. Clinical trial information: NCT02025192.

603 Poster Session (Board #92), Sat, 8:00 AM-11:30 AM

Safety of trastuzumab emtansine (T-DM1) in 373 patients 65 years or older with HER2-positive advanced breast cancer: A subgroup analysis of the Kamilla study. *First Author: Carlos H. Barrios, PUCRS School of Medicine, Porto Alegre, Brazil*

Background: T-DM1 is approved for HER2-positive metastatic breast cancer (MBC). A pooled analysis of T-DM1 trials (N = 884) suggested a higher rate of grade $\geq$ 3 adverse events (AEs) in patients (pts) $\geq$ 65 yrs (n = 122) vs those < 65 (51.6% vs 44.0%). We report the safety profile of T-DM1 in pts $\geq$ 65 yrs from the ongoing phase IIIb global safety study Kamilla. **Methods:** Kamilla enrolled pts with HER2-positive, locally advanced or MBC with progression after chemotherapy and a HER2-directed agent for MBC or within 6 mos of completing adjuvant therapy. T-DM1 3.6 mg/kg was given q3w until unacceptable toxicity, withdrawal of consent or disease progression. **Results:** As of 20 Oct 2014, Kamilla enrolled 2001 pts; 373 pts $\geq$ 65 yrs. Pts $\geq$ 65 yrs had a longer median time since initial BC diagnosis than pts < 65 yrs (6.3 yrs vs 4.8 yrs) and a lower prevalence of brain metastases (10.2% vs 21.6%). Median exposure was 8 cycles in each group (IQR 4.0–13.0 older; 4.0–15.0 younger). AEs by age group, including known T-DM1–associated AEs, are shown. The incidence of grade $\geq$ 3 AEs and AE-related discontinuations were greater in older pts. This resulted from many small differences in AEs rather than any single AE. **Conclusions:** In this largest population of T-DM1–treated pts $\geq$ 65 yrs studied to date, while overall incidence of grade $\geq$ 3 AEs and discontinuation due to AEs was greater, the most common grade $\geq$ 3 AEs were infrequent and similar between age groups. Known T-DM1–associated AEs also occurred with a similar frequency in both groups, suggesting a similar safety profile in older and younger pts. Clinical trial information: NCT01702571.

Outcome, n (%)	≥ 65 yrs (n = 373)	< 65 yrs (n = 1628)
Discontinuation due to AEs (% based on pts who discontinued)	41 (14.3)	112 (9.5)
Fatal AEs	10 (2.7)	17 (1.0)
Grade ≥ 3 AEs	160 (42.9)	540 (33.2)
Grade ≥ 3 AEs in ≥ 2% of either group		
Thrombocytopenia*	13 (3.5)	53 (3.3)
Asthenia	12 (3.2)	18 (1.1)
Anemia	11 (2.9)	32 (2.0)
Fatigue	10 (2.7)	34 (2.1)
GGT increased	8 (2.1)	42 (2.6)
Thrombocytopenia*	49 (13.1)	211 (13.0)
Grade ≥ 3	13 (3.5)	53 (3.3)
Hepatotoxicity*	68 (18.2)	327 (20.1)
Grade ≥ 3	18 (4.8)	114 (7.0)
Hemorrhage*	87 (23.3)	392 (24.1)
Grade ≥ 3	6 (1.6)	28 (1.7)
LVEF < 45%	5 (1.3)**	36 (2.2)

*Based on groupings of related preferred terms; **None < 40%.

604 Poster Session (Board #93), Sat, 8:00 AM-11:30 AM

The clinical utility of *ERBB2* amplification detection in breast carcinoma using a 341 gene hybrid capture-based next generation sequencing (NGS) assay: Comparison with standard immunohistochemistry (IHC) and Fluorescence In Situ Hybridization (FISH) assays. *First Author: Dara S. Ross, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Approximately 15-20% of invasive breast carcinomas (BCA) show HER2/*ERBB2* gene amplification which determines eligibility for treatment by targeted therapy. Traditionally, HER2 status is determined by IHC and FISH. NGS methods can be used to assess HER2 status in clinical practice but concordance with IHC/FISH is not well established. We report our experience using NGS for the assessment of HER2 amplification in conjunction with the detection of potentially targetable mutations. **Methods:** BCA samples (> 10% tumor) were analyzed in a CLIA-certified lab using a hybrid capture-based NGS assay ("MSK-IMPACT") designed to detect somatic genetic alterations in 341 genes, including copy number alterations. Tumor percentage and concurrent IHC/FISH results were recorded (using ASCO/CAP 2013 guidelines). Criteria for amplification by NGS were defined as a fold change (FC) $\geq$ 2, p-value < 0.05. **Results:** A total of 133 BCA samples (63 primaries, 70 mets) were analyzed. Compared to the combined IHC/FISH methodology, *ERBB2* amplification status by NGS had an overall concordance of 97% (129/133) (sensitivity = 82%, specificity = 100%, PPV = 100%). Discordant cases showed low tumor purity, heterogeneous IHC staining, and/or low level amplification by FISH. One sample status post trastuzumab was negative by IHC but *ERBB2* amplified by FISH (ratio 4.0) and NGS (FC 2.3). The assay also uncovered somatic alterations in 133 cancer genes including *TP53*, *PIK3CA*, *CDH1* and *ESR1*. ER and PR IHC results were available for 94 cases; 1/13 triple negative cases showed an actionable *PIK3CA* E542K mutation. Of the 22 *ERBB2* amplified cases, 6 had actionable *PIK3CA* mutations (H1047R or E545K); 4/6 were metastatic lesions in patients previously treated with trastuzumab. **Conclusions:** HER2 status can be reliably determined by hybrid capture NGS methods and allows the concurrent testing for other potentially actionable genomic alterations, particularly in limited material. Samples with low tumor content, heterogeneity and low level amplification may result in false negatives.

605 Poster Session (Board #94), Sat, 8:00 AM-11:30 AM

HER2 quantification by mass spectrometry compared to IHC or ISH in predicting clinical benefit from anti-HER2 therapy in HER2-positive breast cancer (BC). *First Author: Paolo Nuciforo, Molecular Pathology Group, Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain*

Background: To be eligible for an anti-HER therapy, tumors have to be HER2-positive as determined by IHC or in situ hybridization (ISH) analyses. Although gene amplification is generally considered the main mechanism of HER2 protein overexpression in BC, the biologic regulation of HER2 expression is complex and gene amplification may not always correlate quantitatively with HER2 protein levels and with response to anti-HER2 therapies. **Methods:** HER2-positive (n = 123) primary BC samples were microdissected, solubilized and digested in trypsin in Liquid Tissue buffer. Absolute quantitation for HER2 protein was performed using selected reaction monitoring (SRM) mass spectrometry. ISH was centrally performed on all cases. HER2 gene copy number (GCN), HER2/Chr17 ratio, and pattern of amplification were evaluated and correlated with HER2 protein levels. The survival benefit according to protein and gene levels was calculated for patients receiving an adjuvant anti-HER2 therapy (n = 68). **Results:** HER2 SRM levels showed weak positive correlations with HER2 GCN and HER2/Chr17 ratio. Average HER2 protein levels were significantly higher in tumors amplified with homogeneous stained regions (HSR, n = 50) compared to those with double minutes (DM, n = 46). Ten amplified cases showed HER2 protein levels similar to HER2-negative tumors. Eight had a DM and 2 a mixed pattern of amplification. None was amplified in HSR. HER2 protein levels > 2,200 amol/μg predicted better disease-free survival and overall survival in patients treated with adjuvant trastuzumab. Neither HER2 GCN, HER2/Chr17 ratio nor pattern of amplification correlated with outcome. **Conclusions:** By using an objective non-antibody based method we identified a great deal of disparity of HER2 levels in BC patients that are classified as HER2-positive by ISH. Different amplification patterns resulted in significantly different protein levels; with many cases of DM amplification showing no concomitant increase in HER2 protein expression. Our findings indicate that protein abundance rather than gene status predict the clinical benefit from anti-HER2 therapy in HER2-positive BC patients.

606 Poster Session (Board #95), Sat, 8:00 AM-11:30 AM

Crosstalk between PARP-1 and NF-κB signaling pathways as a potential determinant of PARPi sensitivity in trastuzumab resistant HER2+ breast cancer cell lines. *First Author: Monicka Wielgos, Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL*

Background: We have previously found that HER2+ breast cancer cells, despite being DNA repair proficient, are sensitive to poly (ADP-Ribose) polymerase inhibitors (PARPi). In this study, we investigated whether PARPi susceptibility would be retained in HER2+ breast cancer cells that are resistant to the HER2 targeted agent trastuzumab. **Methods:** Human HER2+ breast cancer cell lines BT-474, UACC812, SKBR3 and their trastuzumab resistant counterparts were used in this study. Cells were treated with vehicle or 10μM ABT-888 or transfected with scrambled or PARP-1 siRNA. We assessed cell survival by colony formation assays. Western blot analysis was used to measure protein expression. Cell cycle distribution was evaluated by propidium iodide and measured by flow cytometry. NF-κB transcriptional activity was determined via a NF-κB-driven luciferase reporter assay. The nCounter Gene Expression Assay along with qRT-PCR were used to measure the expression levels of NF-κB target genes. Tumor growth delay was assessed in mice bearing tumor xenografts. **Results:** Similar to parental cells, trastuzumab resistant HER2+ breast cancer cells retained PARPi sensitivity both *in-vitro* and *in-vivo*. The cytotoxicity in these cells was associated with greater than 40% attenuation of NF-κB transcriptional activity. Results were validated with PARP-1 siRNA. Further, re-expression of PARP-1 rescued NF-κB activity in PARP-1 knockdown cells. The expression of several NF-κB target genes, including IL-8, BRCA2, and VEGFC, was reduced with PARP inhibition or knockdown. The effects of PARP inhibition via ABT-888 or PARP-1 siRNA were independent of cell cycle redistribution. **Conclusions:** Inhibition of NF-κB signaling via pharmacological or genetic modulation of PARP-1 induces a cytotoxic response in trastuzumab resistant HER2+ tumors. This warrants the testing of PARP inhibitors as a novel therapeutic strategy for patients with HER2+ breast cancer.

607 Poster Session (Board #96), Sat, 8:00 AM-11:30 AM

Phase II study of weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer (MBC): Updated progression-free survival with overall survival result. *First Author: Lillian Mary Smyth, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: We previously reported results of the phase II breast cancer (BC) trial of weekly paclitaxel (T), trastuzumab (H) and pertuzumab (P) with its primary endpoint of 6-month (mo) progression-free survival (PFS) of 86% (95% CI, 75% to 92%) in patients (pts) with HER2+ metastatic (M) BC treated in first- and second-line settings. At a median (med) follow-up (FU) of 21 mo, med PFS was 19.5 mo overall. Updated PFS and OS analysis from this fully accrued study is presented here. **Methods:** Pts with HER2+ MBC with 0-1 prior treatment (Rx) were eligible. Rx was weekly (w) T (80mg/m2), q3w H (loading dose 8mg/kg → 6mg/kg) and q3w P (loading dose 840mg → 420mg), all given intravenously. Primary endpoint was 6 mo-PFS. Secondary endpoints included 6-mo and median OS. Evaluable pts received at least one full dose of Rx. **Results:** From January 2011 to December 2013, 69 pts were enrolled: 51 (74%) and 18 (26%) treated in first- and second-line metastatic settings, respectively. 67 were evaluable for efficacy. As of 12-01-14, 26/67 pts (39%) remain progression-free (6 CR, 13 PR and 7 SD); 34 pts have progressed and there are 51 survivors. At a med FU of 23 mo (range, 3-40 mo), 6-mo PFS was 85% (95% CI, 74%-92%). Med PFS was 21.4 mo (95% CI, 13.8-NR) overall and 26.1 mo (95% CI, 17.0-NR) and 16.4 mo (95% CI, 8.5-NR) for pts with 0-1 prior Rx, respectively. 6-mo OS was 98% (95% CI, 90%-100%) and med OS was 37.5 mo (95% CI 31-NR). Median duration of ChemoRx was 30 weeks. Rx was well-tolerated; there were no febrile neutropenia and no symptomatic left ventricular systolic dysfunction. **Conclusions:** Updated analysis demonstrates that weekly paclitaxel, when added to H and P, is associated with prolonged PFS and OS and a favourable toxicity profile and should be considered as a therapeutic option in this patient population Clinical trial information: NCT01276041.

608 Poster Session (Board #97), Sat, 8:00 AM-11:30 AM

A phase 1b trial of blood-brain barrier (BBB)-penetrant tyrosine kinase inhibitor (TKI) tesevatinib in combination with trastuzumab for patients with HER2+ metastatic breast cancer (MBC). *First Author: Komal L. Jhaveri, New York Univ Cancer Inst, New York, NY*

Background: Patients with HER2+ breast cancer (BC) have a high incidence of brain metastases (mets). Tesevatinib (formerly KD019) is a TKI with potent activity against EGFR, HER2, and SRC. In contrast to all of the approved anti-HER2 agents in BC, tesevatinib crosses the intact BBB in mouse and rat models and achieves levels in the brain similar to plasma levels. Single-agent trials of tesevatinib in NSCLC defined the maximum tolerated dose as 300 mg daily due to QTc prolongation. **Methods:** This study was designed tofind the Recommended Phase 2 Dose for tesevatinib given daily combined with trastuzumab 6 mg/kg IV every 3 weeks. Secondary endpoints include pharmacokinetic evaluation of the combination. Eligible patients have HER2+ MBC with disease progression with or without brain mets. Three cohorts (tesevatinib 150 mg, 250 mg, and 300 mg/day) were planned. A 3 + 3 design was utilized for evaluating safety during the 21 days of Cycle (C) 1 to determine dose escalation. **Results:** 7 patients were enrolled into 2 dosing cohorts (median age 47). In Cohort 1 (150 mg) there was 1 patient with Gr 3 asymptomatic increased amylase, which resolved to Gr 1; not a DLT by protocol. There was 1 occurrence each of the following Gr 2 adverse events (AEs), all of which resolved: Gr 2 mouth sensitivity, acneiform rash, nausea, & vomiting. One patient in Cohort 1 missed doses of tesevatinib for 7/21 days (not due to AEs), and thus was not evaluable for dose escalation (but all AEs for this patient are included). The only Grade 2 or higher AE during C1 in Cohort 2 (250 mg) was a Gr 2 diarrhea that resolved to Gr 1 after 2 days with anti-diarrheal medications. Enrollment in the final dose cohort (300 mg) is ongoing. **Conclusions:** The combination of tesevatinib and trastuzumab appears to be well tolerated with no QTc prolongation so far and enrollment into the final dose cohort in Phase 1b is proceeding. Tesevatinib is a TKI with anti-HER2 activity that freely crosses the BBB and therefore has promise in the treatment of brain mets in patients with HER2+ MBC. Clinical trial information: NCT02154529.

609 Poster Session (Board #98), Sat, 8:00 AM-11:30 AM

Characterization of dominant T-cell clones by T-cell receptor (TCR) deep sequencing as a potential predictive biomarker to neoadjuvant trastuzumab (tras) in HER2-positive (HER2+) breast cancer. *First Author: David B. Page, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Because TIL quantity by H&E predicts pathologic complete response (pCR) to neoadjuvant tras in HER2+ disease, and because clinical responses to tras could be mediated by dominant T-cell clones reactive to the HER2-protein, we hypothesize that the quantity of dominant clones by TCR deep sequencing may predict tras-induced pCRs. Here, we evaluate the influence of specimen age on feasibility of TCR sequencing on breast cancer FFPE-preserved diagnostic core biopsies (bxs), and explore potential associations with pCR in a HER2+ subset. **Methods:** Two groups with pre-treatment bx's were selected and sequenced using the ImmunoSEQ platform: 12 neoadjuvant tras-treated women with "archival" HER2+ bxs (median 35mo from procurement, 12-54mo; 6 with pCRs) and 14 women treated on an immunotherapy protocol with "contemporary" bxs (median 10mo from procurement, 4-18mo). Viability was assessed by calculating the proportion of nucleotide sequences yielding productive, in-frame amino acid sequences. T-cell quantity (the proportion of T-cell to total DNA) and dominant T-cell clone quantity (# clones in top decile of reads) were measured by TCR sequencing and evaluated for associations with pCR (Wilcoxon rank sum). Accuracy of T-cell quantity was assessed by comparing with H&E TIL count. **Results:** TCR sequencing viability was lower in archival compared to contemporary bxs (median .67 v .81; $p < .0001$), and was inversely correlated with sample age (Spearman $r = -0.62$, $p = .0008$) but not input DNA amount ($r = -.05$, NS). T-cell quantity by TCR sequencing correlated with TIL quantity by H&E in contemporary ($r = 0.66$, $p = 0.03$) but not archival bxs ($r = .21$, NS). In the HER2+ group, dominant T-cell clone quantity (median # clones: pCR, 15; no-pCR, 6, $p = 0.05$) but not TIL nor T-cell quantity were associated with pCR to tras. **Conclusions:** Despite the potential influence of specimen age on accuracy of T-cell quantity by TCR sequencing, the # of dominant clones predicted for pCR in this small dataset, highlighting the possibility that dominant clones may mediate response to tras. These findings warrant further study in a larger dataset.

610 Poster Session (Board #99), Sat, 8:00 AM-11:30 AM

Efficacy and CNS progression analysis from the randomized phase 2 trial of neratinib + paclitaxel vs trastuzumab + paclitaxel as first-line treatment for HER2+ metastatic breast cancer (NEfERTT). *First Author: Ahmad Awada, Jules Bordet Institute, Bruxelles, Belgium*

Background: This large randomized open-label phase 2 trial compared the efficacy and safety of Neratinib (N), the irreversible pan-HER tyrosine kinase inhibitor, + Paclitaxel (P) vs Trastuzumab (T) + P as first-line treatment in HER2+ metastatic breast cancer (MBC). **Methods:** 479 pts were enrolled between 08/2009 and 08/2011. Women ≥18y with locally recurrent or MBC, HER2 gene amplification/HER2 overexpression, no progression within 12m (neo)adjuvant therapy, and no prior treatment for advanced disease were eligible. Pts were randomized to oral N (240mg od) + P or T+P. Dosing: T 4mg/kg iv then 2mg/kg iv weekly, P 80mg/m^2 iv weekly 3/4w. Primary endpoint: progression-free survival (PFS). Secondary endpoints: overall survival (OS); overall response rate (ORR); duration of response; clinical benefit rate; CNS progression; safety. PFS analysis was ITT by stratified log-rank test. Randomization was stratified by region, prior T, prior lapatinib, ER/PR status. 304 PFS events were required to detect 30% improvement in median PFS with 80% power (2-sided α=0.15). **Results:** 479 pts made up the ITT population (6 pts in NP arm and 12 pts in TP arm had known brain metastases at baseline; other baseline characteristics were balanced). Main efficacy findings are shown below. Most common adverse events (AEs) with NP vs TP were: diarrhea 93 vs 33% (G3 30 vs 4%; no G4; G3 median duration of 4.5d); nausea 44 vs 30% (G≥3 2 vs 1%); vomiting 36 vs 16% (G≥3 3 vs 1%); fatigue 32 vs 27% (G≥3 3 vs 3%); rash 31 vs 24% (G≥3 1 vs < 1%); cardiac disorders 2.5 vs 5.1% (G≥3 < 1 vs < 1%). **Conclusions:** NP has similar efficacy to TP; of interest, NP may be more effective than TP in reducing CNS progression. With no primary loperamide prophylaxis, diarrhea was significantly higher with NP than TP; non-GI AEs occurred at similar rates in both arms. Clinical trial information: NCT00915018.

Efficacy endpoint	N + P (n=242)	T + P (n=237)	Hazard ratio (95% CI)	P-value
Median PFS, months (95% CI)	12.9 (11.0–14.8)	12.9 (11.1–14.7)	1.03 (0.83–1.29)	0.777
ORR, n (%)	181 (75)	183 (77)	–	0.595
CNS progression[a], n (%)	19 (8)	38 (16)	–	0.0037
KM cumulative incidence of CNS recurrence, %	14.4	32.1	0.46 (0.26–0.81)	0.006

[a]49 events were CNS only.

611 Poster Session (Board #100), Sat, 8:00 AM-11:30 AM

Whole exome sequencing (WES) in HER2+ metastatic breast cancer (MBC) patients (pts) with extraordinary responses to trastuzumab (T). *First Author: Ines Maria Vaz Duarte Luis, Dana Farber Cancer Inst, Boston, MA*

Background: While 50-70% of pts with HER2+ MBC treated with T respond to therapy, the vast majority eventually develop resistance, after a median duration of 1 year. In rare cases, pts have exceptionally long durations of response to T. Understanding mechanisms of exceptional responses to anticancer therapies may improve patient selection and rational treatment designs. **Methods:** We conducted a retrospective screen for pts with HER2+ MBC at the Dana Farber Cancer Institute treated with T in the metastatic setting for more than 60 months. To date, we have identified 3 pts with extraordinary responses to T who provided consent for genomic studies and had sufficient tumor tissue available for study. All pts had histologic confirmation of metastatic disease and radiologic confirmation of response. Deep WES was performed on DNA extracted from pre-trastuzumab tumor biopsies and matched normal blood samples from all 3 pts, and sequencing data was analyzed for somatic point mutations, small insertions/deletions, and copy number alterations. **Results:** Clinical features are summarized in the Table. Mean target coverage for tumor samples were 181X, 178X, and 191X. Total number of somatic coding mutations were 161, 67, and 156. Somatic copy number analysis demonstrated HER2 amplification in all 3 tumors. Additional somatic genomic alterations included alterations in known breast cancer genes TP53, MAP2K4, and RB1. **Conclusions:** WES in 3 pts with HER2+ MBC treated with T in the metastatic setting for > 60 months demonstrated HER2 amplification as well as additional somatic genomic alterations. WES on tumor and germline samples from additional pts with extraordinary responses to T are underway, which may improve the power to detect underlying mechanisms of exquisite sensitivity to T.

	Receptor Status	Sites of disease	Tumor purity	Site of biopsy	Treatment	Response duration (months)
1	ER/PR negative, HER2 3+ (IHC)	Lymph nodes (LN)	60%	LN	Trastuzmab-paclitaxel*	88 (Ongoing)
2	ER/PR negative, HER2 3+ (IHC)	Skin/Chest wall, LN	40%	LN	Trastuzumab-lapatinib*	72 (Ongoing)
3	ER+(low) / PR negative, HER2 3+ (IHC)	Bone, Liver	50%	Breast	Trastuzumab-epothilone*	100 (Ongoing)

Followed by trastuzumab alone.

612 Poster Session (Board #101), Sat, 8:00 AM-11:30 AM

ONT-380 in the treatment of HER2+ breast cancer central nervous system (CNS) metastases (mets). *First Author: Cristiano Ferrario, Segal Cancer Centre, Jewish General Hospital, Montreal, QC, Canada*

Background: Up to half of pts with HER2+ metastatic breast cancer (MBC) will develop CNS mets. Surgery and/or radiation remain the mainstay of treatment for HER2+ CNS disease as systemic treatment options have limited efficacy and are often associated with significant GI and skin toxicity. ONT-380, a potent, selective small molecule inhibitor of HER2 with minimal EGFR-like side effects, has been associated with increased survival compared to lapatinib or neratinib in animal models of HER2+ CNS disease. Here we describe 9 pts with CNS mets treated with ONT-380 in combination with other systemic therapies. **Methods:** Pts with untreated asymptomatic (asx) or post-treatment progressive CNS mets were enrolled in CNS expansion cohorts of ongoing phase 1b studies of ONT-380 + ado-trastuzumab emtansine (T-DM1) or ONT-380 + trastuzumab (T) +/-capecitabine (C). All pts received treatment in 21 day cycles including ONT-380 300 mg PO BID and approved doses of either T-DM1 or T +/-C. Eligibility criteria included prior treatment with T and a taxane, and for pts receiving T+/-C, prior T-DM1. Prior lapatinib was allowed. Assessments included safety and CNS tumor response on MRI per modified RECIST 1.1 every 2 cycles. **Results:** 9 pts (4 with asx mets and 5 with progressive disease after local therapy) have received ONT-380 plus T-DM1 (n = 5), T (n = 4) or T+C (n = 1) for 1-8 cycles. 8 pts are evaluable for response (at least one follow-up MRI): 3 PR (T-DM1 n = 2; T+C n = 1) and 4 SD (T-DM1 n = 2; T n = 2). 1 pt with 15% increase in target lesion underwent resection; pathology, however, revealed only necrotic tissue. Pts with PR (1 with hx prior lapatinib) all had > 50% decrease in CNS target lesions. One non-evaluable pt (T-DM1) discontinued early due to treatment-related Gr 3 AST/ALT elevation. One other pt in T-DM1 cohort with Gr 3 ALT/AST increase remains on study following dose reduction. No other ≥ Gr 3 ONT-380 related events have been reported. **Conclusions:** ONT-380 has previously shown activity in the CNS in pre-clinical models. This case series demonstrates early clinical signs of promising activity of ONT-380 against HER2+ CNS mets in combination with other systemic agents. Further study of the CNS activity of ONT-380 is ongoing. Updated results will be reported. Clinical trial information: NCT01983501, NCT02025192.

613 Poster Session (Board #102), Sat, 8:00 AM-11:30 AM

Lack of correlation of neoantigens arising from tumor somatic mutations with tumor infiltrating lymphocytes (TILs) or survival in HER2-positive breast cancer (HER2+ BC). *First Author: Peter Stephen Savas, Peter MacCallum Cancer Centre, Thornbury, Australia*

Background: We have previously shown that TILs are positively prognostic in HER2+ BC. TILs comprise mostly CD8+ T cells but the basis for antigen recognition is unclear. Here we investigated the relationship between somatic mutations and TILs. **Methods:** Two cohorts of HER2+ early-stage BC were analysed. Cohort 1: 50 cases from the Responsify-EU project and Cohort 2: 172 cases from The Cancer Genome Atlas with whole exome sequencing, gene expression, germline SNP (inferring HLA genotype) and survival. Cohort 1 received adjuvant trastuzumab and chemotherapy. TILs were quantified from H&E slides in both cohorts using our previously defined method. We performed computational prediction of mutant peptide neoantigens binding patient specific MHC Class I. **Results:** In cohorts 1 and 2, 660/2113 (31%) and 3268/10841 (30%) non-synonymous point mutations were predicted to be immunogenic mutations (iMut), with a median of 9.5 (IQR 3 – 19), and 9 (IQR 6 – 18) per sample per cohort, respectively. The number of iMut predicted was strongly correlated with the total number of mutations (Cohort 1: $R_s = 0.9$; Cohort 2: $R_s = 0.8$, both $p < 0.00001$). TILs were strongly and significantly correlated ($R_s > 0.5$, $p < 0.001$ for all) with gene expression surrogates of immune activation (CD8A, GRZMB, PRF1) and immunosuppression (PDL1, CTLA4, IDO1). In cohorts 1&2, there was no significant correlation between TILs and total mutation count ($R_s = 0.04$; $R_s = 0.02$, respectively), iMut ($R_s = 0$ for both) nor the APOBEC mutation signature ($R_s = 0$). There was no difference in the level of TILs between lowest and highest quartiles of iMut burden in the cohorts combined ($p = 0.7$). In the trastuzumab-treated cohort 1, total mutation count (≤ 100 vs > 100) and iMut count (0 vs ≥ 1) was not associated with invasive disease-free survival (IDFS $p = 0.4$; $p = 0.9$ respectively). The presence of a recently reported melanoma neoantigen signature (Snyder, NEJM 2014) also did not significantly correlate with the presence of TILs ($R_s = 0.03$) or IDFS ($p = 0.6$). **Conclusions:** In HER2+BC, predicted tumor neoantigens did not correlate with TILs or survival. Other mechanisms seem to be eliciting the anti-tumor immune response in HER2+BC.

614 Poster Session (Board #104), Sat, 8:00 AM-11:30 AM

Neuromedin U to increase IL-6 levels and to expand cancer stem cells in HER2-positive breast cancer cells. *First Author: Vanesa Gabriela Martinez, School of Pharmacy & Pharmaceutical Sciences & Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland*

Background: Neuromedin U (NmU) is a neuropeptide belonging to the neuromedin family. Recently, a significant association between NmU signaling and cancer has been described, particularly correlated with increased aggressiveness and resistance to chemotherapy, although the mechanism through which it exerts this effect remains unexplained. **Methods:** HER2-positive breast cancer cells were stably transfected with NmU and IL-6 levels were measured by ELISA. Migration was evaluated in the presence of anti-NMUR antibodies by wound healing assays, while drug toxicity was assessed by the acid phosphatase assay. **Results:** Overexpression of NmU increases secreted levels of IL-6 (0 vs 0.303 ± 0.12 ng/μg, $p = 0.04$), a cytokine involved in promoting migration, expansion of the cancer stem cell population and drug resistance in breast cancer cells. NmU-transfected cells also show an increased proportion of cancer stem cells (CD44+/CD24-) (52.78 ± 5.765 vs 67.42 ± 5.172 in NmU-overexpressing cells, $p = 0.07$; fold change, 1 vs 1.31 ± 0.14, $p = 0.00015$) and increased expression of the lymphocyte activation inhibitor PD-L1, as detected by flow cytometry (49.50 ± 4.213 vs 60.06 ± 1.628, $p = 0.0327$); Furthermore, NmU over-expressing cells were shown to display enhanced resistance to antibody-dependent cell cytotoxicity mediated by Trastuzumab (47.13 ± 3.31% lysis of mock-transfected cells vs 36.46 ± 4.33% lysis in NmU-overexpressing cells, $p = 0.05$). Treatment with antibodies that block NmU receptors NMUR1 and NMUR2 reduces cell migration and enhances toxicity of HER2-targeted drugs in NmU over-expressing cells, suggesting that interaction of NmU with NMUR1 and NMUR2 are necessary for its effects. **Conclusions:** Altogether, our results show a new mechanism of action of NmU in HER2-positive breast cancer cells that enhances resistance to HER2-targeted drugs and the anti-tumor immune response, and is at least partially mediated by IL-6. *Acknowledgements*: Science Foundation Ireland's funding of MTCI 08/SRC/B1410; HRB's Health Research Award [HRA-POR-2014-658]; Irish Cancer Society's Breast-Predict [CCRC13GAL]; and HEA's PRTLI Cycle 5 support of TBSI.

615 Poster Session (Board #105), Sat, 8:00 AM-11:30 AM

Effect of somatic mutations in the four genes of the HER family on occurrence in HER2-positive breast cancer, cell proliferation rates, and resistance to HER2-targeted therapies in vitro. *First Author: Naomi Elster, Medical Oncology, Royal College of Surgeons in Ireland, Dublin, Ireland*

Background: Somatic mutations in the 4 HER family genes (EGFR, HER2, 3, 4) occur in HER2-positive breast cancer (HER2+ BC). (Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumors. Nature 2012; 490(7418): 61-70.) We investigated their frequency in a large set of HER2+ BCs and their therapeutic relevance. **Methods:** Tumors from 246 HER2+ BC patients who received adjuvant trastuzumab-based therapy after surgery were reviewed by a pathologist for tumor content. DNA from 48 matched normal and cancerous samples was sequenced using the Agilent kinome library and a MiSeq. Somatic HER gene mutations identified in this way had their frequency determined by Sequenom MassArray (n=246). HER gene mutations were correlated with patient outcomes. Constructs of 2 hotspot HER3/4 mutations were created and transfected into BT474, HCC1569 and HCC1954 cells. Doubling time, proliferation, Boyden chamber assays and RPPA were used to determine effects of mutations on cell growth, invasion, signalling and response to HER2-targeted therapies. **Results:** 12 somatic deleterious mutually exclusive mutations in the kinase and furin like domains of the 4 HER genes (3 EGFR, 2 HER2, 2 HER3, 5 HER4 mutations) were identified in 6.5 % of HER2+ BCs including 2 hotspot mutations in HER3/4. HER gene mutations did not impact OS or RFS after adjuvant trastuzumab. HER3/4 hotspot mutations increased doubling rates *in vitro* and induced resistance to anti-HER2/EGFR TKIs (Table) but not trastuzumab. Transfected cells were sensitive to the PI3K inhibitor copanlisib and copanlisib also restored sensitivity to these TKIs in these cell lines. **Conclusions:** HER family mutations occur in 6.5% of HER2+BC and affect tumour growth and response to HER2-targeted therapies.

Effects of 2 hotspot HER3/4 mutations on response to TKI's (nM) in vitro in transfected (MUT) vs. wild type (WT) cell lines. '*' indicates a p-value of < 0.05.

	HER3 MUT IC_{50}	HER3 WT IC_{50}
Lapatinib (BT474)	58.3+/-5.2*	42.7 +/- 4.1
Afatinib (HCC1569)	129.8+/-8.8*	38.4 +/- 3.9
Afatinib (HCC1954)	81.5+/-8.0*	52.8 +/- 3.2
	HER4 MUT IC_{50}	HER4 WT IC_{50}
Afatinib (HCC1569)	76.5+/-1.3*	44.1 +/- 4.1

616 Poster Session (Board #106), Sat, 8:00 AM-11:30 AM

Trastuzumab and pertuzumab-based versus other therapy as second-line therapy in HER2-positive metastatic breast cancer: A retrospective study from single center. *First Author: Daniel Fontes Santos De Teive E Argolo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: First line treatment with dual anti-HER2 therapy (Rx) with trastuzumab plus pertuzumab (HP), and a taxane led to significant improvement in outcomes for patients (pts) with HER2+ metastatic breast cancer (MBC). In 2nd line, data on HP-based Rx are limited. We conducted a retrospective analysis of pts with HER2+ MBC who had progressive disease after 1st line treatment. **Methods:** Pts diagnosed with HER2+ MBC evaluated at MSKCC between 1-1-2011 and 6-30-2014 and who progressed on 1st line Rx were eligible. Pts who received ≥ 2 lines of Rxs were classified in two groups: pts treated with HP-based Rx (Group 1) and with other Rxs (Group 2). Primary endpoint was progression-free survival (PFS) in the 2nd line setting. **Results:** 103 pts were identified (Group 1: 24, Group 2: 79). The baseline characteristics and treatments of each group are summarized in table 1. With a median follow-up of 10.9 months (mo) (range 0.32-42.4), median PFS was 11.5 mo (95% CI, 6.5-NR) in Group 1 and 5 mo (95% CI, 3.75-7.25) in Group 2 (p=0.0027). **Conclusions:** In this retrospective analysis, HP-based Rx appeared to be associated with a longer PFS when compared with other Rx in the 2nd line setting.

Baseline characteristics and treatments.

Group 1 (n=24)		
Age (years)		
Median	54.46	
Range	34-86	
Hormone Receptor Status	(n)	(%)
ER and/or PR positive	16	66.7
ER and PR negative	8	33.3
Prior Adj/Neoadjuvant Rx		
No	11	45.8
Yes	13	54.2
Trastuzumab	11	45.8
First-line Rx		
One prior line of therapy	24	100
Anti-HER2-based	18	75
HP-based	6	25
Other	6	25
Second-line Rx		
Chemotherapy + HP	18	75
Endocrine therapy + HP	5	20.8
Other + HP	1	4.2
Group 2 (n=79)		
Age (years)		
Median	53.42	
Range	25-87	
Hormone Receptor Status	(n)	(%)
ER and/or PR positive	49	62.0
ER and PR negative	30	38.0
Prior Adj/Neoadjuvant Rx		
Unknown	1	1.3
No	34	43.0
Yes	44	55.7
Trastuzumab	35	44.3
First-line Rx		
One prior line of therapy	79	100.0
Anti-HER2-based	66	83.5
HP-based	19	24.1
Other	13	16.5
Second-line Rx		
Trastuzumab-based	35	44.3
T-DM1-based	17	21.5
Lapatinib-based	5	6.3
Trastuzumab+Lapatinib-based	9	11.4
Non anti-HER2-based	13	16.5

617 Poster Session (Board #107), Sat, 8:00 AM-11:30 AM

***HLA-DRB1**07:01 biomarker characterization of hepatotoxicity during lapatinib combination therapies in ALTTO.** *First Author: Colin F. Spraggs, GlaxoSmithKline, Stevenage, United Kingdom*

Background: ALTTO (NCT00490139) is a large adjuvant breast cancer (ABC) study evaluating lapatinib, alone and in combinations with trastuzumab and taxanes. Characterization of hepatic abnormalities during lapatinib treatment in ALTTO was conducted using the lapatinib hepatotoxicity risk biomarker *HLA-DRB1**07:01. **Methods:** Germline DNA collection for *HLA-DRB1* genotype determination was achieved for 76% (6323/8270) of ALTTO subjects. Association of *HLA-DRB1**07:01 allele carriage with ALT elevation during study treatments was evaluated by case-control analysis of NCI CTC AE grade 3 ALT elevation ($>$ 5x ULN, ALT). **Results:** A higher incidence of ALT elevation (2-5%, n = 6194) was observed in the three lapatinib-containing treatment arms compared with the trastuzumab monotherapy arm (1%, n = 2076; $p < 0.01$). Also, ALT was higher when lapatinib and taxane were administered concurrently. *HLA-DRB1**07:01 carriage frequency was enriched in lapatinib-treated ALT cases compared with controls (OR 6.5, 95% CI 4.6-9.3, $p = 2x10^{-26}$, n = 4568), with overall negative and positive ALT risk predictive values for the *HLA* allele of 98.6% and 8.7%, respectively. The *HLA* association was weaker when concurrent taxane was administered to lapatinib-treated patients, suggesting an ALT risk independent of *HLA-DRB1**07:01 carriage. Homozygous and heterozygous *HLA-DRB1**07:01 genotype carriers exhibited different ALT elevation risk during lapatinib treatment of 12.1% (n = 67) and 8.5% (n = 965), both higher than the risk for non-carriers (1.4%, n = 3586). Furthermore, homozygous carriers exhibited greater severity with significantly higher maximum ALT elevations. ALT elevation risk was significantly correlated with geographic differences in *HLA-DRB1**07:01 carriage frequency. **Conclusions:** Whilst efficacy of lapatinib plus trastuzumab was not sufficiently improved over trastuzumab alone to support a treatment indication for ABC, the present data provide robust lapatinib ALT risk estimates for *HLA-DRB1**07:01 allele carriage that may discriminate causality and support safety management during the use of lapatinib combinations for treatment of metastatic breast cancer globally. Funding: GlaxoSmithKline. Clinical trial information: NCT00490139.

618 Poster Session (Board #108), Sat, 8:00 AM-11:30 AM

Development of PF-05280014, a potential biosimilar to trastuzumab. *First Author: Ira A Jacobs, Pfizer Inc., New York, NY*

Background: Trastuzumab, a humanized recombinant monoclonal antibody, targets HER2 and is approved for treatment of HER2-overexpressing breast and gastric cancers. PF-05280014 is being developed as a potential biosimilar to trastuzumab. Similarity of PF-05280014 to trastuzumab sourced from the EU and US (trastuzumab-EU and -US) was assessed using structural and functional, nonclinical pharmacokinetic (PK) and tolerability, and clinical studies; the toxicity of PF-05280014 was also assessed. **Methods:** Structural similarity was determined by peptide mapping. Functional similarity was measured using an in vitro tumor cell growth inhibition assay. Comparative PK, tolerability, and anti-drug antibody (ADA) responses were evaluated in male CD-1 mice following a single dose; PK and toxicity of PF-05280014 alone were evaluated in CD-1 mice (both sexes) after 5 doses. In a phase I study, 105 healthy male volunteers received a single 6 mg/kg IV dose of PF-05280014, trastuzumab-EU, or trastuzumab-US. Drug concentration-time data were analysed by noncompartmental methods. PK similarity was considered demonstrated for a given test-to-reference comparison if the 90% CI was within 80.00%-125.00%. **Results:** Peptide mapping showed PF-05280014 was similar to trastuzumab-EU and trastuzumab-US. Dose response curves in the in vitro cell growth inhibition assay were superimposable. In vivo PK profiles were similar in mice and there were no toxicity findings for PF-05280014. In the phase I study, PK similarity was shown between PF-05280014 and trastuzumab-EU and trastuzumab-US, with 90% CI of C_{max}, AUC_T, and $AUC_{0-\infty}$ within 80.00%–125.00% for each pair-wise comparison. Adverse events were similar across groups; only 1 subject (trastuzumab-EU group) was ADA positive postdose. **Conclusions:** Evaluation of PF-05280014 thus far supports its development as a potential biosimilar to trastuzumab. An ongoing, phase III, randomized, double-blind clinical trial is comparing PF-05280014 + paclitaxel with trastuzumab-EU + paclitaxel for first-line treatment of patients with HER2+ metastatic breast cancer. A second phase III, randomized, double-blind trial evaluating PF-05280014 in the neoadjuvant setting for breast cancer is ongoing. Clinical trial information: NCT01603264, NCT02187744, and NCT01989676.

619 Poster Session (Board #109), Sat, 8:00 AM-11:30 AM

Association of tumor infiltrating lymphocytes (TILs) with pathologic response in baseline and post-brief exposure HER2+ breast cancer biopsies from BrUOG-211B. *First Author: Stefanie Avril, Department of Pathology, Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, Cleveland, OH*

Background: Increased TILs are prognostic and predictive of therapy response in HER2+ breast cancer (BC). BrUOG-211B, a phase II neoadjuvant trial included early stage HER2+ BC pts treated with single-agent trastuzumab (T) or nab-paclitaxel (N) followed by 6 cycles of T, N and carboplatin combination. This correlative study evaluated TILs in both baseline and post-brief exposure biopsies in association with pathologic response. **Methods:** Stromal (sTILs) and intratumoral (iTILs) TILs were evaluated on H&E sections at baseline (n = 46) and post-brief exposure (n = 43) and scored by deciles (mean of multiple core biopsies) according to the TILs Working Group guidelines. Pathologic response was assessed by residual cancer burden (RCB) index and grouped as responders (R = pCR/RCB 0 & RCB I) or non-responders (NR = RCB II & III). **Results:** Of 60 eligible pts 49 were available for analysis (49% R). Median iTILs were 10% [range 10-40%] and 20% [10-70%], median sTILs were 30% [10-100%] and 35% [20-100%] at baseline and post-brief exposure respectively. sTILs and iTILs were highly correlated (r = 0.8). Higher iTILs ($p = 0.02$) and sTILs ($p < 0.01$) were significantly associated with ER-neg status. Median sTILs were significantly higher in R vs NR at both baseline (35% vs 25%; $p = 0.02$) and post-brief exposure (50% vs 25%; $p < 0.01$). iTILs were not significantly associated with response. Overall, each 10% increase in baseline (OR 1.4; $p = 0.03$) and post-brief exposure sTILs (OR 1.5; $p = 0.01$) was associated with higher response, independent of ER-status. Lymphocyte predominant BC ($\geq$ 50% sTILs) was seen in 22% and not significantly associated with response (70% vs 47% R; $p = 0.2$). There was no significant change in iTILs or sTILs after brief-exposure to T, and a non-significant trend for increase after N. **Conclusions:** Levels of sTILs do not change significantly in HER2+ BC following brief-exposure to single-agent T or N based on morphologic assessment; however, both baseline and post-brief exposure sTILs significantly predict for pathologic response. Further analyses are needed to determine potential changes in lymphocytic subpopulations.

620 Poster Session (Board #110), Sat, 8:00 AM-11:30 AM

Mechanisms of acquired afatinib resistance in HER2-positive breast cancer cells. *First Author: Alexandra Canonici, Molecular Therapeutics for Cancer Ireland, National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland*

Background: Afatinib is a potent irreversible ErbB family tyrosine kinase inhibitor. We have previously shown that afatinib has anti-proliferative activity in a panel of 8 HER2 positive breast cancer cell lines (IC_{50}values 5-80 nM). The aim of this study was to investigate potential mechanisms by which HER2 positive breast cancer cells may develop acquired resistance to afatinib. **Methods:** SKBR3 cells were continuously exposed to 150 nM afatinib for 6 months. Proliferation assays were performed to determine the IC_{50}values for the parental (SKBR3-P) and the afatinib conditioned cells (SKBR3-A), and to assess sensitivity to lapatinib and neratinib. The molecular profiles of the resistant cells were examined by Reverse Phase Protein Array (RPPA). **Results:** The SKBR3-A cells were more resistant to afatinib than the SKBR3-P cells ($IC_{50} > 500$ nM vs $IC_{50} = 10.9 \pm 3.4$ nM). Furthermore, the resistant cells were cross-resistant to lapatinib ($IC_{50} = 1.0\ \mu M \pm 44.0$ nM vs $IC_{50} = 25.9 \pm 3.0$ nM)and neratinib ($IC_{50} = 287.2 \pm 14.0$ nM vs $IC_{50} < 10$ nM). Of the 73 analytes tested by RPPA, 14 were significantly different in the SKBR3-A cells compared to SKBR3-P ($p < 0.05$). The level of phosphorylation of 5 proteins, including HER3 (Y1289), Akt (S473 and T308) and ERK1/2 (T202/Y204) was decreased in the afatinib resistant cells. The level of 9 proteins, including Akt2, EGFR, p38 MAPK, Bcl2 and phospho-Src (Y416) was increased. **Conclusions:** RPPA analysis of afatinib resistant cells suggests that alternative signaling pathways or alterations in apoptosis may play a role in acquired afatinib resistance. Further investigation of the proteins identified may facilitate the development of novel therapeutic strategies to overcome resistance.

621 Poster Session (Board #111), Sat, 8:00 AM-11:30 AM

HER3, PI3K, and JAK2 pathway activation on reverse phase protein microarray (RPMA) in HER2-amplified residual disease (RD) refractory to preoperative chemotherapy plus trastuzumab (H), lapatinib (L), or both (HL). *First Author: Frankie Ann Holmes, Texas Oncology, US Oncology, Houston, TX*

Background: Pretreatment (preRx) biopsies of HER2-amplified breast cancers (BCs) that did not achieve pCR with preop chemotherapy plus H vs L vs HL had PI3K pathway activation with high p-FOXO levels on RPMA (Holmes BMC Res Notes 2013). The RD obtained at surgery in these pts was enriched for co-mutations in *PIK3CA* and *TP53* (Holmes ASCO 2014, 625). Here we describe activated phosphoproteins in the HER1/2/3 pathway in the RD from these pts who did not achieve pCR with preop H vs L vs HL and in RD with *PIK3CA/TP53* co-mutations. **Methods:** 15 pts' FFPE RD BCs were acceptable for RPMA at a CLIA-certified laboratory (Theranostics Health). Immunostaining with 14 antibodies was directed against HER1/2/3 pathway proteins. Spearman correlation (ρ, p value) and Mann-Whitney U tests (p value) were performed. **Results:** 7 of 15 RD BCs had *PIK3CA/TP53* co-mutations. In the RD with co-mutant *PIK3CA/TP53,* the strongest Pearson correlations (r) were between HER3 and p-HER1 and each with p-mTOR, p-S6K, p-JAK2 and p-STAT3 (all $r > 0.9$) In preop L pts ($n = 8$), the strongest correlations in the RD were p-HER2 and HER3, p-HER2 and p-mTOR, p-HER1 and p-STAT3 , p-HER3 and p-STAT3 (all $r > 0.8$), and p-4EBP1 and p-JAK2 ($r = 0.97$). In preop H and HL pts ($n = 7$), the RD showed strong interactions between HER3 and p-HER1, p-HER2 and p-HER3, HER3 and p-S6K, p-HER1 and p-S6K and p-HER3 and p-JAK2 (all $r > 0.9$). Comparing L- vs H/HL-treated RD, L-treated RD had higher levels of p-Akt ($p = 0.08$), p-S6 ($p = 0.08$) and p-MEK1/2 ($p = 0.02$). PreRx biopsies from pts who had RD all expressed high PI3K or low PTEN ser380 levels and showed strong interactions between p-HER1 and p-IGF1R, p-HER1, PI3K, and MAPK activation, LCB3 (autophagy) and PI3K, and Musashi (stem cell regulator) and β-catenin (all $\rho > 0.8$) (all $p < 0.00006$). **Conclusions:** PreRx biopsies from HER2+ pts who had RD following preop chemotherapy + H, L or HL showed activation of HER1, PI3K and MAPK pathways. Pts' refractory RD demonstrated HER3, PI3K and JAK2 pathway activation under the selective pressure of preop H, L or HL. *PIK3CA/TP53* co-mutated RD demonstrated signaling via p-HER1/HER3 to p-mTOR/p-S6K and p-JAK2/p-STAT3.

622 Poster Session (Board #112), Sat, 8:00 AM-11:30 AM

Final pre-specified analysis of the phase II trial of the AE37+GM-CSF vaccine in high risk breast cancer patients to prevent recurrence. *First Author: Julia M. Greene, San Antonio Military Medical Center, San Antonio, TX*

Background: We are conducting a Phase II clinical trial of the AE37+GM-CSF vaccine for the prevention of breast cancer recurrence in disease-free, node-positive or high-risk node negative patients (pts). AE37, is an MHC Class II epitope capable of stimulating CD4+ helper T cells. Here, we present the final pre-specified analysis of the primary endpoint of disease free survival (DFS) at one year from last enrolled pt. **Methods:** After completion of standard of care therapy, pts with any level of HER2 expression (IHC1-3+) were randomized to the vaccine group (VG) to receive 6 monthly intradermal inoculations of AE37+GM-CSF followed by 4 booster vaccinations every 6 months, or to receive GM-CSF alone on the same schedule as a control group(CG). Demographic, safety, immunologic, and clinical recurrence data are being collected. DFS is compared using Kaplan-Meir methods (5 yr DFS rates and logrank test) and Cox proportional hazards models (HR estimates with 95% CI). Continuous variables are compared using analysis of variance techniques and proportions compared with Fisher's exact test. **Results:** Of 301 enrolled pts, 154 were randomized to the VG and 147 to the CG. There were no differences in age, grade, receptor status, tumor size or nodal status between groups (all $p \geq 0.1$). Five-year DFS rates were not different with 82% (VG) vs 79.9% (CG), HR = 0.96, p = 0.9. There were trends in several subgroups. In HER2 1-2+ pts (77 VG vs 80 CG), 5 yr DFS was 79% (VG) vs 75% (CG), HR 0.76, p = 0.48. In ER/PR- pts (59 VG vs 56 CG), 5 yr DFS was 83% (VG) vs 77% (CG), HR 0.67, p = 0.36. In TNBC pts (25 VG vs 26 CG), 5 yr DFS was 67% (VG) vs 62% (CG), HR 0.65, p = 0.42. **Conclusions:** Overall, the final timed analysis of this phase II trial shows no statistical differences between treatment arms; however, it does identify particular pt populations where the vaccine may have efficacy. The ER/PR negative and triple negative pts appear to derive greatest benefit from AE37 vaccination with reductions in relative risk of recurrence of 33% and 35%, respectively. Further studies are required to confirm these findings and investigate the link between hormone receptor status and induction of clinically beneficial anti-tumor immunity by the AE37 vaccine. Clinical trial information: NCT00524277.

TPS623 Poster Session (Board #113a), Sat, 8:00 AM-11:30 AM

MIRACLE study (CBCSG016): A randomized phase II study of letrozole versus letrozole plus everolimus for hormone receptor positive premenopausal women with recurrent or metastatic breast cancer on goserelin treatment after progession on tamoxifen. *First Author: Binghe Xu, Cancer Hosp Chinese Academy of Medcl Sciences, Beijing, China*

Background: In premenopausal women with HR-positive advanced breast cancer, ovarian function suppression combined with aromatase inhibitors is a standard first-line choice of hormone treatment, especially patients progressed after tamoxifen. An emerging mechanism of endocrine resistance arose from aberrant signaling through the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) signaling pathway. The BOLERO-2 study showed that the addition of everolimus, an mTOR inhibitor, to exemestane significantly improved PFS in postmenopausal HR+/HER2- advanced breast cancer patients progressed on NSAIs. However, different from western countries, the majority (50-55%) of patients are premenopausal women in Asia, including China. The benefits of everolimus plus endocrine therapy in premenopausal women have not yet been well delineated. In addition, the feasibility of patients progressed on the endocrine continue to receive the same endocrine agent plus everolimus is unclear. **Methods:** Two hundred premenopausal HR+/HER2- advanced breast cancer women refractory to tamoxifen (progressed after previous treatment with tamoxifen for at least 6 months during adjuvant treatment and recurred during or within 24 months after the end of adjuvant treatment completion, or progressed during tamoxifen treatment for advanced disease) will be treated by goserelin and randomized at a 1:1 ratio to everolimus plus letrozole arm or letrozole alone arm, with stratification according to presence of visceral metastasis. Treatment will be continued until disease progression, the development of unacceptable toxicity, or withdrawl of consent. After progression in letrozole alone arm, the patients will be treated by everolimus plus letrozole. The primary endpoint is PFS, the secondary endpoints are ORR, CBR, OS and safety profile of each treatment arm. Clinical trial information: NCT02313051.

TPS624 Poster Session (Board #113b), Sat, 8:00 AM-11:30 AM

MONARCH 3: A randomized phase III study of anastrozole or letrozole plus abemaciclib, a CDK4/6 inhibitor, or placebo in first-line treatment of women with HR+, HER2-locoregionally recurrent or metastatic breast cancer (MBC). *First Author: Matthew P. Goetz, Mayo Clinic, Rochester, MN*

Background: Abemaciclib (LY2835219), a cell cycle inhibitor of CDK4/CDK6, demonstrated a clinically manageable safety profile and single-agent anti-tumor activity in MBC; all tumor responses were observed in hormone receptor positive (HR+) disease (Tolaney SM, Rosen LS, Beeram M, et al. San Antonio Breast Cancer Symposium, 2014, Abstract P5-19-13). Non-steroidal aromatase inhibitors (NSAI, letrozole and anastrazole), approved in the first-line setting for postmenopausal women with HR+ MBC, are being evaluated in combination with abemaciclib for safety and tolerability in a phase Ib study (NCT02057133) and in the present study (NCT02246621) to assess clinical efficacy. **Methods:** MONARCH 3 is a randomized, double-blind, placebo-controlled, phase III study of abemaciclib + NSAI vs placebo + NSAI in locoregionally recurrent (not amenable to curative treatment) breast cancer or MBC, with no prior systemic therapy in this disease setting. Patients will be randomized 2:1, and stratified by nature of disease (visceral vs bone-only metastases vs other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitor vs other vs none). Abemaciclib 150 mg or placebo will be given continuously PO every 12 hours until progression, along with anastrozole 1 mg or letrozole 2.5 mg once daily at the investigator's discretion, and assessments will occur every 28 days. Postmenopausal women with HR+, HER2- disease, a disease-free interval > 12 mos after completion of (neo)adjuvant endocrine therapy, ECOG PS ≤ 1, adequate organ function, and measurable disease or nonmeasurable bone-only disease (RECIST v1.1) are eligible. The primary endpoint is progression-free survival (PFS); a key secondary endpoint is overall survival (OS). The study has 80% power to detect an increase in PFS of approximately 40% (hazard ratio = 0.714). Assuming a median PFS of 10 mos in the control arm, this corresponds to a 4-mo increase in the median PFS. PFS and OS will be hierarchically tested to maintain an overall type I error rate of 2.5%. Enrollment began November 2014; planned enrollment is 450 patients. Clinical trial information: NCT02246621.

TPS625 **Poster Session (Board #114a), Sat, 8:00 AM-11:30 AM**

Phase III, randomized, double-blind, placebo-controlled study of ribociclib (LEE011) in combination with either tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with HR+, HER2– advanced breast cancer (aBC): MONALEESA-7. *First Author: Debu Tripathy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tamoxifen or NSAIs with ovarian function suppression are standard first-line endocrine therapy (ET) options for premenopausal women with HR+, HER2– aBC; however resistance eventually occurs. The cyclin D–cyclin dependent kinase (CDK)4/6–INK4–Rb pathway is frequently dysregulated in HR+ BC; preclinical data suggest that CDK4/6 inhibition may abrogate endocrine-resistant cell proliferation in BC subsets. Adding ribociclib, a highly selective CDK4/6 inhibitor, to standard ET may provide therapeutic benefit vs ET alone in HR+, HER2– aBC. **Methods:** A Ph III, randomized, double-blind, placebo-controlled study of continuous tamoxifen (20 mg once daily [QD]) or NSAI (letrozole [2.5 mg QD] or anastrozole [1 mg QD]), with subcutaneous goserelin implant (3.6 mg D1 of each 28-day cycle) and ribociclib (600 mg QD, D1–21 of each 28-day cycle) or matching placebo (MONALEESA-7; NCT02278120). Key inclusion criteria: pre- or perimenopausal women with ER+ and/or PR+, HER2– aBC; ECOG PS $\leq$ 1. Patients that have received $\leq$ 1 line of chemotherapy and/or $\leq$ 14 days of tamoxifen or NSAI (letrozole or anastrozole) with/without goserelin for aBC are eligible, but prior treatment with CDK4/6 inhibitors is prohibited. Patients are randomized (1:1) to receive either ribociclib (Arm 1) or placebo (Arm 2) in combination with tamoxifen + goserelin or NSAI + goserelin. Stratification is based on presence of lung and/or liver metastases; prior chemotherapy for aBC; endocrine combination partner (tamoxifen + goserelin vs NSAI + goserelin). Primary endpoint: PFS (RECIST 1.1); key secondary endpoint: overall survival. Other secondary endpoints include safety, tolerability, response rate, clinical benefit rate, time to response, duration of response. Tumor and blood samples will be collected for biomarker and PK assessments. Approximately 660 patients will be randomized. Global recruitment is ongoing. To our knowledge this is the first Ph III trial investigating a CDK4/6 inhibitor in only pre- or perimenopausal women with aBC. Clinical trial information: NCT02278120.

TPS626 **Poster Session (Board #114b), Sat, 8:00 AM-11:30 AM**

BELLE-3: A Phase III study of the pan-phosphatidylinositol 3-kinase (PI3K) inhibitor buparlisib (BKM120) with fulvestrant in postmenopausal women with HR+/HER2– locally advanced/metastatic breast cancer (BC) pretreated with aromatase inhibitors (AIs) and refractory to mTOR inhibitor (mTORi)-based treatment. *First Author: Angelo Di Leo, Ospedale Misericordia e Dolce, Prato, Italy*

Background: PI3K pathway activation is the most frequent alteration in BC and confers resistance to endocrine and mTORi treatment. The oral pan-PI3K inhibitor buparlisib has shown preliminary activity and a manageable safety profile in patients with HR+/HER2– BC in combination with letrozole or fulvestrant. Buparlisib + fulvestrant exhibits antitumor activity in mTORi-resistant ER+ xenograft models, suggesting that buparlisib may potentially bypass mTORi resistance by blocking upstream PI3K pathway signaling. **Methods:** BELLE-3 (NCT01633060) is a randomized, double-blind, placebo-controlled, Phase III study of fulvestrant $\pm$ buparlisib in postmenopausal women with HR+/HER2– locally advanced/metastatic BC. Key inclusion criteria: prior treatment with AIs, disease progression on or within 30 days of endocrine + mTORi therapy given as the last therapy before study entry, and $\leq$ 1 prior chemotherapy regimen for advanced disease. Approximately 420 women will be randomized (2:1) to receive buparlisib (100 mg/day) or placebo with fulvestrant (500 mg on C1D1, C1D15, D1 of subsequent cycles). Randomization will be stratified by visceral disease status. Tumor assessments will be performed at 6-weekly intervals until disease progression per RECIST v1.1. Primary endpoint: progression-free survival (PFS) per local investigator assessment (per RECIST v1.1). Key secondary endpoint: overall survival (OS). Other secondary endpoints: overall response rate (ORR), clinical benefit rate (CBR), safety, pharmacokinetics of buparlisib + fulvestrant, quality of life, and time to deterioration of ECOG performance status. Statistical methods: PFS and OS will be analyzed by Kaplan–Meier methods using a stratified log-rank test at 1-sided 2.5% level of significance. Hazard ratios will be estimated by stratified Cox regression with 2-sided 95% confidence intervals (CI). ORR and CBR will be calculated with exact 2-sided 95% CI. Recruitment onto the BELLE-3 study is ongoing. Clinical trial information: NCT01633060.

TPS627 **Poster Session (Board #115a), Sat, 8:00 AM-11:30 AM**

LORELEI: A phase II randomized, double-blind study of neoadjuvant letrozole plus taselisib (GDC-0032) versus letrozole plus placebo in postmenopausal women with ER-positive/HER2-negative, early-stage breast cancer. *First Author: Evandro De Azambuja, Jules Bordet Inst, Brussels, Belgium*

Background: Taselisib is an orally bioavailable, potent, selective inhibitor of Class I PI3-kinase (PI3K) alpha, gamma, and delta isoforms, with 30-fold less inhibition of the PI3K beta isoform relative to the alpha isoform showing enhanced activity against *PIK3CA* mutant cancer cell lines. Clinical data have demonstrated confirmed partial responses in patients with *PIK3CA* mutant breast cancer (BC) treated with single-agent taselisib. Enhanced antitumor activity has been noted when taselisib is combined with either letrozole or fulvestrant in preclinical and Phase Ib clinical studies. **Methods:** LORELEI is a Phase II, two-arm, randomized, double-blind, multicenter, study of neoadjuvant letrozole and taselisib versus letrozole and placebo in postmenopausal women with newly diagnosed ER+/HER2-, untreated, Stage I-III operable BC. Other eligibility criteria include tumor size ^{3} 2 cm by magnetic resonance imaging (MRI), ECOG PS 0-1, and evaluable tumor tissue for *PIK3CA* genotyping. Patients treated with anti-diabetic drugs are not eligible. Patients are randomized (1:1) to receive continuous letrozole (2.5 mg) with either taselisib (4 mg on a 5 days on/ 2 days off schedule) or placebo for 16 weeks, followed by surgery. Stratification is based on tumor size and nodal status. The co-primary endpoints are overall objective response rate (ORR) by centrally assessed breast MRI via modified RECIST criteria and pathologic complete response (pCR) rate in breast and axilla at time of surgery in all randomized patients and *PIK3CA* mutant patients. Secondary endpoints include ORR by centrally-assessed MRI and pCR rate in *PIK3CA* wild-type patients. The sample size was calculated to detect an absolute percentage increase of 24% in ORR with 80% power and an absolute percentage increase of 18% in pCR rate. An interim safety analysis will be conducted by an Independent Data Monitoring Committee. As of 28 Jan 2015, 15 of the 330 patients have been enrolled, and global enrollment is ongoing (clinicaltrials.gov NCT02273973). Clinical trial information: NCT02273973.

TPS628 **Poster Session (Board #115b), Sat, 8:00 AM-11:30 AM**

A phase 2, randomized, open-label study of lucitanib in patients with FGF aberrant metastatic breast cancer. *First Author: Maysa M. Abu-Khalaf, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Lucitanib is a potent, oral inhibitor of the tyrosine kinase activity of Fibroblast Growth Factor Receptors 1-3 (FGFR1-3), Vascular Endothelial Growth Factor Receptors 1-3 (VEGFR1-3) and Platelet-Derived Growth Factor Receptors α/β (PDGFRα/β). FGF aberrancy is a hallmark genomic alteration observed in up to 25% of patients with breast cancer and is defined by amplification of *FGFR1, and* or *11q* (containing FGF ligands 3, 4, 19, and CyclinD1). In a recent phase 1/2 clinical trial of lucitanib at daily doses of 5 to 20 mg, heavily pretreated patients with advanced breast cancer patients and FGF aberrancy experienced an objective response rate (ORR) of 50% and a median progression-free survival (PFS) of over 9 months (Soria et al, 2014). This compelling clinical activity has led to the initiation of a global clinical development program for lucitanib in breast cancer. **Methods:** The current phase 2 study was designed to evaluate the efficacy and safety of 2 different doses (10 and 15 mg) of lucitanib monotherapy in patients with metastatic breast cancer. Patient enrollment initiated in Sep 2014 at 32 sites in the United States. Key inclusion criteria are metastatic breast cancer, relapsed or refractory to approved standard treatment, ECOG 0 or 1, and normal organ function. Patients with uncontrolled hypertension are excluded. One hundred sixty patients with FGF-aberrant metastatic breast cancer, as determined by local testing, will be randomized 1:1 to the 10 and 15 mg daily dosing groups. An additional cohort of up to forty patients without evidence of FGF aberrancy will be enrolled to receive 15 mg of lucitanib daily in a Simon 2-stage design. FGF aberrancy will be confirmed centrally by fluorescent *in situ* hybridization testing. The primary objectives are PFS in patients who are FGF-aberrant and ORR in patients without evidence of FGF aberrancy. Secondary objectives are ORR (PFS for FGF non-aberrant cohort), duration of response, disease control rate, overall survival, patient-reported outcomes, safety, and population PK. Exploratory endpoints include analysis of tissue and blood-based biomarkers that may be predictive of response and primary resistance to treatment with lucitanib. Clinical trial information: NCT02202746.

TPS629 Poster Session (Board #116a), Sat, 8:00 AM-11:30 AM

SANDPIPER: Phase III study of the PI3-kinase (PI3K) inhibitor taselisib (GDC-0032) plus fulvestrant in patients (pts) with estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer (BC) enriched for pts with *PIK3CA* mutant tumors. *First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *PIK3CA* mutations are one of the most frequent genomic alterations in BC, being present in ~40% of ER-positive, HER2-negative breast tumors. *PIK3CA* mutations promote growth and proliferation of tumors and mediate resistance to endocrine therapies in BC. Taselisib is a potent and selective PI3K inhibitor of the alpha, gamma, and delta isoforms, with 30-fold less inhibition of the PI3K beta isoform relative to the alpha isoform. Taselisib has enhanced activity against *PIK3CA*-mutant BC cell lines, and clinical data include confirmed partial responses in pts with *PIK3CA*-mutant BC treated with taselisib either as a single agent or in combination with fulvestrant. SANDPIPER, a double-blind, placebo-controlled, randomized, phase III study, is designed to evaluate efficacy and safety of taselisib plus fulvestrant in postmenopausal pts with ER-positive, HER2-negative, *PIK3CA*-mutant locally advanced or metastatic BC. **Methods:** Pts with disease recurrence or progression during or after aromatase inhibitor treatment will be randomized 2:1 to receive either taselisib (4 mg qd) or placebo in combination with fulvestrant (500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each subsequent 28-day cycle). Randomization will be stratified by visceral disease, endocrine sensitivity, and geographical region. Pts with *PIK3CA*-mutant tumors (n = 480) will be randomized separately from pts with non-mutant tumors (n = 120); a valid *PIK3CA*-mutation result via central assessment is required prior to enrollment. Primary efficacy endpoint is investigator-assessed progression-free survival in pts with *PIK3CA*-mutant tumors. Other endpoints include overall survival, objective response rate, clinical benefit rate, duration of objective response, safety, pharmacokinetics, and patient-reported outcomes. Target enrollment is 600 pts from ~165 sites and ~23 countries. The study is active as of February 2015. NCT02340221. Clinical trial information: NCT02340221.

TPS630 Poster Session (Board #116b), Sat, 8:00 AM-11:30 AM

A phase II trial of neoadjuvant aromatase inhibitor therapy and the mTOR inhibitor everolimus in postmenopausal women with hormone receptor positive/HER2 negative breast cancer and a low/intermediate risk Oncotype Dx Recurrence Score (≤ 25). *First Author: Maysa M. Abu-Khalaf, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Breast cancer (BC) patients (pts) with low/intermediate Oncotype Dx recurrence scores (RS) ≤ 25 represent a large fraction of BC cases, and a substantial number of distant recurrences occur in this group despite their low to moderate risk and high sensitivity to endocrine therapy. These pts are also the least likely to be sensitive to or benefit from adjuvant chemotherapy. Anatomical risk factors (nodal status, tumor size) continue to define a higher risk group among these endocrine sensitive and molecularly low risk BC pts. The goal of this study is to assess tumor response to a combination of the mTOR inhibitor everolimus and an aromatase inhibitor (AI) in this patient population, utilizing the preoperative endocrine prognostic index (PEPI). Our hypothesis is that everolimus will improve the efficacy of AI in this setting. **Methods:** This is a phase II study evaluating the efficacy and safety of neoadjuvant AI and everolimus in postmenopausal pts with hormone receptor positive (HR+)/HER2 negative clinical stage II-III BC with low/intermediate risk RS (≤ 25). Patient enrollment initiated in November 2014 at the Yale Cancer Center/Smilow Cancer Hospital and Care Centers. The study will enroll up to 66 pts. Key inclusion criteria are ECOG 0-2, adequate organ function, a fasting cholesterol ≤ 300 mg/dl and triglycerides ≤ 2.5 x IULN. Pts who had prior surgical resection of their BC, uncontrolled diabetes mellitus (HbA1c > 7%), and a prior exposure to mTOR inhibitors are excluded. Eligible pts will receive daily AI therapy (anastrozole 1 mg, letrozole 2.5 mg or exemestane 25 mg) and everolimus 10 mg daily for a total of 26 weeks. The primary objective of the study is to determine the percent of postmenopausal pts with clinical stage II-III HR+ BC and a RS ≤ 25 who achieve a PEPI score of 0 following neoadjuvant AI and everolimus. The secondary objectives are to assess the tolerability and side effect profile and to identify biologic markers predictive of a pathologic response (PEPI 0) to neoadjuvant AI and everolimus in this patient population. Clinical trial information: NCT02236572.

TPS631 Poster Session (Board #117a), Sat, 8:00 AM-11:30 AM

Phase III study of Palbociclib in combination with Exemestane vs. Capecitabine, in Hormonal Receptor (HR) positive/HER2 negative Metastatic Breast Cancer (MBC) patients with Resistance to non-steroidal Aromatase inhibitors (NSAI): PEARL study (GEICAM/2013-02_CECOG/BC.1.3.006) *First Author: Miguel Martin, Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain*

Background: Endocrine therapy (ET) is the cornerstone treatment for HR–positive, HER2-negative breast cancer (BC) patients. AIs have become the treatment of choice in postmenopausal patients. The high efficacy with ET in these patients is partially undermined by the resistance developed by most of them over time. On early disease recurrence/progression to AIs, treatment options include other AI, estrogen-receptor antagonists or chemotherapy (being capecitabine one of the best options). Preclinical data suggest that ER+/HER2- BC are dependent on cyclin-dependent kinases 4/6 (CDK4/6) function; inhibition of this target may be effective in delaying/reverting endocrine resistance. Palbociclib is an oral novel CDK4/6 inhibitor that seems to be synergistic with ET in preclinical and clinical studies. **Methods:** Phase III, international (5 countries) study. Patients are randomized 1:1 to exemestane (25 mg daily) plus palbociclib (125 mg daily x3 weeks q4w) vs. capecitabine (1,250 mg/m^2 twice daily x2 weeks q3w). Postmenopausal patients with HR+/HER2- MBC are eligible if resistant to previous NSAI (letrozole or anastrozole) defined as: recurrence while on or within 12 months after adjuvant treatment or progression while on or within 1 month after the end of treatment for MBC. Previous chemotherapy is permitted either in the (neo)adjuvant setting and/or as first line for MBC. Patients must have *measurable disease according to RECIST 1.1 or lytic bone lesions in the absence of measurable disease*. The primary objective is Progression-Free Survival (PFS); secondary objectives are overall survival, response rate, clinical benefit rate, response duration, safety, quality of life and biomarker's defined changes. The study will recruit 348 patients to detect a difference of 2.75 months in the median PFS (from 6 to 8.75 months; hazard ratio = 0.686), with a power of 80% and a 5% two sided significance level. Recruitment started in March 2014 and 87 patients have been included so far (ClinTrials.gov reference NCT02028507). Clinical trial information: NCT0208507.

TPS632 Poster Session (Board #117b), Sat, 8:00 AM-11:30 AM

A phase I trial assessing the maximum tolerated dose (MTD) and pharmacokinetics of intrapleural bevacizumab after pleural puncture in breast cancer patients with symptomatic recurrent metastatic pleural effusion: The BEVAP trial. *First Author: Benoit Rousseau, Medical Oncology, Hopital Henri Mondor, INSERM U955, Creteil, France*

Background: Metastatic pleural effusion (MPE) is frequently observed in advanced cancer, especially in breast carcinoma. Invalidating symptoms may be associated with these effusions as shortness of breath, pain or asthenia, decreased quality of life and survival. Despite effective systemic treatment, many patient still experiment local discomfort and respiratory symptoms. Local management remains the cornerstone, not edged out by the development of new systemic agents. Surgical talc pleurodesis is indeed the main validated local management to prevent recurrence in patients with good performance status, but it is often not possible. Other techniques, as intrapleural (IP) catheter to facilitate puncture, are attractive in order to relieve symptoms, improve quality of life of patients and deliver IP agents. VEGF is a proangiogenic factor increasing endothelial permeability implicated in MPE. Bevacizumab is an anti-VEGF monoclonal antibody. Encouraging results were observed with high dose IV bevacizumab in MPE and with intraperitoneal bevacizumab in metastatic ascites. IP bevacizumab may improve puncture-free survival in breast cancer patients with symptomatic MPE. To address this question, we have designed a phase I trial aiming to determine the MTD and to investigate the pharmacokinetics of IP bevacizumab in breast cancer patients with recurrent and symptomatic MPE. **Methods:** The BEVAP trial is a 3+3 phase I trial with a single IP administration of bevacizumab and a 3 dose level escalation: 1 mg/kg, 3 mg/kg, 5 mg/kg. Main inclusion criteria are: ≥ 18 years old, PS ≤ 2, breast cancer related unilateral MPE requiring an IP catheter (at least 2 punctures in the last month), life expectancy > 2 months. Primary objective is to determine the MTD of IP bevacizumab to use for phase 2 trial. Secondary objectives include puncture-free survival, safety and bevacizumab pharmacokinetics. Up to 24 patients will be enrolled in the program. Further investigations will be performed only if IP bevacizumab proves to be safe with a median puncture-free survival > 30 days. Funded by French PHRC. Clinical trial information: NCT02250118.

TPS633 Poster Session (Board #118a), Sat, 8:00 AM-11:30 AM

A Phase II study of the safety and efficacy of alpelisib or buparlisib plus letrozole in neoadjuvant treatment of postmenopausal women with HR+/HER2–, *PIK3CA* mutant or wild-type breast cancer. *First Author: Ingrid A. Mayer, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: The PI3K/AKT/mTOR pathway is the most frequently activated signaling pathway in breast cancer (BC). *PIK3CA*-activating mutations are the most common genetic alteration observed in hormone receptor-positive (HR+) BC. In preclinical studies of HR+ BC, alpelisib (PI3Kα inhibitor) and buparlisib (pan-PI3K inhibitor) demonstrated significant antitumor effects both *in vitro* and *in vivo* when combined with hormone therapy. **Methods:** A Phase II, randomized, double-blind, placebo-controlled trial of alpelisib/placebo (300 mg once daily [QD]) or buparlisib/placebo (100 mg QD; intermittent regimen [5 days on; 2 days off]) plus letrozole (2.5 mg QD) for the neoadjuvant treatment of postmenopausal women with HR+/HER2– BC (NCT01923168). Key inclusion criteria are stage T1c–T3, any N, M0 operable BC; measurable disease; HR+/HER2– BC; known *PIK3CA*status (mutant vs wild-type [WT]) and Ki67 level; and Eastern Cooperative Oncology Group performance status ≤ 1. Key exclusion criteria are locally recurrent/metastatic disease and prior systemic therapy or radiotherapy for current BC. Patients (pts) will be assigned to 1 of 2 cohorts (*PIK3CA*mutant or WT) and randomized to 1 of 3 arms (letrozole + alpelisib, + buparlisib, or + placebo), stratified by Ki67 level ($< 14\%$ vs $\geq 14\%$) and lymph node status (positive vs negative). Pts will be treated for 24 weeks until surgery, disease progression, unacceptable toxicity, or study discontinuation for any other reason. The primary endpoint is pathologic complete response (pCR; ypT0/Tis, ypN0) at 24 weeks. The secondary endpoints are objective response rate (complete or partial; RECIST v1.1); safety and tolerability; rate of breast-conserving surgery; correlation between pCR and Ki67 changes from baseline to Day 15 and to surgery; response (central preoperative endocrine prognostic index score of 0); and pharmacokinetic profiles of alpelisib/buparlisib plus letrozole. For each cohort, pCR rates will be summarized by treatment arm with 90% confidence intervals. Proof of concept will be assessed. Global recruitment is ongoing, with planned enrollment of 360 pts. Clinical trial information: NCT01923168.

TPS634 Poster Session (Board #118b), Sat, 8:00 AM-11:30 AM

TARGIT-U.S.: A registry trial of targeted intraoperative radiation therapy following breast-conserving surgery. *First Author: Michael Alvarado, UC San Francisco, San Francisco, CA*

Background: The TARGIT-US trial is a pragmatic registry trial for women with clinically localized breast cancers who will undergo breast intraoperative radiation therapy (IORT) as sole radiation therapy post-breast conserving surgery. The TARGIT-A randomized trial of IORT versus whole breast radiation that preceded this trial has published equivalent local control outcomes for these patients (Vaidya et al. *Lancet* 2013). The objectives of this registry trial, therefore, are to establish eligibility criteria based on previously published trials and studies in order to allow women who meet these criteria to receive IORT on an IRB-approved protocol and to systematically collect and assess acute and long-term toxicity and outcomes in a larger cohort of patients. This will increase the general knowledge regarding this particular form of accelerated partial breast irradiation and allow further assessment of risk groups. **Methods:** Patients age 45 or older with small (< 3.5cm) ER+, Her2- tumors planning to undergo breast conserving surgery are eligible for this single-arm trial. All patients will receive a single dose IORT (20 Gy at the surface of the applicator) from the Zeiss Intrabeam device immediately after tumor excision. If high risk features are detected on final pathology (EIC, positive node, or invasive lobular histology) the patient will undergo additional EBRT (excluding boost). Patients enrolled in this trial will be followed for at least 5 years. The primary endpoint is in-breast local failure with secondary endpoints being toxicity and morbidity, relapse-free survival and overall survival. TARGIT-US is currently enrolling at 11 sites in the US with 11 additional sites opening in 2015. Target enrollment is 789 patients and as of January 2015, TARGIT-US has enrolled 120 patients. Clinical trial information: NCT01570998 Clinical trial information: NCT01570998.

TPS635 Poster Session (Board #119a), Sat, 8:00 AM-11:30 AM

I-SPY 2 low risk registry: An I-SPY 2 trial sub-study for women with clinically advanced, ER+, HER2- breast cancer and molecular good-prognosis gene signature. *First Author: Tufia C. Haddad, Mayo Clinic, Rochester, MN*

Background: With the increased utilization of molecular gene signatures, clinicians have identified a population of breast cancer patients that have clinically advanced disease associated with a low risk molecular profile. This discordance between tumor stage and molecular prognosis results in a dilemma for which consensus and evidence to guide treatment decisions are lacking. The I-SPY 2 Low Risk Registry (LRR) was therefore developed to capture the critical treatment data and clinicopathologic outcomes of these patients. A correlative biomarker study to characterize the biology and heterogeneity amongst these tumors is also planned. The goals of the LRR are to observe treatment patterns, determine tumor chemoendocrine sensitivity, and monitor clinical outcomes of these patients in order to inform the development of future studies aimed to optimize their management and outcomes. **Methods**: Patients with stage II or III breast cancer are recruited from the ongoing phase 2 neoadjuvant I-SPY 2 TRIAL. In this study, patients with Hormone Receptor-positive, HER2-negative disease are not eligible to be randomized to standard chemotherapy and a novel agent if their tumor has a 70-gene good-prognosis signature; instead, they are encouraged to enroll in the LRR. Treatment on the LRR is not pre-specified and at the discretion of the oncology team and patient. Data collection includes: screening MRI and tumor biospecimen, surgical pathology, menopause status, treatment administered, quality of life assessment, recurrence events and survival. Follow up for 15 years is planned. Biomarker analyses will include, but are not limited to, Ki-67, SET Index, GREB1, and HOXB13:IL17BR ratio. As of January 2015, 156 patients across 20 sites were eligible for the LRR, and 72 have enrolled to the Low Risk Registry. Clinical trial information: NCT01042379.

TPS636 Poster Session (Board #119b), Sat, 8:00 AM-11:30 AM

E2112: Randomized phase III trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor-positive advanced breast cancer. *First Author: Roisin M. Connolly, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: A potential mechanism of resistance to endocrine therapy in breast cancer involves changes in gene expression secondary to epigenetic modifications, which might be modulated with the use of histone deacetylase (HDAC) inhibitors such as entinostat. ENCORE 301, a phase II study evaluating the addition of entinostat to the steroidal aromatase inhibitor (AI) exemestane in patients with hormone receptor (HR)-positive advanced breast cancer who had experienced disease progression after a non-steroidal AI (NSAI), showed a significant improvement in progression-free survival (PFS), and overall survival (OS). Entinostat has been designated a Breakthrough Therapy by the FDA. **Methods:** E2112 is a multicenter randomized double-blind placebo-controlled phase III study (NCT02115282) enrolling patients with advanced HR-positive, HER2-negative breast cancer with prior disease progression on a NSAI ($n = 600$). Patients receive exemestane 25mg po daily and entinostat/placebo 5mg po every week. Eligibility: Postmenopausal women and men, ECOG 0-1, locally advanced/metastatic invasive adenocarcinoma of the breast: ER/PR-positive, HER2-negative, measurable or non-measurable (20% cap) disease. Disease progression after NSAI use in the metastatic setting OR relapse while on or within ≤ 12 months of end of adjuvant NSAI therapy. Statistics: Both PFS (central review) and OS are primary endpoints, and the study is designed to show an improvement in either PFS or OS.Secondary endpoints include:Safety and tolerability, objective response rate, changes in lysine acetylation status in peripheral blood mononuclear cells, patient-reported symptom burden and treatment toxicities, adherence. One-sided type 1 error 0.025 split between two hypotheses tests: 0.001 for PFS test and 0.024 for OS. PFS is tested in the first 360 pts, 88.5% power to detect 42% reduction in the hazard of PFS failure (median PFS 4.1 to 7.1 months); OS is tested in all 600 pts, 80% power to detect 25% reduction in the hazard of death (median OS 22 to 29.3 months). E2112 was activated in March 2014 and accrual is anticipated to complete in 40 months. Clinical trial information: NCT02115282.

TPS637 Poster Session (Board #120a), Sat, 8:00 AM-11:30 AM

Phase III randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy +/- one year of everolimus in patients with high-risk, hormone receptor (HR) positive and HER2-negative breast cancer (BC): SWOG/NRG/Alliance S1207 (NCT01674140). *First Author: Mariana Chavez-Mac Gregor, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Abnormalities of the PI3kinase/AKT/mTOR signaling network are common in BC. This pathway is associated with resistance to endocrine therapies among HR+ tumors. Everolimus, an mTOR-inhibitor, increases the biological activity of endocrine therapy. S1207 evaluates the role of everolimus in combination with endocrine therapy in the adjuvant setting. **Methods:** Specific aims/ design: Randomized phase III double-blinded, placebo-controlled trial. Primary objective is to assess whether the addition of everolimus to standard adjuvant endocrine therapy improves invasive disease-free survival (DFS) among patients with high risk, HR+ BC. Secondary objectives include overall survival, distant recurrence-free survival, safety, adherence and QoL. Patients are randomized to receive standard adjuvant endocrine therapy in combination with one year of everolimus (10 mg PO daily) or placebo. Submission of tissue specimens/ blood samples is required for translational studies Eligibility criteria: Patients with histologically confirmed HER2-negative and HR+ invasive BC treated with surgery, adjuvant chemotherapy and radiation therapy (if indicated) are eligible if they have: node-negative disease and tumors >2cm and a recurrence score (RS) >25; 1-3 positive nodes and RS >25 or grade 3 in the absence of RS; >4 positive lymph nodes regardless of RS. Patients >1 positive lymph node after completing neoadjuvant chemotherapy are eligible. Statistics/Target accrual:Parallel randomization design with equal allocation to the two treatment groups, the study will randomize 3,500 patients. All analyses are intent-to-treat with the primary analysis conducted 3 years after the last patient is randomized. The study has 90% power (with 2-sided α=0.05) to detect an effective hazard ratio of 0.75 for everolimus versus placebo, corresponding to a gain in DFS of approximately 4.3% at 5 years. All patients will be followed for 10 years. Support: NIH/NCI NCTN Grants CA180888, 180819, 180868, 180821,180822 189867, and in part by Novartis Clinical trial information: NCT01674140.

TPS638 Poster Session (Board #120b), Sat, 8:00 AM-11:30 AM

A phase I study of RAD1901, an oral selective estrogen receptor degrader, in ER–positive, HER2–negative, postmenopausal advanced breast cancer patients. *First Author: Wael A. Harb, Horizon Oncology Center, Lafayette, IN*

Background: RAD1901 is a novel, non-steroidal, orally bioavailable selective estrogen receptor degrader (SERD). Preclinical studies demonstrated a favorable tissue selectivity profile, dose dependent ER degradation and potent inhibition of in vitro breast cancer cell proliferation. In an MCF7 xenograft model, significant tumor regression was consistently observed with RAD1901 treatment, compared to Tamoxifen or Fulvestrant. A phase I clinical study conducted in healthy postmenopausal female volunteers evaluated once daily doses up to 1000mg/day for 7 days. All dose levels were tolerated and pharmacokinetic analysis demonstrated good plasma exposure with dose proportional increases. 18F-estradiol positron emission tomography (FES-PET) was performed at baseline and after 6 days of treatment with RAD1901, to assess estrogen receptor engagement. Standardized uptake values (SUV) pre- and post-treatment demonstrated a complete attenuation of FES-PET signal in ER-rich tissues such as the uterus at both the 200mg/day and 500mg/day dose levels. Based on these preclinical and clinical results, RAD1901 is currently being investigated in a phase I study for the treatment of hormone driven and hormone resistant metastatic breast cancers. **Methods:** RAD1901-005 is phase I study consisting of two phases: a dose escalation phase and a safety expansion phase. The dose escalation will follow a 3+3 design to establish the maximum tolerated dose (MTD), the primary objective of the study. Once the MTD has been established, the expansion will evaluate the safety, tolerability and preliminary efficacy of the recommended phase II dose (RP2D), the secondary objectives of the study. RAD1901 will be administered orally on a continuous once daily schedule until disease progression, unacceptable toxicity or patient's choice. Key inclusion criteria include post-menopausal women aged 18 years or older, with advanced ER–positive, HER2–negative breast cancer, who have received $\leq$ 2 prior chemotherapy regimens in the metastatic setting and > 6 months of prior endocrine therapy. Patient enrollment started in early 2015. Clinical trial information: NCT02338349.

TPS639 Poster Session (Board #121a), Sat, 8:00 AM-11:30 AM

Brain Metastases in Breast Cancer Network Germany (BMBC; GBG 79): Multicentric, retro- and prospective collection of patient data and biomaterial from patients with brain metastases. *First Author: Volkmar Mueller, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: The incidence of brain metastases in breast cancer patients is rising and has become a mayor clinical challenge in the last years. So far, limited therapeutic options and insights into the biology of brain metastases exist. Most reports include patients with brain metastases from different tumor entities. Few studies so far analyzed exclusively patient data and tumor samples from brain metastases of breast cancer patients. Therefore, an open, multicentric registry and biobank should be helpful for analysis of a large number of breast cancer patients with brain metastases. Therefore we initiated the Brain Metastases in Breast Cancer Network Germany (BMBC; GBG79) **Methods:** Registration of patient data is allowed retrospectively as well as prospectively. To enable an easy multicentric access, an internet-based database was chosen ("MedCodes" of the German Breast Group). Captured data include incidence, number and localization of brain metastases, histopathologic characteristics, imaging methods applied, outcome and therapy modalities. Tissue of brain metastases and primary tumors will be collected for translational research projects. Planned analyses include treatment patterns in Germany, patient outcome, as well as validation of prognostic scoring systems in a multicenter setting and in the context of new targeted therapies. Planned translational research projects include the impact of glycosylation, resistance mechanisms against HER2-targeted therapies, the role of the blood brain barrier, evaluation of markers of radioresistance and specific genomic alterations associated with brain tropism of breast cancer cells. The accrual target is 1000 patients in the database and 400 tissues of brain metastases from participating German centers. The study was opened for documentation in 2014 with 70 participating centers and more than 600 patients with started documentation as of February 2015.

TPS640 Poster Session (Board #121b), Sat, 8:00 AM-11:30 AM

A phase 2 single-arm study to assess clinical activity, efficacy and safety of enzalutamide (ENZA) with trastuzumab in HER2+ AR+ metastatic or locally advanced breast cancer. *First Author: Maureen E. Trudeau, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) expression have been found to correlate, with one series of breast carcinomas demonstrating AR expression in 77% of HER2+ tumors (Barton V et al. Mol Cancer Res. 2013;11:abstr A047). In vitro, ENZA inhibits proliferation of AR+/HER2+ cell lines and enhances the activity of trastuzumab. ENZA also inhibits proliferation of trastuzumab-resistant HER2+ cells (Micello D et al. Virchows Arch. 2010;457:467-476). **Methods:** Women with metastatic or locally advanced HER2+/ER-/PR- and AR+ (local or central) breast cancer will be enrolled in a phase 2 single-arm study (NCT02091960). Patients will receive daily ENZA (160 mg) continuously and trastuzumab (6 mg/kg) administered every 21 days until disease progression. Patients must have measurable disease per RECIST v1.1 and have received 1–4 prior lines of anti-HER2 therapy in the advanced/metastatic setting. Brain imaging is required to exclude patients with CNS metastases. Patients with a seizure history are excluded. The primary endpoint is clinical benefit rate (CBR), where benefit is defined as complete or partial response or stable disease $\geq$ 24 weeks according to RECIST v1.1 criteria. Additional endpoints include safety, tolerability, and the relationship between AR expression and ENZA activity. If the CBR is $\geq$ 3 in 21 evaluable patients, the sample size will increase to 66 patients. The primary endpoint will be analyzed in patients with centrally confirmed AR expression ($\geq$ 10% nuclear staining by immunohistochemistry), who have received at least 1 dose of ENZA and have $\geq$ 1 postbaseline tumor assessment. The null hypothesis, that the true CBR is 10%, will be tested against a 1-sided alternative. This Simon's 2-stage design yields 90% power when the true response rate is 25% with a 1-sided type 1 error rate of 5%. As of the date of abstract submission, 5 patients have been enrolled; enrollment is expected to continue through 2016. Clinical trial information: NCT02091960.

TPS641 Poster Session (Board #122a), Sat, 8:00 AM-11:30 AM

HERMIONE: A Phase 2, randomized, open label trial comparing MM-302 plus trastuzumab with chemotherapy of physician's choice plus trastuzumab, in anthracycline naive HER2-positive, locally advanced/metastatic breast cancer patients previously treated with pertuzumab and ado-trastuzumab emtansine (T-DM1). *First Author: Kathy Miller, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Although HER2-targeted therapies such as pertuzumab and T-DM1 have improved patient outcomes, treatment resistance typically occurs. MM-302 is a HER2-targeted liposomal doxorubicin in development by Merrimack Pharmaceuticals. In a Phase 1 study, patients with HER2-positive metastatic breast cancer (MBC) were treated with MM-302 alone and in combination with trastuzumab with or without cyclophosphamide. MM-302 had an acceptable safety profile and promising efficacy was observed in patients not previously exposed to an anthracycline. **Methods:** *Trial design:* HERMIONE (NCT02213744) is a randomized Phase 2, two-arm, open-label trial designed to evaluate if MM-302 can address an unmet medical need in patients with anthracycline naïve, trastuzumab-, pertuzumab- and T-DM1-pretreated HER2-positive locally advanced breast cancer (LABC)/MBC. Patients are randomized 1:1 to receive MM-302 (30mg/m^2, Q3W) plus trastuzumab (6mg/kg, Q3W) or chemotherapy of physician's choice (vinorelbine, capecitabine, or gemcitabine) plus trastuzumab (6mg/kg, Q3W). *Eligibility criteria:* Centrally confirmed HER2-positive LABC/MBC, no prior anthracycline exposure, prior trastuzumab in any setting, prior pertuzumab and T-DM1 in the LABC/MBC setting, unlimited prior lines of therapy, ECOG 0-1 and LVEF $\geq$50%. CNS metastases are permitted if stable and without symptoms or steroids for 4 weeks. *Specific aims:* The primary endpoint is independently assessed progression free survival (PFS). Secondary endpoints include investigator assessed PFS, overall survival, response rate, safety and patient related outcomes. *Statistics:* 250 patients will be enrolled to observe 191 PFS events for 90% power to detect a Hazard Ratio of 0.625. The MM-302 arm will be compared to the control arm on the primary endpoint of PFS using a stratified log-rank test at one-sided 0.025 level. *Accrual status:* Recruitment began in July 2014 and is expected to be complete in late 2016. Sites will be open in the US, Canada and Western Europe. Clinical trial information: NCT02213744.

TPS642 Poster Session (Board #122b), Sat, 8:00 AM-11:30 AM

PATRICIA: A phase II study of palbociclib and trastuzumab with or without letrozole in previously treated, postmenopausal patients with HER2-positive metastatic breast cancer. *First Author: Patricia Villagrasa, SOLTI Breast Cancer Research Group, Barcelona, Spain*

Background: Despite the great efficacy of anti HER2-agents, HER2+ metastatic breast cancer remains incurable and in need of additional options. Palbociclib, a CDK4/6 inhibitor, has demonstrated unprecedented clinical activity in HER2-/ER+ disease. Its potential in HER2+ disease, however, remains to be explored. Preclinical evidence suggests a potentially complementary role with trastuzumab based on their effects on the cell cycle. Our hypothesis is that the addition of palbociclib to trastuzumab-based therapy could offer clinical benefit in this population. Moreover, given that the expression of ER dictates two biologically different HER2+ subgroups, we will explore this activity accordingly, in addition to endocrine therapy. **Methods:** This is an exploratory, prospective, open-label, multicenter trial of palbociclib plus trastuzumab. Patients must have histologically confirmed HER2+ adenocarcinoma of the breast and have received 2-4 lines of anti-HER2-containing regimens for their advanced disease. The study is based on a Simon 2-stage design comprising three cohorts: cohort A includes ER- patients and cohorts B1 and B2, ER+ patients. All patients receive trastuzumab with an 8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks, and 200 mg daily palbociclib for 2 weeks, with 1 week off. Additionally, patients in cohort B2 receive 2.5 mg daily letrozole. A 2-cycle safety run-in with the first 6 patients of each regimen will be performed. The primary objective is to assess clinical efficacy measured as progression-free survival rate at 6 months (PFS6). Assuming an increase of at least 20% in PFS6 by the addition of palbociclib +/- letrozole to trastuzumab, PFS6 should be $\geq$ 50% for a cohort to be successful, and proceed to stage 2. According to this, it will be necessary to include 15 patients in each cohort in stage 1. In stage 2, each cohort may continue for up to 46 patients. A treatment regimen will be considered efficacious if $\geq$ 18 patients are progression-free at 6 months, with an 80% power and α = 0.05. Based on this, a maximum of 138 patients may be included. Translational research searching for predictive biomarkers will be implemented. Clinical trial information: 2014-005006-38.

1000 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

TITAN: Phase III study of doxorubicin/cyclophosphamide (AC) followed by ixabepilone (Ixa) or paclitaxel (Pac) in early-stage, triple-negative breast cancer (TNBC). *First Author: Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: Ixa is a microtubule stabilizer able to target mechanisms conferring taxane resistance including high b tubulin III expression, seen in TNBC. Here, we present preliminary results of a phase III study of AC followed by Ixa or Pac in patients (pts) with early stage TNBC. **Methods:** Patients with resected TNBC (ER and PR < 10% by local IHC, HER2 IHC 0-1+ or FISH/CISH negative) and no evidence of metastatic disease were eligible. Pts were randomized 1:1 to AC (60/600mg/m^2) q3wks x4 followed by either Ixa (40mg/m^2 q 3wks x4) (AC/Ixa) or weekly Pac (80mg/m^{2}x12 weeks) (AC/Pac). Growth factor use was allowed per MD discretion. Following phase II neoadjuvant results that demonstrated no AC/Ixa efficacy advantage compared to AC/Pac (including in tumors with high b III tubulin levels), the sample size of this study was revised to 590 patients to detect a 30% reduction in risk of recurrence with AC/Ixa. **Results:** Between December 2008 and March 2011, 614 pts (median age 54, 18% African American, 32% lymph node positive, 50% T2) were randomized (AC/Ixa, 306; AC/Pac, 308). 84% AC/Ixa and 77% AC/Pac pts completed protocol treatment (tx). 23 (8%) Ixa pts and 47 (16%) Pac pts discontinued tx due to toxicity. Dose reductions/dose delays occurred in 78 (26%)/121 (39%) Ixa pts and in 99 (33%)/158 (52%) Pac pts. Neuropathy was the major reason for dose reduction and tx discontinuation. G3/4 neutropenia rates were low at 11% with Ixa vs 6% with Pac, accompanied by fever in only 4 patients. At a median follow up of 46 mo, 75 pts have relapsed (AC/Ixa, 37; AC/Pac, 38). Median time from initial diagnosis to relapse was 20.8 mo. The 3 year disease-free survival of the Ixa arm was 88% (95% CI: 0.84, 0.91) and 89% (95% CI:0.85, 0.92) for the Pac arm. The hazard ratio (Ixa arm vs Pac arm) was 0.99 (95% CI: 0.63, 1.56, p = 0.98). 51 pts (AC/Ixa, 28; AC/Pac, 23) have died, 42 due to disease. **Conclusions:** AC with Ixa or Pac performed well in this early stage TNBC population with no difference in efficacy evident. Pts receiving AC/Pac had higher rates of neuropathy and more dose modifications. Clinical trial information: NCT00789581.

1001 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Phase III trial of etirinotecan pegol (EP) versus Treatment of Physician's Choice (TPC) in patients (pts) with advanced breast cancer (aBC) whose disease has progressed following anthracycline (A), taxane (T) and capecitabine (C): The BEACON study. *First Author: Edith A. Perez, Mayo Clinic, Jacksonville, FL*

Background: EP is the first long-acting topoisomerase 1 inhibitor providing sustained levels of SN38. In Phase II, EP demonstrated a 29% ORR following a median of 2 prior regimens for aBC. BEACON study (NCT01492101) randomized (1:1) pts with aBC and progressive disease following A,T and C to EP (145 mg/m^{2}q3w over 90 minutes) or TPC (any of 7 cytotoxics). **Methods**: Eligible pts had any ER/HER2 and ECOG 0-1; stable brain metastases were allowed. 852 pts enrolled over 20 months and reached target for events in Dec2014. The choice of TPC: eribulin 40%, vinorelbine 23%, gemcitabine 18%, taxane 15%, ixabepilone 4%. Primary efficacy endpoint was overall survival (OS) by 2-sided log-rank test stratified by region, prior eribulin and receptor status; the study had 90% power to detect a target Hazard Ratio (HR) of 0.77. Circulating tumor cells (CTCs) were isolated in ~80% of pts and analyzed for target-specific pharmacodynamic biomarkers. This is the first presentation of these data. **Results**: EP provided a 2.1 month improvement in median OS over TPC (12.4 vs 10.3 months; HR 0.87, p = 0.08). In a pre-specified subgroup of 67 pts with brain metastases, EP showed an improvement of 5.2 months in median OS (10.0 vs 4.8 months; HR 0.51, p < 0.01); the proportion of pts with brain metastases alive at 12-mo survival was higher with EP (44.4% vs 19.4%). Similarly, in pts with liver metastases (n = 456) median OS improved with EP (10.9 vs 8.3 months; HR 0.73, p = 0.002). Grade (G) ≥ 3 AEs were lower with EP (48%) than TPC (63%). Common G ≥ 3 AE with EP: diarrhea (9.6%), neutropenia (9.6%), anemia (4.7%) and fatigue (4.5%); TPC: neutropenia (30.5%), anemia (4.7%) and dyspnea (4.4%). Severe neuropathy: 3.7% of pts (TPC) vs 0.5% (EP). Alopecia was less with EP (10% vs 23%). Data on efficacy in CTC biomarker defined sub-groups (TOP1, TOP2) will be presented. **Conclusions**: EP provided a clinically meaningful benefit to pts with late-stage aBC, although this did not reach statistical significance. In pts with brain metastases, median OS doubled; improved survival was also seen in other pt subsets. Toxicity with EP was less than with TPC. Clinical trial information: NCT01492101.

1002 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Low-dose oral cyclophosphamide-methotrexate maintenance (CMM) for receptor-negative early breast cancer (BC). *First Author: Marco Colleoni, European Institute of Oncology, Milano, MI, Italy*

Background: IBCSG Trial 22-00 was designed to test the efficacy of the CMM regimen, hypothesized to have anti-angiogenic activity, administered following standard chemotherapy in patients (pts) whose tumors are hormone receptor negative. **Methods:** 1,086 women (ITT 1081) with hormone receptor-negative (< 10% positive cells by IHC) early BC, any nodal and HER-2 status were randomized to CMM (C, cyclophosphamide 50 mg/day orally continuously and M, methotrexate 2.5 mg twice/day orally days 1 and 2 of every week for 1 year) vs no further treatment (no CMM). 814 (75%) had triple-negative (TN) BC and 350 (43%) of them had node positive (N+) disease. The primary end point was disease free survival (DFS), and 307 DFS events were required for 80% power. **Results**: At 82.6 months' median follow-up, 271 DFS events had been observed. Overall, 71 (13%) of 527 pts randomized to CMM did not receive CMM therapy and only 177 (39%) of the 456 pts who started received 75% or more of the scheduled doses. Nevertheless, pts assigned to CMM had a reduced risk of a DFS event compared with no CMM, which was not statistically significant (p = 0.14; table). The magnitude of effect appeared to be greater for those with TNBC, especially for those with N+ disease. Multivariable allowance for baseline prognostic factors suggested a greater treatment effect within those with TN and N+ BC. A total of 64 pts, 13.5% of those receiving at least one dose of CMM, had a grade 3 or 4 treatment-related AE. Elevated SGPT was most frequently reported, followed by leukopenia. **Conclusions**: Adding CMM to adjuvant chemotherapy showed a non-significant 16% reduction in risk of a DFS event in the overall population of hormone receptor-negative early BC. Women with TN disease at higher risk of recurrence, for whom no maintenance regimen is currently available, had a greater benefit. Clinical trial information: NCT00022516.

Group	Treatment	No. of Patients	DFS events	5-year DFS %	Univariate HR (95% CI)	Multivariable HR (95% CI)
All pts	CMM	542	124	78.1%	0.84 (0.66,1.06)	0.82 (0.65,1.05)
	No CMM	539	147	74.7%		
TN	CMM	408	89	78.7%	0.80 (0.60,1.06)	0.79 (0.60,1.04)
	No CMM	406	110	74.6%		
TN & N+	CMM	175	48	71.9%	0.71 (0.49,1.03)	0.68 (0.47,0.99)
	No CMM	175	64	64.2%		

1003 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC). *First Author: Tiffany A. Traina, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The AR may be a therapeutic target for pts with androgen-driven TNBC. ENZA, a potent AR inhibitor, is approved in men with metastatic castration-resistant prostate cancer (mCRPC) and improves median PFS compared to bicalutamide in men with mCRPC (15.7 vs 5.8 mos; HR 0.44; p<0.0001). **Methods:** MDV3100-11 was an open-label, Simon 2-stage study evaluating single agent ENZA in advanced AR+ TNBC (AR >0% by IHC; NCT01889238). Pts could be prescreened for AR, and have non-measurable bone disease and unlimited prior regimens; CNS metastases or seizure history were exclusionary. The primary endpoint was clinical benefit (CR, PR or SD) at 16 wks (CBR16) in 'Evaluable' pts defined as having both AR IHC ≥10% *and* a response assessment. CBR24, PFS, response rate, and safety were assessed. An androgen-driven gene signature (Dx) was created from gene profiling and outcomes were assessed accordingly. Stage 2 enrolled if CBR16 was ≥3 of 26 Evaluable pts; H_0 was rejected if CBR16 was ≥9 in 62 yielding 85% power at 5% significance to test against a 1-sided alternative (CBR16 ≥20%). **Results:** As of 16 JAN 2015, 404 samples were tested for AR IHC: 79% had AR >0%; 55% had AR ≥10%. 118 pts were treated with ENZA; 43 pts were not Evaluable (29 AR <10%; 14 AR ≥10% but no response assessment). Key outcomes in the defined populations are below as shown in the Table. Over 50% received ENZA as 1st or 2nd line; mPFS in these pts was 32 wks in Dx+ and 9 wks in Dx-. Two CRs and 5 PRs have been observed. Related AEs in ≥10% of 118 pts were fatigue (34%), nausea (25%), decreased appetite (13%), diarrhea and hot flush (10%). Fatigue (5%) was the only AE ≥ Grade 3 in ≥5%. **Conclusions:** This is the largest study of an AR inhibitor in TNBC. IHC results suggest AR prevalence is higher than previously reported. 47% of pts had an androgen-related gene signature (Dx+) and clinical outcomes appeared superior in this group. AEs from ENZA were consistent with its known profile. ENZA may represent a novel therapeutic option in pts with TNBC who would otherwise receive cytotoxic chemotherapy. Clinical trial information: NCT01889238.

	Evaluable n=75	Dx+ n=56	Dx- n=62
CBR16, % (95% CI)	35 (24-46)	39 (27-53)	11 (5-21)
CBR24, % (95% CI)	29 (20-41)	36 (24-49)	7 (2-16)
mPFS, wks (95% CI)	14 (8-19)	16 (10-32)	8 (7-13)

1004 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Prediction of pathological complete response (pCR) by Homologous Recombination Deficiency (HRD) after carboplatin-containing neoadjuvant chemotherapy in patients with TNBC: Results from GeparSixto. *First Author: Gunter Von Minckwitz, German Breast Group, Neu-Isenburg, Germany*

Background: We previously showed that adding carboplatin to paclitaxel/liposomal doxorubicin (PM) can improve pCR rates in patients with TNBC at the cost of added toxicity (von Minckwitz, Lancet Oncology 2014). In this study we examine whether HRD, together with BRCA mutation in the primary tumor (tmBRCA), can predict pCR (ypT0/is ypN0). **Methods:** In GeparSixto, patients were randomized to receive PM or PM plus carboplatin stratified by subtype (TNBC, HER2+/HR-, HER2+/HR+) and Ki67 level. FFPE tumor samples with sufficient DNA were available in 193 (61.3%) out of 315 participants of GeparSixto with TNBC. TmBRCA and HRD scores (defined as the unweighted sum of LOH (Abkevich, 2012), TAI (Birkbak, 2012), and LST (Popova, 2012) scores) were determined. HR deficiency was defined as either a high HRD score (predefined with ≥ 42) or tmBRCA (HRD Positive). **Results:** Patients included in this analysis did not differ clinically from all study patients with TNBC in GeparSixto, except for Ki67 levels which were higher for patients included in the current analysis. HR deficiency was found in 136 (70.5%) tumors; 82 (60.3%) of them showed high HRD score without tmBRCA. HR deficient tumors were more likely to respond with a pCR (55.9%) than HR non-deficient tumors (29.8%; $p = 0.001$). Adding carboplatin to PM increased the pCR rate from 45.2% to 64.9% in HR deficient tumors ($p = 0.025$). The response rate in HR non-deficient patients was 20% and 40.7% in the PM vs PM plus carboplatin respectively and was not significant ($p = 0.146$). In patients with non-tmBRCA a high HRD score was associated with a higher pCR rate (49.4%) than a low HRD score (30.9%; $p = 0.050$) irrespective of the use of carboplatin. **Conclusions:** HR deficiency in TNBC as well as HRD score in non-tmBRCA TNBC are predictors of response to neoadjuvant anthracycline and taxane containing chemotherapy irrespective of the use of carboplatin with the highest response rate being in the HR-deficient group treated with carboplatin (pCR rate of 64.9%). HR deficiency may be used to identify patients likely to have a high response to DNA-damaging agents. Clinical trial information: NCT01426880.

1005 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Prevalence and predictors of androgen receptor (AR) and programmed death-ligand 1 (PD-L1) expression in *BRCA1*-associated and sporadic triple negative breast cancer (TNBC). *First Author: Nadine M. Tung, Beth Israel Deaconess Medical Center, Boston, MA*

Background: TNBC comprise 15% of breast cancers and are more common in women with germline *BRCA1* mutations. However, considerable heterogeneity exists among TNBC. While most have basal cell gene expression signatures, others resemble luminal tumors with expression of AR-related genes. In addition, a subset of TNBC expresses the immunoinhibitory protein PD-L1. Given the availability of clinical trials evaluating AR-targeted and immune therapies in TNBC, determining predictors of AR and PD-L1 expression and whether expression differs by *BRCA1* status is of interest. **Methods:** We studied 197 TNBC: 78 (39.6%) from women with germline *BRCA1* mutations (*BRCA1*+) and 119 (60.4%) from women without a *BRCA1* mutation (sporadic). Histologic type, grade, lymphovascular invasion (LVI), and lymphocytic infiltrates (LI) were evaluated on H and E sections. Tissue microarrays were constructed (three 0.6mm cores/tumor) and sections were immunostained for AR, PD-L1, CK5/6, CK14 and EGFR (to define basal features). Adjusted odds ratio (OR) are presented. **Results:** Among 194 TNBC with AR results, 18.0% were AR-positive (AR+; $\geq 1\%$ nuclei staining) and 11.3% strongly AR+ ($\geq 10\%$ nuclei staining). Among 193 TNBC with PD-L1 results, 26% were PD-L1+ ($\geq 1\%$ cancer cells staining). *BRCA1*+ TNBC were less often AR+ than sporadic TNBC (9.2% vs 23.7%; $p = 0.01$). There was no significant difference in PD-L1 positivity between BRCA1+ and sporadic TNBC ($p = 0.35$). LI were more common in BRCA1+ than sporadic TNBC (OR, 3.0; 95% CI, 1.1-8.0). PD-L1+ TNBC were more likely to be AR+ (OR, 2.6; 95% CI, 1.1-6.1). Grade 1 or 2 TNBC (OR, 4.6; 95% CI, 1.1-19.7) and TNBC in older women (OR, 1.3; 95% CI 1.03-1.7 for each 5 years of age) were more likely to be strongly AR+. Both LI (OR, 3.3; 95% CI, 1.1-10.4) and AR positivity (OR, 3.2; 95% CI, 1.4-7.5) were associated with PD-L1 positivity, while TNBC with LVI (OR, 0.41; 95% CI, 0.18-0.92) were less likely to be PD-L1+. **Conclusions:** *BRCA1*+ TNBC are significantly less often AR+ than sporadic TNBC. The frequency of PD-L1+ TNBC does not differ by BRCA1 status. These results confirm the heterogeneity of TNBC and highlight differences between *BRCA1*+ and sporadic TNBC.

1006 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

The survival benefit offered by the surgical management of low-grade ductal carcinoma in situ of the breast. *First Author: Yasuaki Sagara, Department of Surgery, Brigham and Women's Hospital, Boston, MA*

Background: The current management of ductal carcinoma in situ (DCIS) of the breast includes lumpectomy with/without whole breast radiation or mastectomy, however the magnitude of benefit for surgery has not been well established. We sought to identify the survival benefit conferred by surgical resection over non-operative management in patients with low-grade DCIS. **Methods:** We performed a retrospective longitudinal cohort study using the Surveillance Epidemiology and End Results database. Between 1988 and 2011, 57,222 eligible cases of DCIS were identified. Patients (pts) were divided into a surgery and a non-surgery group; propensity score weighting was used to balance clinico-pathologic factors between groups. Breast cancer specific and overall survival (BCSS/OS) were assessed using a log-rank test and Cox proportional hazards model. **Results:** Of 57,222 cases of DCIS, 56,053 cases (98.0%) received definitive surgery (lumpectomy: 34,439 pts, mastectomy: 16,334 pts) and 1,169 cases (2.0%) were managed non-operatively. The proportion of the following clinico-pathologic factors was higher in the non-surgery group compared to the surgery group: age > 60, diagnosis after year 2000, black race, low-grade DCIS and absence of radiation therapy. There were 576 breast cancer-specific deaths over the 72-month median follow-up period. The weighted ten-year BCSS for the surgery group was 98.5%, compared to 93.5% ($p < 0.001$) for the non-surgery group. Survival benefit for the surgery group differed by nuclear grade ($p = 0.003$). The weighted ten-year BCSS of low-grade DCIS was similar between patients managed with and without surgery (98.8% and 98.6%, respectively; $p = 0.93$). **Conclusions:** The survival benefit offered by surgery for DCIS varies by nuclear grade. In contrast to high/intermediate grade DCIS, definitive local therapy of low-grade DCIS does not offer a significant survival advantage over non-operative management.

Hazard ratio (HR) comparison between DCIS patients managed surgically versus non-operatively as adjusted by clinico-pathologic factors.

Grade	BCSS Weighted HR	95% CI	OS Weighted HR	95% CI
I	0.88	0.21 - 3.71	0.86	0.53 - 1.40
II	0.25	0.15 - 0.42	0.70	0.52 - 0.94
III	0.16	0.11 - 0.23	0.40	0.32 - 0.51

1007 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Impact of neoadjuvant therapy on breast conservation rates in triple-negative and HER2-positive breast cancer: Combined results of CALGB 40603 and 40601 (Alliance). *First Author: Mehra Golshan, Department of Surgery, Brigham and Women's Hospital, Boston, MA*

Background: Neoadjuvant therapy (NAT) improves breast conserving therapy (BCT) rates, but the extent by tumor subtype is unknown. To quantify this effect for triple-negative breast cancer (TNBC) and HER2-positive breast cancer (HER2+ BC), we reviewed surgical outcomes from CALGB 40603, a randomized phase II trial of weekly paclitaxel (P) +/- carboplatin (Cb) followed by doxorubicin + cyclophosphamide (AC) +/- bevacizumab (B) for stage (stg) II-III TNBC, and CALGB 40601, a randomized phase III trial of paclitaxel (P)+ HER2 blockade with trastuzumab (P+H), lapatinib (P+L) or both (P+H+L) for stg II-III HER2+ BC, by requiring surgeons to prospectively evaluate BCT eligibility before and after NAT. **Methods:** Patients (pts) with stg II-III TNBC (n = 404) were randomized in CALGB 40603. Pts with stg II-III HER2+ BC (n = 292) were randomized in CALGB 40601. The treating surgeon assessed BCT candidacy based on clinico-radiographic criteria before and after NAT. Subsequent surgical management was at surgeon and patient discretion. We determined (1) conversion rate from BCT-ineligible to BCT-eligible and vice-versa, and (2) rate of successful BCT, as defined by tumor-free surgical margins. **Results:** Pre- and post-treatment surgical assessments were received for 94% of 742 pts treated in the two trials. Of 696 evaluable pts, 340 (49%) were considered BCT candidates prior to NAT. Of these, 310 (91%) remained BCT eligible after NAT; BCT was successful in 209/232 (90%) in whom it was attempted. Of 356 pts (51%) considered BCT ineligible prior to NAT, 151(42%) converted to BCT eligible; BCT was successful in 87/102(85%) in whom it was attempted. The rates were similar across the two studies. Results will be broken down by treatment arm. Of 461 pts judged BCT candidates post NAT, 127(28%) chose mastectomy with no attempt at BCT. **Conclusions:** We present the largest combined prospective analysis of NAT trials showing a BCT-ineligible to BCT-eligible conversion rate of 42% in both TNBC and HER2+ BC subtypes. BCT was successful in approximately 88% of pts who chose this approach; however, a substantial fraction of BCT-eligible pts opted for mastectomy. Clinical trial information: NCT00861705.

1008 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Relationship of omission of adjuvant radiotherapy to outcomes of locoregional control and disease-free survival in patients with or without pCR after neoadjuvant chemotherapy for breast cancer: A meta-analysis on 3481 patients from the Gepar-trials. *First Author: David Krug, University Hospital Heidelberg, Heidelberg, Germany*

Background: There is controversy whether the response to neoadjuvant chemotherapy should be incorporated into the decision-making process for adjuvant radiotherapy in breast cancer. **Methods:** We presenta pooled analysis of the randomized neoadjuvant trials GeparTrio, GeparQuattro and GeparQuinto including 3,481 patients with operable and non-operable breast cancer for which information on the use of radiotherapy (RT) was available. 94% received any RT. Locoregional recurrence was defined as a recurrence in the breast, at the chest wall or in the regional lymph nodes. **Results:** Patients in the RT-group were older and received more mastectomies. Their tumors were more likely to be HER2-positive and there was a higher rate of pathologic complete response (pCR, ypT0 ypN0). The overall risk of locoregional recurrence (LR) was 8.3% after a median follow-up of 55.9 months. RT conferred a significant benefit in terms of 5-year LR-free survival (LRFS, 90% vs. 81.5% without RT, logrank $p < 0.001$) and 5-year disease-free survival (DFS, 75.4% vs. 67.4%, logrank $p < 0.001$). The absolute advantage of RT regarding both LRFS and DFS was highest among patients with clinically positive lymph nodes at first diagnosis (HR 2.32, 95% CI 1.54-3.50; $p < 0.001$; HR 1.97, 95% CI 1.48-2.62; $p < 0.001$ respectively). In patients with pCR, the 5-yr LRFS was 95.7%% with RT vs 86.6% without RT (HR 3.32, 95% CI 1.00-11.08; $p = 0.051$) and 5-yr DFS was 86.9% and 56.1% (HR 3.52, 95% CI 1.82-6.83; $p < 0.001$). In patients without pCR, the LRFS was 88.6% with RT vs 80.7% without RT (HR 1.86, 95% CI 1.29-2.67; $p < 0.001$) and 5-yr DFS was 72.6% vs 65.7%; HR 1.39, 95% CI 1.07-1.81; $p = 0.014$). Multivariate analyses with adjustment for baseline parameters as well as for pathologic tumor stage and pCR confirmed RT as an independent prognostic factor for LRFS (HR 0.54, 95% CI 0.35-0.82; $p = 0.004$) and DFS (HR 0.69, 95% CI 0.51-0.93; $p = 0.016$). **Conclusions:** This retrospective analysis suggests thatpatients managed withoutRT after neoadjuvant chemotherapy for breast cancer have a significantly worse outcome even if they achieved a pCR.

1009 Poster Discussion Session; Displayed in Poster Session (Board #123), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Outcomes of adjuvant ACT vs. TC chemotherapy in older women with breast cancer. *First Author: Sarah Schellhorn Mougalian, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Chemotherapy with both anthracyclines and taxanes sequentially or concurrently (ACT) has improved survival in breast cancer. A regimen containing docetaxel and cyclophosphamide (TC) was developed to avoid cardiac side effects, which are of particular concern in older women. The efficacy of ACT vs. TC is under investigation in NSABP B-49, but results are not yet available. We examined temporal trends and clinical associations with ACT vs. TC use in clinical practice in older women and compared the overall survival of patients receiving adjuvant ACT vs. TC. **Methods:** We used the SEER-Medicare database for women over 65 diagnosed 2004-2009. Women were classified by regimen received: ACT, TC, and other (including anthracycline without taxane and cyclophosphamide, methotrexate, and 5-fluorouracil). We excluded women who received trastuzumab. We used chi-square and logistic regression to identify factors associated with ACT vs. TC receipt and Cox proportional hazards models to assess survival differences by treatment. **Results:** We identified a total of 4391 patients: 1577 (36%) received ACT, 1174 (22%) received TC, and 1640 received other regimens. Use of ACT decreased from 26% in 2004 to 21% in 2009, whereas use of TC increased from 1% to 43% in the same period. Receipt of ACT vs. TC was associated with younger age; fewer comorbidities; lack of history of coronary artery disease, diabetes, or atrial fibrillation; higher stage and lymph node involvement; and living in the Northeast United States (as compared to the West or South). Five-year overall survival (OS) estimates were 81% for patients receiving ACT and 86% for patients receiving TC ($p = .21$); 3-year unadjusted survival for stage III patients was 87% for ACT and 79% for TC (0.002). The adjusted Cox proportional hazard ratio for all patients, adjusted for stage, comorbidities, and other significant associations, was 1.10 (95% CI 0.64-1.91). The hazard ratio for ACT vs. TC was not significant for stage I/II patients, but for stage III patients was 0.59 (95% CI 0.40-0.89). **Conclusions:** TC has become a common choice for adjuvant chemotherapy among older patients. In all patients, 5-year OS was similar between groups, but OS may be higher for patients with stage III disease receiving ACT.

1010 Poster Discussion Session; Displayed in Poster Session (Board #124), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Absence of disease-specific survival improvement over time among breast cancer patients age 70 and older: 1990-2007. *First Author: Henry G. Kaplan, Swedish Cancer Inst, Seattle, WA*

Background: 5 year disease specific survival (DSS) improvement among breast cancer (BC) patients has been observed over the past two decades. It is not known if this improvement extends to elderly women. **Methods:** Retrospective cohort study of BC patients from a dedicated BC registry database, years 1990-2007 (N = 1889). Chi square tests for bivariate proportional differences and Kaplan Meier survival analysis were used. The disease specific survival (DSS) endpoint was death from breast cancer. **Results:** Invasive breast cancer in patients age 65 and older was 62% mammography detected between 1990 and 2007 with no difference in detection method or stage by age (61% stage I, 27% stage II, 12% stage III). As age increased, patients were more often treated with surgery and radiation only [65-69 = 60%, 70-74 = 72%, 75-79 = 79%, 80+ = 82%, ($p < .001$)], and less often with chemotherapy [65-69 = 32%, 70-74 = 19%, 75-79 = 12%, 80+ = 82% ($p < .001$)] or hormonal therapy [65-69 = 74%, 70-74 = 71%, 75-79 = 66%, 80+ = 63% ($p < .001$)]. Patients 70 and older (n = 1302) had higher overall death rates [65-69 = 31%, 70-74 = 48%, 75-79 = 57%, 80+ = 62%] but an equal likelihood of breast cancer death [65-69 = 8%, 70-74 = 10%, 75-79 = 11%, 80+ = 7%]. Five year DSS improved significantly from 1990 to 2007 for patients age 65-69 from 93% to 98% but no improvement over time was observed among 70 and older patients (survival distribution equality test: $p = .004$). 5 year DSS did not improve over time for stage I breast cancer patients at any age. For stage II/III BC patients 5 year DSS only improved significantly over time for 65-69 year old patients [65-69: 1990-94 = 86%, 1995-99 = 94%, 2000-07 = 98% ($p = .031$) ; 70+: 1990-94 = 85%, 1995-99 = 90%, 2000-07 = 86% ($p = .178$)]. **Conclusions:** Breast cancer specific survival did not improve for higher stage breast cancer patients age 70 and older from 1990-2007, a time period in which both early detection and treatment improved. To improve survival in elderly women, consultation with oncologists regarding hormonal therapy options for estrogen receptor positive patients, early diagnosis by screening and development of tolerable treatment options for later stage disease are important priorities.

1011 Poster Discussion Session; Displayed in Poster Session (Board #125), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Contralateral prophylactic mastectomy decision-making in the population-based iCanCare study of early-stage breast cancer patients: Knowledge and physician influence. *First Author: Reshma Jagsi, University of Michigan Health System, Ann Arbor, MI*

Background: Contralateral prophylactic mastectomy (CPM) use is increasing in women who are not at increased risk of contralateral cancer development and will experience no survival benefit from the more morbid procedure. Little is known about treatment decision-making or provider interactions. **Methods:** We surveyed patients newly diagnosed with breast cancer in 2013-14, identified through the population-based SEER registries of Los Angeles and Georgia, about 6 months after diagnosis, to determine receipt of diagnostic tests and factors related to the decision about surgery (including knowledge and perceived physician recommendation). Survey return is ongoing with an expected final response rate > 70%; current response rate 68%. **Results:** Nearly half of 1949 respondents with unilateral cancer considered CPM (20% very strongly, 6% strongly, 9% moderately, 10% weakly). Only 37% of those who considered CPM knew that it does not improve survival for all women with breast cancer (23% believed it does, 49% didn't know). Among women receiving CPM, 36% believed it generally improves survival. Ultimately, 1138 (58%) received BCS and 811 (42%) mastectomy (387, or 20% overall, with CPM). On multivariable analysis, pts who received CPM were younger, more likely to be white, and more likely to have a family history, private rather than Medicaid insurance, and received MRI. Even among pts without a deleterious genetic mutation or family history in multiple relatives (1,849), 354 (19%) received CPM; CPM was uncommon among pts who reported that their surgeons recommended against it (3.7% [13/649]) but much higher (22.7% [197/869]) among those who reported no surgeon recommendation regarding CPM and (58.7% [138/235]) among those who perceived their surgeons to have recommended it. **Conclusions:** Many patients consider CPM, but knowledge is low and discussions with surgeons appear incomplete. Use of CPM is substantial among patients without clinical indications but is low when patients report their surgeon recommended against it. More effective discussion and navigation about CPM is needed to reduce potential overtreatment. Funding: P01-CA-163233.

1012 Poster Discussion Session; Displayed in Poster Session (Board #126), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Can routine cavity shave margins (CSM) improve local control in breast cancer? Initial results of the SHAVE trial, a prospective randomized controlled trial of routine CSM vs. standard partial mastectomy (SPM). *First Author: Anees B. Chagpar, Yale School of Medicine, New Haven, CT*

Background: Considerable controversy exists regarding the utility of routine CSM in patients undergoing partial mastectomy for breast cancer. We performed a prospective RCT to determine whether this practice results in a lower positive (+) margin rate. **Methods:** 251 patients with preoperative Stage 0-3 breast cancer undergoing partial mastectomy were randomized 1:1 to SPM or CSM (80% power to detect a reduction in (+) margin rate from 30% to 15%). Prior to intraoperative randomization, surgeons performed SPM per their usual practice. The sealed randomization envelope was then opened and surgeons were instructed either to take circumferential CSM or close. (+) margins were defined as tumor at ink for invasive cancer, and < 1 mm for DCIS. **Results:** The median patient age was 61 (range; 33-94). 61 (24.3%) had invasive cancer only, 50 (19.9%) had DCIS alone, and 129 (51.4%) had a combination of both. The median invasive tumor size was 1 cm (range; 0-6.5), and median DCIS size was 0.9 cm (range; 0-9.3). The groups were well-matched in terms of baseline characteristics (see table below). Margin status prior to randomization was not significantly different between the two groups (34.9% vs. 33.6%, p = 0.894). After randomization, those randomized to CSM had a significantly lower (+) margin rate than SPM (18.3% vs. 33.6%, p = 0.006). This was the primary endpoint of the study. Not all (+) margins were re-excised due to anatomic considerations; however, CSM resulted in a significantly lower re-excision rate than SPM (9.5% vs. 20.8%, p = 0.014). **Conclusions:** This is the first RCT to conclusively demonstrate that CSM halves the (+) margin and re-excision rate of SPM. Use of routine CSM may significantly reduce morbidity and cost of reoperation for margin clearance. Clinical trial information: NCT01452399.

	CSM (n = 126)	SPM (n = 125)	p-value
Age (yrs); median	62	60	0.525
Invasive tumor size (cm); median (range)	1.0 (0 – 6.0)	1.0 (0 – 6.5)	0.639
Palpable (%)	20.6%	22.4%	0.761
Invasive lobular histology (%)	11.0%	7.8%	0.744
DCIS component (%)	69.0%	73.6%	0.486
DCIS size (cm); median (range)	0.9 (0 – 9.3)	1.0 (0 – 8.1)	0.775
Node positive	10.3%	10.4%	1.000
ER+	90.6%	87.5%	0.527

1013 Poster Discussion Session; Displayed in Poster Session (Board #127), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Risk after local excision alone for DCIS patients. *First Author: Eileen Rakovitch, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: The DCIS Score (DS) was validated as a predictor of ipsilateral breast recurrence (IBR; DCIS or invasive) in E5194 pts tx by breast-conserving surgery (BCS) w/o RT. The Ontario population-based study of 3,320 pts w/ DCIS from 1994 to 2003 (Rakovitch, 2013) tested the DS as a predictor of IBR risk in a broader, more contemporary population of pts tx w/ BCS alone - w/ & w/o clear margins (CM). **Methods:** DS was obtained per E5194. The pre-specified 1º objective was to determine the relationship (HR/50 units) between the risk of an IBR and the continuous DS (using Cox models) in pts tx w/ BCS alone w/ ER+ DCIS and CM (no ink on tumor). The association between the continuous DS in all pts with BCS alone w/ & w/o CM was explored. **Results:** 1,751 pt blocks were collected; 718 had BCS alone (571 w/ CM). Median f/u was 9.4 yrs. Among 718 pts w/ BCS alone, 136 had an IBR (DCIS, N=57; invasive, N=80). Among 571 pts w/ CM, 100 had IBR (DCIS, N=44; invasive, N=57). In the 1ºanalysis, among pts tx by BCS alone w/ CM the continuous DS was significantly associated with IBR in ER+ pts (HR 2.26; 95%CI 1.41,3.59; P=0.001) and in all pts (HR 2.15; 95%CI 1.43,3.22;P=<0.001). DS was associated w/ invasive IBR (HR 1.78; 95%CI 1.03,3.05;P=0.04). In multivariable analysis for IBR, the HR/50 units for the DS among pts tx w/BCS alone w/ CM was 1.68 (95%CI 1.08,2.62; P=0.022) adjusting for multifocality, tumor size, subtype, and age. Among all 718 pts tx by BCS alone w/ and w/o CM, the DS was associated w/ IBR, and the HR/50 units for the DS was 2.04 (95%CI 1.39,2.98; P=<0.001) adjusting for multifocality, size, subtype, and age. **Conclusions:** The DS quantifies IBR risk for DCIS pts tx by BCS w/ or w/o CM. Integrating the DS with established risk factors can more accurately identify DCIS pts tx with BCS alone with low (<10%) or high (>25%) 10yr average IBR risk.

10 yr KM IBR rate (95%CI).

DS Risk Group	CM N	CM	CM & unifocal DCIS N	CM & unifocal DCIS	All pts regardless of margin status N	All pts regardless of margin status	Positive or uncertain margins N	Positive or uncertain margins
Low (<39)	355	12.7% (9.5%, 16.9%)	298	9.7% (6.8%, 13.8%)	450	13.6% (10.6%, 17.3%)	95	16.8% (10.4%, 26.3%)
Int (39-54)	95	33.0% (23.6%, 44.8%)	72	27.1% (17.7%, 40.2%)	118	32.4% (24.0%, 42.8%)	23	29.5% (14.4%, 54.4%)
High (≥55)	121	27.8% (20.0%, 37.8%)	87	27.0% (18.2%, 38.9%)	150	31.6% (24.2%, 40.6%)	29	47.8% (30.4%, 68.8%)
Log rank P-value	571	<0.001	457	<0.001	718	<0.001	147	0.004

1014 Poster Discussion Session; Displayed in Poster Session (Board #128), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A phase II, open-label, neoadjuvant, randomized study of LCL161 with paclitaxel in patients with triple-negative breast cancer (TNBC). *First Author: Marina Parton, The Royal Marsden Hospital, London, United Kingdom*

Background: LCL161 is a small molecule that induces apoptosis by inactivating inhibitor of apoptosis proteins (IAPs). LCL161 preferentially synergizes with paclitaxel in TNBC models with a defined gene expression signature (GS) that reflects the biology of IAP antagonists. Here we present preliminary safety and efficacy data from a completed Phase II study of neoadjuvant LCL161 with paclitaxel in patients with GS+ and GS– TNBC (NCT01617668). **Methods:** Women with operable, newly diagnosed TNBC (T2, N0–N2, M0) were stratified into GS+ and GS– groups upfront, then randomized to receive paclitaxel (80 mg/m^2/week) ± LCL161 (1800 mg/week) for 12 weeks. Patients then received surgery to assess pathological complete response (pCR), followed by investigator's choice of adjuvant therapy. Primary objective: To assess whether LCL161 enhances the efficacy of paclitaxel in patients with GS+ or GS– TNBC, defined by a ≥ 7.5% increase in pCR rate after 12 weeks of combination treatment vs paclitaxel alone. **Results:** All 209 treated patients completed the study; 17/106 patients (16.0%) in the combination arm and 17/103 patients (16.5%) in the control arm achieved pCR. In the GS+ group (30.1% of patients), 13/34 patients (38.2%) in the combination arm and 5/29 patients (17.2%) in the control arm achieved pCR; the posterior probability of a ≥7.5% increase in pCR rate was 88.8%. In the GS– group, 4/72 patients (5.6%) in the combination arm and 12/73 patients (16.4%) in the control arm achieved pCR. The most frequent adverse events (AEs; ≥ 30% of patients, all grades) are shown in the table below. Serious AEs of pyrexia (combination 17.9%; control 1.0%), pneumonia (10.4%; 1.9%), and pneumonitis (9.4%; 0%) were significantly increased in the combination arm. **Conclusions:** Neoadjuvant LCL161 with paclitaxel shows promising signs of efficacy in a GS+ subset of TNBC (~30% of patients), but with notable toxicity at the 1800 mg/week dose. Clinical trial information: NCT01617668.

	LCL161 + paclitaxel (N = 106), %		Paclitaxel (N = 103), %	
	All grades	G3/4	All grades	G3/4
Diarrhea	71.7	5.7	22.3	1.0
Alopecia	67.9	–	67.0	1.0
Pyrexia	48.1	4.7	9.7	–
Fatigue	45.3	3.8	36.9	–
Nausea	42.5	0.9	31.1	–
Rash	41.5	3.8	27.2	–
Neutropenia	39.6	23.6	10.7	3.9
Headache	33.0	0.9	17.5	–

1015 Poster Discussion Session; Displayed in Poster Session (Board #129), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A phase I study of veliparib (ABT-888) in combination with weekly carboplatin and paclitaxel in advanced solid malignancies and enriched for triple-negative breast cancer (TNBC). *First Author: Shalu Pahuja, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Veliparib (ABT-888) is an oral, potent small molecule inhibitor of poly-ADP-ribose polymerase (PARP). The combination of veliparib (V) with carboplatin (C) and paclitaxel (P) dosed every 3 weeks has been shown to be safe with early signs of efficacy in a phase I study conducted by our group. In breast cancer patients (pts), weekly P improves disease-free and overall survival vs. every three week P with comparable safety (ECOG 1199), thus supporting the exploration of weekly C and P in combination with V. This study is designed to determine the recommended phase 2 dose (RP2D), maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), adverse events (AEs), anti-tumor activity, and pharmacokinetic (PK) parameters of this combination. **Methods:** A standard 3+3 design was used with 4 escalating V dose levels ranging from 50-200 mg bid. C (AUC 2) and P (80 mg/m^2) were administered on a weekly basis over a 21-day cycle on all dose levels. Dose escalation was followed by dose expansion in pts with TNBC with mandatory tumor biopsies. **Results:** A total of 30 pts were enrolled (median age 52 yr [range 33-83]; 27 female; median prior treatments 3 [range 0-8]; 24 breast [22 TNBC], 2 lung, 1 cervix, 1 ovarian, 1 prostate, 1 gastric). DLTs occurred at the following dose levels: prolonged gr 2 thrombocytopenia at 150 mg bid, and gr 4 neutropenia at 200 mg bid. The RP2D of veliparib was established to be 150 mg bid. The most common all-grade and grade 3/4 AEs included: neutropenia (gr 3/4 in 18 pts [60%]), anemia (gr 3/4 in 5 pts [17%]), and thrombocytopenia (gr 3/4 in 3 pts [10%]). PK parameters of V in this trial were comparable to historical single-agent V. Of the 27 evaluable pts, 13 (48%) responded (1 CR, 12 PR), 10 (37%) had SD, and 4 (15%) had PD. Objective response rate in TNBC was 52%. Among 21 evaluable TNBC pts, response was 60% in *BRCA1/2*+ pts (3/5 PR), 67% in non-*BRCA1/2* pts (1/9 CR; 5/9 PR) and 29% in unknown status pts (2/7 PR). The only ovarian cancer pt was *BRCA2*+ and had PR. **Conclusions:** V in combination with weekly C and P was well tolerated with acceptable safety profile. Promising anti-tumor activity was observed, particularly in TNBC. Clinical trial information: NCT01281150.

1016 Poster Discussion Session; Displayed in Poster Session (Board #130), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Therapy of refractory/relapsed metastatic triple-negative breast cancer (TNBC) with an anti-Trop-2-SN-38 antibody-drug conjugate (ADC), sacituzumab govitecan (IMMU-132): Phase I/II clinical experience. *First Author: Aditya Bardia, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Background: Patients with metastatic TNBC have an aggressive disease with limited therapy options. The duration of response with standard chemotherapy is usually short, with median PFS of about 3-4 months, and there is an unmet need for better therapies. Trop-2 is highly expressed in most epithelial cancers, including TNBC (> 90%). IMMU-132 is a conjugate of a humanized anti-Trop-2 (trophoblast cell-surface antigen) mAb coupled site-specifically to SN-38 (7.6 moles SN-38/IgG), the active metabolite of irinotecan, using a proprietary linker. **Methods:** In an ongoing Phase I/II clinical trial (ClinicalTrials.gov, NCT01631552), patients with metastatic TNBC patients refractory or relapsing to prior therapies, including topoisomerase inhibitors, received IMMU-132 i.v. on days 1 and 8 of 21-day treatment cycles. Treatment was continued based on tolerance or until progression, with safety and response assessments (RECIST1.1) made every week and at 8-12 weeks, respectively. Dose reductions/delays allowed most patients to continue treatment until progression. **Results:** As of Feb 2, 2015, a total of 174 pts with relapsed/refractory diverse epithelial tumors have been treated with IMMU-132. Forty-eight pts with TNBC were treated: median age = 51 ys (range, 33-81), median of 4 prior chemotherapies (range, 1-11). In TNBC, Grade 3/4 toxicities included neutropenia (G3, 24%; G4, 6%) and febrile neutropenia (G4, 3%). Other G3 toxicities included diarrhea (3%), anemia (3%), leucopenia (3%), lymphopenia (3%), caecitis (3%). No pt developed antibodies to the conjugate; no one discontinued due to toxicity. Thirty-four TNBC pts had at least 1 response assessment, with an objective response rate (ORR) of 21% (including one complete response), a disease stabilization rate (CR+PR+SD) of 74%, and a clinical benefit ratio with CR+PR+SD ≥ 6 mo = 37% (7 of 15 pt with SD are still on treatment). **Conclusions:** IMMU-132 therapy is associated with encouraging clinical activity and limited toxicity in patients with metastatic TNBC s/p multiple prior lines of therapy. It warrants further evaluation for this refractory disease. Clinical trial information: NCT01631552.

1017 Poster Discussion Session; Displayed in Poster Session (Board #131), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Phase II neoadjuvant clinical trial of carboplatin and eribulin in women with triple negative early stage breast cancer (NCT01372579). *First Author: Virginia G. Kaklamani, Northwestern University Division of Hematology/Oncology, Chicago, IL*

Background: Platinum-based chemotherapy has been reported to have efficacy in patients with Triple Negative Breast Cancer (TNBC). Germline *BRCA1/2* mutation status has been shown to be predictive of platinum response in patients with metastatic TNBC. In the neoadjuvant setting some, but not all patients with sporadic TNBC also achieve a pathologic complete response (pCR). This study evaluated the efficacy and toxicity of neoadjuvant treatment with carboplatin and eribulin in patients with early stage TNBC, and assessed the role of a HRD (homologous recombination deficiency) test to predict response. **Methods:** Patients with histologically confirmed early stage TNBC received carboplatin AUC 6 iv every 21 days and eribulin 1.4 mg/m^2 day1 and day 8 every 21 days for four cycles. The primary endpoint of the study was pCR, with secondary endpoints including clinical response rate and safety of the combination. Tumor specimens were evaluated for *BRCA1/BRCA2* mutations, *BRCA1* promoter methylation, and HRD status. **Results:** A total of 30 patients enrolled in the study. 13 (43.3%) achieved pCR. The combination was safe with mostly grade 1 and 2 toxicities. 28 pre-treatment samples were available for HR deficiency assessment and 26 obtained passing HRD scores. HR deficiency (HRD positive with HRD score ≥ 42), significantly predicted pCR in the full cohort ($P = 0.0012$) and in the subset of *BRCA1/2* wild type patients ($P = 0.0018$). **Conclusions:** The combination of carboplatin and eribulin is safe and efficacious in the treatment of early stage TNBC. The use of an HRD test can predict pCR after carboplatin and eribulin treatment in this patient population and with further validation can be used to identify patients beyond those with a germline BRCA mutation who will respond to a platinum-containing regimen. Clinical trial information: NCT01372579.

1018 Poster Discussion Session; Displayed in Poster Session (Board #132), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Combined Homologous Recombination Deficiency (HRD) scores and response to neoadjuvant platinum-based chemotherapy in triple-negative and/or *BRCA1/2* mutation-associated breast cancer. *First Author: Melinda L. Telli, Stanford University School of Medicine, Stanford, CA*

Background: The HRD-LOH (loss of heterozygosity) score is significantly associated with favorable response to neoadjuvant platinum-based therapy in PrECOG 0105. We set out here to assess the combined HRD score, an unweighted sum of LOH, telomeric allelic imbalance (TAI) and large-scale state transitions (LST) scores. In combination, these measures are a more robust predictor of HR deficiency than the individual components. **Methods:** The HRD threshold was previously established by analyzing scores in a training cohort of 497 breast and 561 ovarian chemotherapy naive tumors with known defects in HR, and defining a cut-off with 95% sensitivity to detect those HR deficient tumors. This threshold, along with *BRCA1/2* tumor mutation data, was used to predefine tumors from the PrECOG 0105 cohort (N = 93; 72 with molecular data) as either HR deficient (HRD score ≥ the threshold OR a tumor *BRCA1/2* mutation) or HR non-deficient (HRD score < the threshold and no tumor *BRCA1/2* mutation). **Results:** In univariate analysis, a HRD score ≥ 42 was significantly associated with both RCB 0/1 and pCR (p = 0.0086; p = 0.010). In addition, HR deficiency was significantly associated with both RCB 0/1 and pCR (OR = 5.00 [1.65, 15.2], p = 0.0029; OR = 6.65 [1.40, 31.6], p = 0.0050), and identified responders lacking a deleterious *BRCA1/2* mutation. When the analysis was confined to tumors with intact *BRCA1/2,* HR deficiency was no longer significantly associated with RCB 0/1 or pCR; however power to detect this association was limited. HR deficiency remained a significant predictor of RCB 0/1 when the score was adjusted by clinical variables including grade, stage, cycles of chemotherapy, and age at diagnosis (p = 0.0075). **Conclusions:** In this study, HRD status provides significant improvement over clinical variables, or *BRCA1/2* status, in identifying tumors with an increased likelihood of response to platinum-based neoadjuvant therapy among patients with TNBC. Clinical use of the HRD test has the potential to identify TNBC patients likely to respond beyond those currently identified by germline *BRCA1/2* mutation screening. Prospective evaluation is warranted. Clinical trial information: NCT00540358.

1019 Poster Discussion Session; Displayed in Poster Session (Board #133), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Concordance of intrinsic subtyping and risk of recurrence (ROR) scores between matched primary and metastatic tissue from Triple Negative Breast Cancer Trial (TNT). *First Author: Maggie Chon U Cheang, Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU), London, United Kingdom*

Background: The majority of triple negative breast cancers are of basal-like subtype (BLBC). There is uncertainty about concordance of intrinsic subtypes and ROR scores by PAM50 between matched primary and metastasis samples. We sought to examine agreement of intrinsic subtypes and ROR groups using tissue in the TNT trial. **Methods:** TNT is a phase III, multicentre, randomized trial of carboplatin vs docetaxel in women with ER- PgR-HER2- metastatic/recurrent locally advanced breast cancer. Using Prosigna test on Nanostring nCounter, intrinsic subtyping was performed in a central laboratory on primary tumour (PT) from 216 patients, 66 positive lymph nodes (PLN) and 13 recurrent tissue samples (RC). The ROR-S (ROR based on subtype contents) and ROR-P (ROR based on subtype contents and proliferation index) were calculated using research-based PAM50 classifier (Parker JCO 2009). Agreement on classification was assessed by kappa statistics (k). **Results:** Of 216 PT, 175 (81%) were BLBC, 23 (11%) HER2enriched (HER2E), 13 (6%) Luminal A (LumA), 5 (2%) Luminal B (LumB). Of 66 PLN, 49 (74%) were BLBC, 12 (18%) HER2E, 2 (3%) LumA, 3 (5%) LumB. Of RC, majority were BLBC (12/13, 92%) with 1 HER2E. There were 63 matched PT and PLN pairs, with substantial agreement between subtype calls (k = 0.74 (95% CI 0.56-0.92), p < 0.0001; Table 1). 1 BLBC PT was classified HER2E in PLN. Of the 8 LumA PT, 5 (63%) were HER2E, 1 (13%) LumB, 2 (25%) LumA in their matched PLN. Comparing ROR risk groups, all high risk cases remained high risk (Table 1), while low/med switched to med/high risk groups. **Conclusions:** Our study confirms that BLBC and high risk ROR assignments in PT were substantially conserved with matched PLN and RC. None of the PT/non-BLBC was classified as BLBC in matched PLN or RC. LumA appeared to switch to aggressive subtypes or higher ROR-defined risk groups in matched PLN and RC. Gene expression profiles of matched samples will be presented.

Comparison of intrinsic subtypes and ROR groups between matched PT/PLN.

	PLN				
	BLBC	**HER2E**	**LumA**	**LumB**	**Total**
PT					
BLBC	46	1	0	0	47
HER2E	0	6	0	0	6
LumA	0	5	2	1	8
LumB	0	0	0	2	2
		ROR-S			
	High	Med	Low		
High	46	1	0		47
Med	6	3	0		9
Low	0	5	2		7
		ROR-P			
	High	Med	Low		
High	48	1	0		49
Med	4	8	0		12
Low	0	1	1		2

1020 Poster Discussion Session; Displayed in Poster Session (Board #134), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

RespondR: A genomic score to predict the responsiveness of triple-negative breast cancer patients to chemotherapy. *First Author: Steven Buechler, Notre Dame University, South Bend, IN*

Background: A significant number of triple-negative breast cancer (TNBC) patients achieve pathological complete response (pCR) and improved relapse free survival from neoadjuvant taxane-anthracycline (AT) based chemotherapy. However, the 3-year distant relapse free survival (DRFS) probability for AT-treated TNBC patients is only about 0.50. A test is needed that identifies the AT-insensitive patients who are candidates for an alternative therapy. **Methods:** Gene expression measurements of 242 AT-treated TNBC patients were divided into training and validation sets balanced for clinical traits and pCR. An innovative multistate gene methodology was used to identify predictors of pCR in the training set and confirmed in validation set, along with higher DRFS in the predicted TF-sensitive group. **Results:** Analysis of the training set (n = 129; 38 pCR) identified 15 genes that were most predictive of pCR. RespondR Score was developed using these genes to continuously stratify patients by probability of pCR. In the validation set (n = 133; 60 pCR), RespondR stratifies patients into groups of low (RR-low, 55%), moderate (RR-moderate, 21%) and high (RR-high, 24%) sensitivity with rate of pCR 0.24 (RR-low), 0.29 (RR-moderate), 0.62 (RR-high) and 5-year DRFS probability 0.49 (RR-low), 0.61 (RR-moderate) and 0.80 (RR-high). In the RR-high group mitosis-related genes are up-regulated and genes involved in extracellular matrix organization and cell adhesion are down-regulated. **Conclusions:** The RespondR Score accurately predicts those TNBC patients likely to achieve pCR and improved survival using AT neoadjuvant chemotherapy. RespondR can provide critical information to patients and physicians deciding between AT and an alternative therapy.

1021 Poster Session (Board #135), Sat, 8:00 AM-11:30 AM

Role of β blocker and angiotensin antagonist for the prophylaxis of early onset anthracycline-induced ventricular dysfunction: A meta-analysis of five randomized controlled trials. *First Author: Nicole Vincelette, Mayo Clinic, Rochseter, MN*

Background: Anthracycline is one of the most effective and commonly used chemotherapeutic agents in patients with breast cancer, Hodgkin and non-Hodgkin lymphomas. However, it is associated with cardiomyopathy that is accumulative dose related and irreversible. We performed a meta-analysis to determine the efficacy of β blocker or angiotensin antagonist to prevent early onset anthracycline-induced ventricular dysfunction and cardiac events. **Methods:** Relevant articles were searched in PubMed, EMBASE and Cochrane database. Eligible studies were limited to randomized controlled trials comparing cardioprotective agents (β blocker and angiotensin antagonist) to control in adult patients treated with anthracycline based regimens. Relative risks and 95% CI were calculated using random effect model and statistical analysis was performed by using RevMan 5.3 software. **Results:** The combined estimate demonstrated an association of β blocker and angiotensin antagonist treatment with higher post-chemotherapy LVEF with 63.61% vs. 56.19% (MD 7.15, 95% CI, 0.47 to 13.84, $p = 0.04$). Cardiac events rate in experimental group was non-significantly lower than control with 9.7% vs. 27.4% (RD -0.15, 95% CI, -0.38 to 0.08, $p = 0.2$). In a subgroup analysis, the benefit of experimental agents on LVEF preservation was significant in patients treated with higher anthracycline accumulative dose (MD 14.61, 95% CI, 12.26 to 16.97, $p < 0.00001$), however not in lower dose (MD 1.79, 95% CI, -3.11 to 6.70, $p = 0.47$). **Conclusions:** In a meta-analysis of randomized controlled trials in patients treated with anthracycline, β blocker and angitensin antagonist treatment was associated with significantly better LVEF preservation, and the benefit was prominent in patients with higher anthracycline accumulative dose. Collectively, these results suggest that routine use of β blocker or angiotensin antagonist should be encouraged in patients undergoing anthracycline based chemotherapy, especially when higher accumulative dose is expected.

1022 Poster Session (Board #136), Sat, 8:00 AM-11:30 AM

Standard chemotherapy versus capcitabine for older women with early stage breast cancer: An update of CALGB/CTSU/Alliance 49907. *First Author: Hyman B. Muss, UNC Chapel Hill, Chapel Hill, NC*

Background: CALGB 49907 compared capecitabine (X) with standard (S) chemotherapy in BC patients (pts) 65 yrs and older. Initial results: inferiority of X for both RFS and OS at 2.4 yrs median follow-up (NEJM 2009;360:2055). Current median 9 yrs. **Methods:** Pts $\geq$ 65 years with Stage I-IIIB BC. Randomization: Xx6 vs S (physician choice: CMFx6 or ACx4 (q3wk)). Endocrine therapy recommended for hormone receptor (HmR) positive. Endpoints: relapse-free (RFS) and overall survival (OS). We now include recurrence-free interval (RFI) and BC-specific survival (BCSS) to separate competing risk from other-cause mortality. All endpoints defined by the STEEP. Primary analysis: Bayesian probability of X inferiority in RFS for early stopping and final. **Results:** At first interim analysis, after 633 pts (9/2001–12/2006), met the criterion for early stopping. Final Bayesian probability of inferiority of X to S was > 99% for both RFS and OS. Accrual closed (2006) and results published (2009). At 7-yrs for S vs X: RFS 60% vs 52%; RFI 83% vs 75%; OS 79% vs 68%; BCSS 91% vs 83% - all $p < .05$. Table shows hazard ratios (HR) of X:S and 95% confidence intervals (CI). The magnitude of S effect and its interaction with HmR status has decreased; its benefit in HmR-neg tumors remains. There are 45 new primary cancers (S: 29; X: 16): breast 13 (S:5, X:8), AML/MDS 6 (CMF: 2; AC: 3; X:1). **Conclusions:** Long-term follow-up shows X inferior to S. Competing risks are important contributors to mortality in this population. Clinical trial information: NCT00024102.

HR of X:S (95% CI) by time of analysis and HmR status.

Endpt (events)	NEJM2009				Current			
	RFS(95)	OS(62)	RFI(66)	BCSS(29)	RFS(243)	OS(208)	RFI(130)	BCSS(78)
All	2.09* 1.38-3.17	1.85* 1.11-3.08	2.54* 1.51-4.27	2.49* 1.13-5.50	1.35* 1.05-1.74	1.37* 1.04-1.80	1.62* 1.14-2.30	1.67* 1.06-2.62
HmR-neg	3.13* 1.68-5.84	2.90* 1.33-6.31	2.68* 1.39-5.17	2.18 0.87-5.42	1.71* 1.13-2.59	1.61* 1.03-2.51	1.88* 1.12-3.16	1.71 0.88-3.33
HmR-pos	1.43 0.80-2.54	1.23 0.61-2.48	2.32 0.99-5.42	3.63 0.73-18.1	1.18 0.85-1.62	1.24 0.88-1.75	1.42 0.88-2.30	1.63 0.88-3.02

*Significant at $P < .05$.

1023 Poster Session (Board #137), Sat, 8:00 AM-11:30 AM

Association of disregulated neuronal and peripheral BDNF with vulnerability to paclitaxel-induced peripheral neuropathy. *First Author: David Azoulay, Galilee Medical Center, Naharia, Israel*

Background: Brain Derived Neurotrophic Factor (BDNF) is important for neuronal survival and repair. We hypothesized that a disregulated neuronal and peripheral BDNF may enhance vulnerability to Paclitaxel-Induced Peripheral Neuropathy (PIPN). **Methods:** 21 women with breast cancer were examined for peripheral neuropathy at baseline and during paclitaxel treatment, using the Total Neuropathy Score (TNSr) and the neurotoxicity subscale; Fact/GOG-NTx. Allelic discrimination of val66met BDNF polymorphism, which is reported to cause a deficit in the cellular distribution and regulated secretion of neuronal BDNF, was done by PCR and DNA sequencing. Peripheral BDNF was studied by analyzing the delta between the BDNF protein levels at baseline and after 8 weeks of treatment in each patient as was measured by ELISA. **Results:** Seven of the patients (33.3%) had TNSr $\geq$ 2 at baseline and identified to have pre-existing peripheral neuropathy (PEX-PN). The remaining 14 patients (66.7%) were identified as non-pre-existing peripheral neuropathy (NPEX-PN). The frequency of BDNF-SNP in the study population was Val/Val in 13 patients (62%) and Val/Met in 8 patients (38%). None of the patients were Met/Met (0%). We found a significantly higher incidence of the Val/Met genotype in the PEX-PN group than in NPEX-PN (5 out of 7 (71.4%) vs. 3 out of 14 (21.4%) respectively). Correspondingly, patients carrying the Val/Met genotype reached higher maximal TNSr and Fact-GOG scores in response to paclitaxel compared to Val/Val patients (4.69 ± 0.74 vs. 8.87 ± 2, respectively, prob > t 0.02; and 8.69 ± 1.96 vs. 20.37 ± 3.24, respectively, prob > t 0.002). As regards peripheral BDNF we found that BDNF decreased in patients with PEX-PN along their treatment with paclitaxel while it increased in NPEX-PN (-1.58 ± 2.80 ng/ml vs. $+6.16 \pm 2.58$ ng/ml, respectively, prob > $t = 0.03$). **Conclusions:** BDNF may play a protective role in PIPN, and exhaustion of its peripheral resources may lead to the exacerbation of PIPN. The genetic data presented here suggests that dysfunctional neuronal BDNF-induced repair mechanism due to BDNF-SNP may be a predisposing condition that exacerbates PIPN.

1024 Poster Session (Board #138), Sat, 8:00 AM-11:30 AM

Hippocampal memory impairment in breast cancer survivors after chemotherapy measurement using covert testing. *First Author: Anthony J. Ryals, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Cognitive impairments are frequently reported following adjuvant chemotherapy, yet potential neuropathological substrates remain uncertain. Chemotherapy and anti-estrogen therapy have neurotoxic effects in rodent models, with disproportionate impairment of the structure and function of the hippocampus, a critical structure for long-term declarative and relational memory. To date, there have been no detailed assessments of human hippocampal function following adjuvant chemotherapy. **Methods:** We used a specialized test of covert long-term memory processing sensitive to hippocampal impairment, involving eye-movement tracking coupled with functional MRI (fMRI). We compared 13 premenopausal breast cancer survivors on tamoxifen who were within 18 months of completing adjuvant chemotherapy to 14 healthy controls. **Results:** Relative to controls, patients were not impaired on standard delayed overt recognition memory testing or on neuropsychological tests. In contrast, patients were impaired in eye-movement-based discrimination of repeated visual scenes matched on configural similarity. Impairments were associated with less recruitment of hippocampal activity during covert memory testing. The location of hippocampal relative hypoactivity co-localized with regions of hippocampus that showed significant local volume reductions in survivors, demonstrating concurrence of structural and functional measures of hippocampal impairment. **Conclusions:** We identified hippocampal and memory abnormalities in breast cancer survivors that were not evident using standard testing. These deficits mapped onto structural measurements of hippocampal atrophy, possibly indicating a neurologic basis of self-reported cognitive difficulties frequently experienced by cancer survivors.

1025 Poster Session (Board #139), Sat, 8:00 AM-11:30 AM

Randomized study of tailored neoadjuvant chemotherapy according to the expression of tau, topo II α, and ERCC1 versus standard chemotherapy in HER2-negative breast cancer. *First Author: Yen-Shen Lu, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

Background: We hypothesized that selecting chemotherapy (CT) agents according to the expressions of drug sensitivity predictive biomarkers from tumor sample may improve the treatment efficacy for breast cancer (BC). **Methods:** Patients (pts) with stage II/III HER2 negative BC were eligible. Tumor biopsy samples were tested with immunohistochemistry study for the expression of tau, topo II α, and ERCC1. Four cycles of neoadjuvant CT were given after randomization, followed by operation. For control arm, Docetaxel (T)/ epirubicin (E) was given. For tailored arm, 1 of the 7 different CT regimens that containing 2 drugs among T, E, cisplatin, vinorelbine, and weekly high dose 5FU/leucovorin were given according to the expression of tumor biomarkers. After operation, 2-4 cycles of adjuvant CT were given and the choice of regimens were at investigators discretion. The primary endpoint was the primary tumor (T) pathological complete response (pCR) rate, and 268 pts were planned to be recruited. In the pre-planned interim analysis after recruitment of 60% of pts, the independent data monitoring committee decided to stop the recruitment because the difference between the two arms was too small to continue this study. **Results:** From April 2009 to March 2014, a total of 161 pts were enrolled, 78 and 83 of them were randomized to control arm and tailored arm, respectively. Median age was 49, 111 (68.9%) pts were ER positive, 65 (40.4%) pts were stage III. Among the tailored arm, 58 (69.9%), 41 (49.4%), and 64 (77.1%) of pts were positive for tau, topo II α, and ERCC1, respectively. The results of efficacy were listed in table. There were significantly higher incidence of grade 3/4 leukopenia (11.7% vs. 4.4%) and febrile neutropenia (2.9% vs. 0.3%) in control arm. **Conclusions:** Using the strategy of tailored CT according to the expression of tau, topo II α, and ERCC1 did not increase the efficacy neoadjuvant CT in BC. Clinical trial information: NCT00776724.

	T pCR	T+N pCR	Clinical response (CR+PR)	3-year event free survival
Control arm	5 (6.4%)	5 (6.4%)	63 (80.8%)	74.6%
Tailored arm	6 (7.2%)	3 (3.6%)	45 (54.2%)	77.5%
p value	1.000	0.483	0.0004	0.858*

*Log-rank test of median survival, median follow up 37.7 ms.

1026 Poster Session (Board #140), Sat, 8:00 AM-11:30 AM

The utility of bi-weekly eribulin therapy for metastatic breast cancer: A Japanese multicenter phase II study (JUST-STUDY). *First Author: Tetsuhiro Yoshinami, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan*

Background: The EMBRACE study established eribulin as a standard treatment for metastatic breast cancer (MBC). However, eribulin at the standard dose and schedule (1.4 mg/m^2 on days 1 and 8 every 3 weeks) frequently leads to adverse events. The aim of this study was to investigate a new approach to control eribulin toxicity by schedule modification rather than dose modification. **Methods:** We conducted a multicenter phase 2 study to evaluate the efficacy and safety of bi-weekly eribulin. Eligibility criteria included MBC treated with both anthracycline and taxane, and up to three prior regimens of chemotherapy for MBC. Eribulin was started at the standard dose and schedule, but the schedule was changed to bi-weekly without dose reduction, if any of administration criteria were not satisfied by day 8 of the 1st cycle or day 1 of the 2nd cycle, or remained unchanged if all administration criteria were met at both time points. The primary endpoint was clinical benefit rate (CBR) of bi-weekly therapy based on RECIST v. 1.1. Secondary endpoints included time to treatment failure (TTF), OS, and safety. **Results:** From July 2012 to April 2014, 86 patients were enrolled, and 42 and 38 patients were placed in bi-weekly and standard therapy, respectively. The remaining 6 patients did not continue eribulin mainly due to disease progression just after first administration. Both treatment groups had a median of 2 prior chemotherapy regimens for MBC and similar characteristics. In the bi-weekly and standard therapy groups, the median dose intensity was 60.4% and 94.8% and the CBR was 31.0% and 21.1%, respectively. The median TTF was 81.5 days, and the median OS was 486 days in the bi-weekly group. No severe adverse event was reported in both groups. **Conclusions:** Bi-weekly eribulin therapy is effective and safe for patients unable to continue on the standard schedule of eribulin. This is the first report to show the utility of bi-weekly scheduling about eribulin. A phase 3 standard-of care trial of bi-weekly eribulin is needed.Clinical trial information: UMIN000008491.

1027 Poster Session (Board #141), Sat, 8:00 AM-11:30 AM

Utilization of neoadjuvant systemic therapy (NST) for breast cancer. *First Author: Jahan J. Mohiuddin, UNC Chapel Hill School of Medicine, Chapel Hill, NC*

Background: Multiple clinical trials demonstrated the efficacy of NST to downstage cancers and increase breast conservation. NCCN guidelines recommend NST for clinical stage IIA-IIIA patients who desire breast conservation. Understanding the national patterns of NST use is especially important in light of increasing mastectomy rates. **Methods:** Women diagnosed 2006-12 were included from the National Cancer Data Base, which contains 70% of incident cancers across the US. Logistic regression was used to examine factors associated with NST use. **Results:** Among 474,333 women, NST use increased by clinical stage: IIA (15%), IIB (39%), IIIA (52%), and IIIB (77%). Use for inflammatory breast cancer was 89%. NST use also varied by age and receptor status (Table). Mastectomy rates in patients who did not receive NST were: stage IIA (50%), IIB (69%), and IIIA (75%). On multivariable analysis, age, stage and receptor status remained significantly associated with NST. Compared to hormone receptor (HR)+/HER2- patients, adjusted odds ratios (aOR) for other groups were: HR+/HER2+ (1.91, 95% CI 1.83-2.00), HR-/HER2+ (2.56, 2.41-2.72), triple negative (2.62, 2.51-2.74). There was lower use of NST in the community (vs academic centers, aOR 0.58, 0.55-0.61) and in patients with higher vs lower Charlson comorbidity score (aOR 0.77, 0.74-0.81). There was higher use in Black vs White patients (aOR 1.11, 1.06-1.16). Medicaid and uninsured patients did not have lower NST use compared to private insurance. NST use increased over time (2012 vs 2010, aOR 1.20, 1.15-1.24). **Conclusions:** NST is an increasingly common approach, particularly for high risk clinical and biologic subtypes. However, many stage IIA-IIIA patients undergo mastectomy without attempting NST to downstage their cancers.

Percentage of patients receiving NST by stage 2010-2012.

IIA					
Age	<50	50-59	60-69	70-79	80+
HR+/HER2-	16	12	9	7	7
HR+/HER2+	31	23	19	11	9
HR-/HER2+	35	28	24	16	12
Triple negative	34	29	22	16	16
IIB					
HR+/HER2-	42	36	29	22	12
HR+/HER2+	56	49	43	30	23
HR-/HER2+	62	58	48	39	14
Triple negative	61	58	47	35	17
IIIA					
HR+/HER2-	60	49	43	30	17
HR+/HER2+	63	62	51	37	25
HR-/HER2+	76	66	60	38	24
Triple negative	74	72	62	51	48
IIIB					
HR+/HER2-	83	81	76	57	33
HR+/HER2+	91	87	80	65	55
HR-/HER2+	91	93	87	74	75
Triple negative	89	88	85	83	73

1028 Poster Session (Board #142), Sat, 8:00 AM-11:30 AM

A comparison of toxicity profiles between standard and lower dose capecitabine (CAP) in breast cancer (BC): a meta-analysis. *First Author: Tomohiro Funakoshi, The Univ of North Carolina, Chapel Hill, NC*

Background: CAP 1,250 mg/m2 BID x 14 days every 21 days (14/21) as monotherapy is the FDA approved dose and schedule for metastatic breast cancer (MBC). In trials of CAP 1,250 mg/m2 BID (14/21), 26%–65% of patients required a dose reduction due to toxicities. A more favorable toxicity profile has been reported in trials of CAP 1,000 mg/m2 BID (14/21). We performed a systematic review and meta-analysis to compare a safety profile between CAP starting dose of 1,250 and 1,000 mg/m2. **Methods:** Studies were identified using PubMed, and ASCO and San Antonio Breast Cancer Symposium abstract databases from 1966 to November 2014. Eligible studies included phase II and III trials of CAP monotherapy at 1,250 or 1,000 mg/m2 BID (14/21) for BC patients that reported adequate safety data for grade 1-4 or 3-4 adverse events (hand foot syndrome (HFS), diarrhea, fatigue, nausea, vomiting, stomatitis, neutropenia, thrombocytopenia, or anemia), dose reduction or treatment discontinuation. The summary incidence was calculated from CAP monotherapy arms of the included studies using random- effects models (comprehensive meta-analysis program Ver. 2, Englewood, NJ). **Results:** A total of 4,283 patients from 32 trials (12 phase III and 20 phase II) of CAP monotherapy were included. 29 trials were in the locally advanced or MBC setting, 2 trials were neoadjuvant, and 1 trial was adjuvant. 3,065 and 1,218 patients were treated with CAP 1,250 and 1,000 mg/m2, respectively. A significantly lower incidence of dose reductions, high grade HFS, diarrhea, neutropenia and anemia as well as all grade neutropenia was seen in CAP 1,000 mg/m2 compared to 1,250 mg/m2. (Table) **Conclusions:** CAP monotherapy at 1,000 mg/m2 BID (14/21) has a clinically meaningful and significantly better toxicity profile compared to 1,250 mg/m2 BID (14/21).

	CAP 1,250 mg/m2 Incidence % (95% CI)	CAP 1,000 mg/m2 Incidence % (95% CI)	P value
Dose reduction	39.0 (32.4-45.9)	15.9 (7.5-30.5)	0.0007
HFS (G3-4)	18.6 (14.9-22.9)	12.0 (9.0-15.7)	0.0122
Diarrhea (G3-4)	10.0 (7.4-13.2)	5.3 (3.9-7.0)	0.0050
Neutropenia (G3-4)	7.0 (5.4-9.1)	1.8 (1.1-2.9)	0.0001
Anemia (G3-4)	3.4 (2.7-4.2)	1.9 (1.0-3.5)	0.0465
Neutropenia (G1-4)	25.4 (17.3-35.7)	5.8 (1.8-17.5)	0.0015

1029 Poster Session (Board #143), Sat, 8:00 AM-11:30 AM

Phase II randomized study of nab-paclitaxel versus conventional paclitaxel as first-line therapy of metastatic HER2-negative breast cancer for neurotoxicity characterization: An Oncosur Study Group study. *First Author: Eva Ciruelos, Hospital Universitario 12 De Octubre, Madrid, Spain*

Background: Nab-paclitaxel (Nab-P) is a nanoparticle albumin-bound form of paclitaxel commonly used in various tumor types. Its main toxicity is neuropathy; however, it has not been clinically and physiologically characterized properly. **Methods:** 1st-line patients (pt) with confirmed HER2-negative metastatic breast cancer were treated with: A) conventional P 80 mg/m2 on days 1, 8 and 15; B) Nab-P 100 mg/m2 on days 1, 8 and 15; C) Nab-P 150 mg/m2 on days 1, 8 and 15; D) Nab-P 150 mg/m2 on days 1 and 15, in 28-day cycles. Primary objective: characterize neurotoxicity according to Total Neuropathy Score (TNS) and electromyographic changes. Secondary objectives: rate of induced NP, pharmacogenetic study for NP, activity, toxicity profile and QoL. **Results:** Sixty pt included from Jan 2013 until Jul 2014 in 7 centers. Median age: 59 (37-84); main sites of mets: liver (60%), bone (42%), and lung (23%). Sixteen (27%) pt stage IV at diagnosis; 52 (87%) received prior adjuvant CT (52% anthracyclines, 35% taxanes). Twelve pt remain on therapy (median 6 cycles), while 48 pt stopped treatment mainly due to disease progression (20 pt) or toxicity (17 pt, 13 NP). Most common AEs (all grades) per pt: asthenia (62%), NP (75%), alopecia (30%), neutropenia (23%) and nail toxicity (28%). Forty five pt had NP: 20 G1 (4 pt A, 6 pt B, 3 pt C, 7 pt D), 18 G2 (4 pt A, 6 pt B, 4 pt C, 4 pt D) and 7 G3 (1 pt A, 6 pt C). Median time to develop grade > 1 NP was 8.8 months (4 months in arm C; NR arms A and D). TNS scores showed a rapid deterioration in first assessments followed by a plateau. At current follow up, changes in TNS and toxicity were not statistically different between arms. Concerning genetic variants, the strongest association to NP risk corresponded to *EPHA5*-rs7349683. **Conclusions:** Median time to development of significant NP was longer than expected, except for higher Nab-P doses (arm C). No stat. differences in NP rates were observed (small simple size); numerically arm C had higher risk of G3 NP. EPHA-rs7349683 SNP is associated with higher NP risk. Detailed genomic data and EMG results will be presented. Clinical trial information: NCT01763710.

1031 Poster Session (Board #145), Sat, 8:00 AM-11:30 AM

A randomized phase III study of vinflunine versus an alkylating agent of physician's choice in metastatic breast cancer (MBC) previously treated with or resistant to an anthracycline, a taxane, an antimetabolite and a vinca-alkaloid. *First Author: Javier Cortes, Vall D'Hebron University Hospital, Barcelona, Spain*

Background: There is currently no consensus on the efficacy of chemotherapy (CT) beyond 3rd line in MBC and only eribulin (which has been recently approved) has shown to improve survival. No proven treatment options are available. VFL was tested in comparison with an AA of physician's choice in MBC treated in $> 3^{rd}$line. **Methods:** This open-label phase 3 study enrolled 594 MBC pts who have received at least 2 prior CT regimens for MBC including an anthracycline (A), a taxane (T), an antimetabolite (AM) and a vinca-alkaloid (VA). Pts were no longer candidate for those CT because of resistance and/or intolerance. Pts were randomised to VFL 280 mg/m^2 every 3 w (N=298) or to an AA used as a single agent every 3 w (N=296). Randomization was stratified by performance status (PS), number of prior CT lines for MBC and disease measurability. Primary endpoint was OS population assuming a median OS of 6.5 m for AA and a 2 m difference between arms. **Results:** Pts had a median age of 58 y [range: 28-79]; visceral metastases for 81.5% them; and had received a median of 4 prior CT regimens for MBC. Resistance was the main reason for no retreatment with A (59.9%), T (82.5%), AM (93.3%) and VA (87.4%). In the AA arm, the most frequently used agents were cyclophosphamide (33.4% of pts), carboplatin (31.4%) and cisplatin (15.5%). Median OS did not differ between arms: 9.1 m for VFL and 9.3 m for AA. Response rates were similar for VFL (6.4%) and for AA (4.4%); disease control rate was higher for VFL than for AA (43.6% vs 35.5%, P=0.0424). Median PFS was 2.4 m for VFL and 1.9 m for AA (P=0.4927). For VFL, the main grade 3-4 drug related adverse events were neutropenia (19.2% of pts vs 10.8% for AA) rarely complicated (0.7% of febrile neutropenia and 2% of neutropenic infection) and asthenia/fatigue (10.8% with grade 3; no grade 4). For AA, they were thrombocytopenia (7.7% of pts vs 3% for VFL) and asthenia/fatigue (3.1% of grade 3 only). **Conclusions:** VFL 280 mg/m^2 every 3 w did not improve OS compared to an AA of physician's choice in MBC pts treated in $> 3^{rd}$ line. The safety profile of VFL was acceptable and allows to consider testing VFL at 320 mg/m^2. Clinical trial information: NCT01091168.

1032 Poster Session (Board #146), Sat, 8:00 AM-11:30 AM

Efficacy of 12 weeks neoadjuvant nab-paclitaxel combined with carboplatinum vs. gemcitabine in triple-negative breast cancer: WSG-ADAPT TN randomized phase II trial. *First Author: Oleg Gluz, West German Study Group, Moenchengladbach, Germany*

Background: Pathological complete response (pCR) is associated with improved prognosis in TNBC, but optimal chemotherapy remains unclear. Neoadjuvant weekly nab-paclitaxel (Nab-Pac) has higher efficacy than conventional paclitaxel, with maximum benefit in TNBC. Both gemcitabine (Gem) and carboplatinum (Carbo) are interesting partners for taxane combinations, as metastastic BC data reveal. **Methods:** ADAPT TN compares 12-week neoadjuvant regimens: Carbo vs. Gem combined with Nab-Pac and aims to identify early-response markers for pCR (yPN0 and ypT0/is). TNBC patients (ER/PR $< 1\%$, centrally HER2 neg.), cT1c-cT4c, cN0/+ were randomized to arm A (Nab-Pac 125/Gem 1000 d1,8 q3w) vs. B (Nab-Pac 125/Carbo AUC2 d1,8 q3w). The trial is powered for pCR comparison by therapy arm and by presence vs. absence of early response. Pre-planned interim analysis aimed to identify a dynamic biomarker, e.g. drop of 3-week Ki-67, and to validate trial assumptions. **Results:** The first 130 randomized patients were assessed for interim analysis: 69 in arm A, 61 in arm B; 84% vs. 93% completed study therapy ($p = 0.1$), respectively. Median age was 50y. At baseline, 93% had G3 tumors, median Ki-67 was 65%; 64% had cT2-4c tumors, 23% cN+. SAE analysis: 20 SAEs in 10 patients (A) vs. 5 SAEs in 5 patients (B) were reported ($p = 0.3$). pCR occurred in 36% of patients overall; A: 25%, B: 49.2% ($p = .006$). In contrast to a strong association of baseline Ki-67 with pCR, no significant association between pCR and dynamic Ki-67 change was detected among patients with at least 500 tumor cells in the 3-week biopsy; however, 49% of patients had less than 500 tumor cells, and this condition appeared to be positively associated with pCR. **Conclusions:** Early results suggest rather intriguing high efficacy and favorable toxicity of short-term therapy with Nab-Pac + Carbo vs. Gem in unselected TNBC. Identification of early-proliferation responders by prespecified protocol for Ki-67 drop failed, possibly due to substantial tumor necrosis already after first therapy cycle. 336 pts were enrolled at 45 sites by 01/2015. The study will be completed in April, 2015. Clinical trial information: NCT01815242.

1033 Poster Session (Board #147), Sat, 8:00 AM-11:30 AM

Clinical predictors of failure of granulocyte colony stimulating factor (G-CSF) prophylaxis in patients with breast cancer treated with dose dense epirubicin (E), cyclophosphomide (C) + paclitaxel (T) Adjuvant chemotherapy: Subgroup analysis of the NCIC CTG MA.21 study (NCT00014222). *First Author: Ravi Ramjeesingh, NCIC Clinical Trials Group, Cancer Research Institute, Queen's University, Kingston, ON, Canada*

Background: Administration of prophylactic GCSF is recommended for curative chemotherapy regimens with an estimated incidence of febrile neutropenia of ≥ 20% (Smith *et al.*,JCO 24:3187-3205, 2006). Clinical predictors of failure of prophylaxis are poorly understood. **Methods:** We retrospectively analyzed data pertaining to patients treated with dose dense EC-T chemotherapy (E: 120 mg/m^2 IV Day 1 + C: 830 mg/m^2 IV Day 1, q14days x 6 cycles followed by T: 175 mg/m^2 IV q21days x 4 cycles) and primary prophylaxis with GCSF (5 μg/kg subcutaneously, days 2-13) on the NCIC CTG MA21 phase III study which compared 3 different anthracycline based chemotherapy regimens. An interim analysis has been published (Burnell *et al.,* JCO, 2010). **Results:** 695 patients were randomized to the EC-T arm and received at least one dose of protocol therapy and primary GCSF prophylaxis. 139 (20.0%) patients experienced a febrile neutropenic event; of which 46 (33.1%) were hospitalized. There were no deaths secondary to febrile neutropenia. In a multivariate analysis, no significantly detrimental role of the covariates, including the ones listed, were identified. **Conclusions:** In the context of the MA.21 study, the failure rate of primary prophylaxis with GCSF therapy for prevention of febrile neutropenia in patients treated with dose dense EC-T therapy was 20% with an associated hospitalization rate of 30%. In multivariate analysis, none of the patient variables analyzed was significantly associated with failure of GCSF prophylaxis.

Selected Covariates	OR	95% CI	P-Value
Age	0.997	0.958 - 1.038	0.883
BMI	0.995	0.966 - 1.025	0.741
Diabetes	1.597	0.42 - 6.07	0.492
Liver Disease	1.335	0.149 - 11.94	0.796
Menopausal Status	1.152	0.559 - 2.215	0.672
Performance Status	1.21	0.661 - 2.214	0.537

1034 Poster Session (Board #148), Sat, 8:00 AM-11:30 AM

A nomogram to predict axillary response to neoadjuvant chemotherapy in clinically node positive breast patients. *First Author: Jose Vila, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Many clinically node positive breast cancer patients receive neoadjuvant chemotherapy (NAC), with 40% converting to node negative. Recent trials suggest a potential role for limiting axillary surgery in these patients. This study was undertaken to develop a nomogram predicting the likelihood of axillary pathologic complete response (pCR) in biopsy-proven cN1 patients receiving NAC. **Methods:** Patients with cT1-4N1M0 disease who received NAC and underwent axillary lymph node dissection were identified. Patients received anthracycline- and/or taxane-based therapy with trastuzumab in HER2+ patients. Estrogen receptor (ER) was recorded as the percentage of cells staining positive. Univariate and multivariate logistic regression analyses were performed to determine factors predictive of nodal conversion. A nomogram to predict the likelihood of nodal pCR was constructed. **Results:** A total of 614 cN1 patients were included: 93 (15%) cT1, 367 (60%) cT2, 107 (17%) cT3, and 47 (8%) cT4. Imaging showed multifocal disease in 24% (146/614). Receptor status was ER+ in 75% (458/614), PR+ in 64% (394/612), and HER2+ in 20% (124/614). Axillary pCR was achieved in 37% (228/614). On univariate analysis, nuclear grade (OR 13.67 grade 3 vs. 1, p = < .001) and HER2+ status (OR 4.6, p < .0001) were predictive of nodal pCR. Significant negative factors included multifocality on imaging (OR 0.67, p = 0.045), lobular histology (OR 0.53, p < .0001), PR+ (OR 0.24, p < .0001), ER percentage as a continuous variable (OR 0.98, p < .0001) as well as ER+ categorized as > 1% staining (OR 0.29, p < .0001). Nomograms to predict nodal pCR were created using these variables in addition to the clinically significant factors of T stage and number of abnormal nodes on US (< 4 vs. ≥ 4). The discrimination of the nomogram using ER positive (> 1% staining) versus negative (AUC = 0.775) was improved using the percentage of ER staining (AUC = 0.789). **Conclusions:** Multifocality, histology, nuclear grade, ER, PR, and HER2 status predict the ability to achieve nodal pCR with NAC. A nomogram incorporating these factors predicts the likelihood of nodal pCR with NAC which may help guide decisions regarding surgical management of the axilla in these patients.

1035 Poster Session (Board #149), Sat, 8:00 AM-11:30 AM

Direct effects on bone metabolism induced by perioperative anthracycline- and/or taxane-based chemotherapy depend on the menopausal status of patients with primary breast cancer. *First Author: Nadine Rauschenbach, Gynecologic Center Bonn-Friedensplatz, Bonn, Germany*

Background: Whereas cancer therapy-induced bone loss (CTIBL) is among the well-known sequelae of adjuvant endocrine therapy in patients (pts) with primary breast cancer (PBC), the knowledge about direct effects of modern perioperative Ctx protocols on bone metabolism is limited. This translational project was initiated to gain detailed insights into the influence of anthracycline (A)- and/or taxane (T)-based Ctx on bone turnover of both pre- and postmenopausal PBC pts in the clinical routine. **Methods:** Data of 109 pts (premenopausal: 49; postmenopausal: 60) receiving A- and/or-T-based neoadjuvant or adjuvant Ctx were included. Serum bone markers including the C-telopeptide of type I collagen (ICTP) indicating osteoclast activity, the N-propeptide of type I collagen (P1NP) measuring osteoblast activity, and bone alkaline phosphatase (BALP) were determined at baseline and prior to each subsequent Ctx cycle (C) up to C6. Changes of ICTP, P1NP, and BALP over time were analyzed by repeated-measure ANOVA. **Results:** 600 Ctx cycles were analyzed. Baseline levels of ICTP (p = 0.0027), P1NP (p = 0.0063), and BALP (p = 0.0007) were significantly higher in post- versus premenopausal pts. BALP levels remained largely unchanged during Ctx. Trends showing an increase of ICTP from baseline until C6 in premenopausal pts and a decrease in postmenopausal pts did not reach statistical significance. In contrast, P1NP significantly declined in postmenopausal pts from baseline to C6 (p = 0.0152). In premenopausal pts, P1NP declined from baseline to C3 and thereafter increased to C6. These changes were highly significant (p = 0.0024). **Conclusions:** Our study represents one of the first systematic evaluations of bone turnover in pts exposed to A- and/or T-based Ctx for PBC in the clinical routine. In postmenopausal pts, Ctx was associated with a sustained suppression of osteoblast activity whereas osteoblast suppression recovered until the end of Ctx in premenopausal pts. Whether these effects will translate into an increased risk of CTIBL remains a matter of further investigations which should clearly focus on the individual menopausal status.

1036 Poster Session (Board #150), Sat, 8:00 AM-11:30 AM

Death during study treatment: An evaluation of events in 31 German clinical trials. *First Author: Jenny Furlanetto, German Breast Group, Neu-Isenburg, Germany*

Background: Information on deaths occurring during oncological clinical trials has never been systematically assessed to describe patient, tumor, and treatment characteristics. **Methods:** Information on patients´ deaths during German Breast Group (GBG) led breast cancer (BC) trials was prospectively captured. In addition to the trial databases, data were derived from death narratives that included autopsy results if performed. All deaths were evaluated for possible causes, underlying conditions, treatment relatedness, time point and rate of autopsies. **Results:** From 12/1996 to 12/2014 23,570 patients were treated within 31 trials. Of those 75 (0.3%) died on therapy within 14 trials. 29/12,956 patients died in neoadjuvant (0.2%), 35/9,851 in adjuvant (0.3%) and 11/763 in metastatic studies (1.4%). Median age was 64 yrs (range 35-84), 63.5% of patients had an abnormal BMI (25.7% underweight, 32.4% overweight, 5.4% obese); 60% had 1-3 and 13.3% ≥ 4 comorbidities; 56% had 1-2 cardiovascular risk factors (CRFs); 45.3% took ≥ 3 drugs; 80% had an ECOG 0. Over 50% of patients had a stage III tumor at baseline with a luminal B-like BC subtype (HR+/Her2-/G3). More patients with advanced disease had a high BMI (p = 0.024), ≥ 3 comorbidities (p = 0.013) and CRFs (p = 0.001) compared to early stage patients. Main causes of death were infections (34.7%; febrile neutropenia 4%), cardiac (14.7%) and respiratory disorders (12%). 13% of patients (4 in metastatic BC, 6 in early BC) had a disease progression. 42.5% of patients received taxane (T)-based chemotherapy (CT) and the event mostly occurred in the first 4 cycles. Relatedness to chemotherapy was declared in 55% of patients, mainly when a T-based CT was given (51.2% for T-based CT, 14.6% for anthracycline (A)-based CT, 22% for A-T-based CT, 12.2% for other regimens (capecitabine, bevacizumab, lapatinib, CMF, celecoxib), none for hormone therapy); p = 0.001). An autopsy was performed in 13% of patients. **Conclusions:** Death during study treatment was mainly related to infections, and patients with advanced disease, high BMI, underlying comorbidities and CRFs. If considered for study participation these patients need careful monitoring due to their higher risk for death on study.

1037 Poster Session (Board #151), Sat, 8:00 AM-11:30 AM

Tumor infiltrating lymphocytes (TILs) in HER2 positive breast cancer: Evaluation according to the new recommendations by the international TILs working group 2014. *First Author: Houman Nafisi, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Assessment of TILS has gained interest in oncologic pathology especially as a predictor of outcome in HER2+ and triple negative breast cancer (BC). Recently, a standardized approach to assess TILs on routine histopathology slides as a biomarker in BC was recommended by an international panel of experts. Using this approach, we assessed the inter rater reliability and predictive value of TILs in HER2+ locally advanced BC cases. **Methods:** Core biopsies from52 HER2+ BC patients obtained prior to neoadjuvant (NAT) chemotherapy with or without trastuzumab (T) were identified. Two pathologists independently quantified stromal TILs, intratumoral heterogeneity (ITH), presence of lymphocyte predominant (LPBC, ≥ 60%) BC and tertiary lymphoid structure (TLS) using H&E-stained slides following 2014 international guidelines. Discordant results were resolved by reviewing on a double headed microscope. The association of TILs as continous and categorical (LPBC) variables with complete pathological response (pCR) rates was determined by Mann-Whitney WIlcox test. Inter rater reliability was measured using Cohen's Kappa coefficient. **Results:** An average of 4 cores per case were assessed. 8/52 (15%) cases had LPBC. Heterogeneity was mild in 30, moderate in 16 and severe in 6 cases. The pathologists agreed on 90%, 96% and 88% of the cases for quantitative TILs, LPBC(≥ 60%) and ITH, inter rater reliability was excellent (Cohen's Kappa 0.89, 0.85 and 0.81 respectively). On univariate analysis, high levels of TILs and LPBC were associated with greater pCR rates for the cohort of patients who received NAT with T (p= 0.004, p = 0.05 respectively). **Conclusions:** Our results show that the levels of TILs can be reliably assessed on breast core biopsies. High levels of TILs as a continous variable and LPBC are candidate predictors of pCR in Her2+ BC patients receiving NAT T.

1038 Poster Session (Board #152), Sat, 8:00 AM-11:30 AM

A phase I/II trial of olaparib in combination with eribulin in patients with advanced or metastatic triple negative breast cancer (TNBC) previously treated with anthracyclines and taxanes: First results from phase I. *First Author: Hiroyuki Yasojima, National Hospital Organization Osaka National Hospital, Osaka, Japan*

Background: Olaparib is a PARP inhibitor which has been reported to be effective against some solid tumors and the recommended dose is 300 mg bid as monotherapy. Eribulin is currently a global standard drug after treatment with anthracyclines and taxanes in advanced TNBC; however, olaparib has also shown promising efficacy in breast cancer with BRCA mutations, which are associated particularly with TNBC. Therefore, we designed this phase I/II trial (UMIN000009498) with an expectation of synergistic effects. **Methods:** By the traditional 3+3 design, 1.4 mg/m^2 of eribulin was administered intravenously on days 1 and 8. Olaparib tablet was orally administered twice daily according to dose escalation method from level 1: 25 mg bid to level 7: 300 mg bid. Dose-limiting toxicities (DLTs) consist of neutropenia G4 over seven days, thrombocytopenia G4, febrile neutropenia, non-hematotoxicity G3/4, administration of eribulin deferred on both days 8 and 15 due to adverse events, and onset of cycle 2 delayed over 14 days. **Results:** Twenty-four patients were enrolled from February 2013 to April 2014. The median age was 52 years old (range: 36 to 77). The median number of prior chemotherapy regimens was 3 (range: 2 to 7). Significant adverse events (G3 or higher) were neutropenia (87.5%), febrile neutropenia (20.8%) and anemia (16.7%). Nausea (54.2%) of any grade was also observed, for which most subjects required antiemetic. There was only one DLT observed through phase I part; a subject in level 7 could not be administered eribulin on both day8 and 15 due to neutropenia. In respect to efficacy, PR in 4 patients and SD in 12 patients were observed. The response rate was 18.2% [n = 4/22], while the disease control rate (PR and SD) was 72.7% [n = 16/22]. C_{max} and AUC of olaparib were correlated with its dose. PK parameters of both eribulin and olaparib were not influenced by each other. **Conclusions:** RD of olaparib was estimated to 300 mg bid because MTD was not attained. Now we are conducting phase II part. Enrollment has already completed and the final results will be available reported in the third quarter of 2015. Clinical trial information: 000009498.

1039 Poster Session (Board #153), Sat, 8:00 AM-11:30 AM

Neoadjuvant chemotherapy plus trastuzumab in stage II/III breast cancer with low HER2 expression. *First Author: Qamar J. Khan, University of Kansas Medical Center, Kansas City, MO*

Background: Adjuvant trials have demonstrated that addition of trastuzumab (T) to chemotherapy reduces risk of recurrence and death in women with HER2 overexpressed or gene amplified early breast cancer (BC). Central testing of specimens from patients in NSABP B-31 demonstrated that ~ 10% of patients without overexpression/gene amplification of HER2 had similar benefit from adjuvant T. Aim of this study was to assess pathologic complete response (pCR) when T is added to neo-adjuvant (NA) chemotherapy in women not exhibiting HER2 FISH amplification but had low level of protein (IHC) expression (1+ or 2+). **Methods:** Single arm phase II trial of clinical stage II/III operable BC with HER2 expression of 1+ or 2+ by IHC and FISH negative (Ratio < 2). All clinically suspicious axillary nodes were biopsied. Eligible women received 12 weeks of weekly nab-paclitaxel (100mg/m2) + weekly T (4mg/kg LD then 2mg/kg) followed by 4 cycles of dose dense AC (60/600), followed by surgery. Women with + axillary nodes at diagnosis had ALND. **Results:** 32 subjects were enrolled between 7/2009-9/2013. Median age was 53. 59% were postmenopausal. 6% had grade 1, 41% grade 2 and 53% had grade 3 tumor. All but 1 were ER + (97%) with average ER expression of 85% (range 50-99%). 22 tumors (70%) were 1+ by IHC; 10 (30%) were 2+. Median tumor size was 4.1 cm (range 1.5 to 8cm). 17 (53%) had biopsy proven + axillary nodes. 14 subjects had clinical CR after 12 weeks of nab-paclitaxel/trastuzumab. 18 had cCR at completion of AC. 8 (25%) patients had pCR in breast. 7 (22%) had pCR in breast + axilla. Of 17 biopsy proven node + patients at diagnosis, 9 (53%) were rendered node negative at surgery. 14 (44%) had one or more grade 3 toxicity. Neuropathy was noted in 23 (72%) subjects (53% grade 1, 19% grade 2). No cardiac events observed. 29/32 women completed all therapy. **Conclusions:** Neo-adjuvant T/nab-paclitaxel followed by AC in HER2 negative, ER + BC resulted in pCR rates higher than expected for this population. Among patients with positive axillary nodes, a very high (53%) complete response rate was noted in axilla. Correlative studies are underway to identify biomarkers of response. Benefit of T in BC with low HER2 expression should be studied in a randomized neo-adjuvant trial. Clinical trial information: NCT00944047.

1040 Poster Session (Board #154), Sat, 8:00 AM-11:30 AM

Mechanistic and clinical analysis of Sperm associated antigen 5 (SPAG5) as a novel prognostic, predictive, actionable gene in Breast Cancer (BC). *First Author: Tarek M. A. Abdel-Fatah, Nottingham University City Hospital NHS Trust, Nottingham, United Kingdom*

Background: Clinicopathological implications of SPAG5 were investigated in BC. **Methods:** *SPAG5* copy number changes and gene expression were investigated in 1980 cases of BC (METABRIC cohort) and validated in multicentre databases (n = 3500). SPAG5 protein expression was evaluated in three primary BC cohorts (n = 2250) with 20-year-median follow-up. The response to chemotherapy (CT) was investigated in two cohorts in whom pathological complete response (pCR) was the primary endpoint: a) Multicentre phase II trial (NCT00455533; n = 295) received doxorubicin/cyclophosphamide followed by 1:1 randomisation to ixabepilone or paclitaxel and b) 250 BC treated with neoadjuvant-anthracycline (AC). BC cell lines with high (+) and low (-) SPAG5 expressions were tested for CT sensitivity. **Results:** 10-20% of BC showed gain/amplification of SPAG5 locus at Ch17q11.2. *SPAG5* gain/amplification and mRNA+ were significantly associated with: TP53 mutation; PAM50 Her2; PAM50 Basal; PAM50 LumB and integrative molecular clusters 1, 5, 9 and 10 ($p < 0.0001$). *SPAG5* gain/amplification, mRNA+ and protein+ were associated with poor survival and were independent prognostic factor ($p < 0.0001$). In the clinical trial, *SPAG5* mRNA+ was associated with higher pCR (OR = 2.3, 95% CI = 1.2-4.2, p = 0.008), especially among ER- BC (OR = 2.8, 95% CI = 1.3-5.9, p = 0.007). Patients with *SPAG5*-mRNA+ in the ixapeblone arm achieved higher pCR in all patients (OR = 3.0, 95% CI = 1.3-7.1, p = 0.01) and ER- cases (OR = 4.2, 95% CI = 1.3-13.0, p = 0.01). In the paclitaxel arm there was no statistical association between pCR and SPAG5 mRNA level. SPAG5-protien+ was shown to be an independent predictor for pCR (OR; 2.4; 95% CI = 1.6-3.9, $p < 0.001$). In *in vitro* cell line models, SPAG5+ expression was linked to cell response to CT drugs, irrespective of ER and TP53 status. For instance, T47D and BT549 cell lines with SPAG5+ expression were sensitive to Doxorubicin and knocking-down of SPAG5 made cells resistant to CT agents. **Conclusions:** SPAG5 is a novel amplified gene on ch17.q11 and is an independent prognostic factor. SPAG5 could help in the selection of patients who will benefit from AC-CT. and its interaction with TP53 need to be explored.

1041 Poster Session (Board #155), Sat, 8:00 AM-11:30 AM

A model-based approach to dose optimization of neurotoxic chemotherapy for metastatic breast cancer (MBC). *First Author: Manish Sharma, The University of Chicago Medicine, Chicago, IL*

Background: CALGB 40502 (Alliance) randomized patients (pts) with MBC to paclitaxel 90 mg/m^2, nab-paclitaxel 150 mg/m^2, or ixabepilone 16 mg/m^2 on days 1, 8 and 15 every 28 days, with or without bevacizumab. The aims of this analysis were to develop a model of chemotherapy-induced peripheral neuropathy (CIPN) using dosing data and patient-reported symptoms, and to use this model to inform a dose adjustment algorithm to reduce CIPN. **Methods:** FGSUM4 is the sum of scores from 4 questions of the FACT/GOG Neurotoxicity subscale, which are scored 0-4 on a Likert scale and inquire about numbness/tingling and discomfort in the hands and feet. Of 799 pts, data from 655 with baseline FGSUM4 $\leq$ 4 were used to develop a kinetic-pharmacodynamic model of CIPN. Baseline height, weight, age, race and prior taxane therapy were evaluated as covariates. The model was evaluated by standard diagnostic plots and bootstrapping. Simulations evaluated the model's ability to predict later CIPN from early CIPN data. Simulations were also used to explore dose adjustments to minimize later CIPN. **Results:** The model identified paclitaxel as the least neurotoxic drug in the study: for paclitaxel, the median average dose per day divided by SDK_{50} (a parameter that reflects clearance and intrinsic toxicity) was 0.56, compared to 0.95 for nab-paclitaxel and 1.02 for ixabepilone. Using the first 3 cycles of data, the model predicts mean FGSUM4 $\geq$ 5 at later time points with 73% sensitivity and 73% specificity. Simulations support a dose adjustment algorithm in which pts with 4 $\leq$ FGSUM4 $<$ 8 after 3 cycles skip the day 8 dose in subsequent cycles, while pts with FGSUM4 $\geq$ 8 skip the day 8 dose and reduce the day 1 and 15 doses by 50%. This algorithm reduces the number of pts with FGSUM4 $\geq$ 8 after 6 cycles by 33% compared to no dose adjustment. **Conclusions:** A model of CIPN in pts with MBC treated with neurotoxic chemotherapy was developed using patient-reported symptoms from CALGB 40502. The model can use early CIPN assessments to predict later CIPN with good sensitivity and specificity. Simulations support a dose adjustment algorithm after the first 3 cycles of therapy that reduces later CIPN. Validation of the model with an independent data set is necessary before clinical use.

1042 Poster Session (Board #156), Sat, 8:00 AM-11:30 AM

Association of non-disruptive P53 mutations with poor progression-free survival (PFS) in resected breast cancer treated with neoadjuvant chemotherapy. *First Author: Alejandro Martinez-Bueno, Instituto Oncológico Dr Rosell, Hospital Universitario Quirón Dexeus, Barcelona, Spain*

Background: Neoadjuvant chemotherapy is generally used for treatment of both early stage and locally advanced breast cancer. However, robust prognostic or predictive biomarkers are needed in this setting. *TP53* is mutated in 23% of breast cancers, although this frequency varies widely among different histologies. HER-2 amplified and basal-like tumors show the higher rates of mutation: 37% and 45%, respectively. We tested whether *TP53* mutations influence disease free-survival (DFS) in breast cancer patients treated with neoadjuvant chemotherapy (NACT). **Methods:** We assessed *TP53* status in pretreatment paraffin-embedded tumor samples from a cohort of 79 breast cancer patients (p) treated homogenously with NACT. Of these, 26 were HER2+ and 53 HER2 negative. *TP53* mutations were classified as "disruptive" (D) and "non disruptive" (ND) according to the degree of disturbance of p53 protein function and structure. **Results:** Mutations in exons 5-8 of *TP53* were detected in 16 patients (20%). Of those, 6 harbored disruptive and 10 non-disruptive mutations. As previously reported, *TP53* mutations were more common in non-luminal subgroups. After 40 months of follow-up, no recurrences had occurred among *TP53* D patients (0%), compared with 7 in the *TP53* WT group (11.1%) and 5 in *TP53* ND (50%). No deaths were registered in *TP53* D group, compared with 4 (6.3%) in TP53 WT and 2 (20%) in *TP53* ND. Median progression-free survival (PFS) in patients with ND mutations was 24.5 months (CI 95% 15.2-41.7) while it was not reached in patients *TP53*-wt or carrying D mutations ($P < 0.0001$ in a Log Rank test). The association of ND mutations with shorter PFS was maintained when patients were divided according to HER2 status. **Conclusions:** Non-disruptive mutations in the *TP53* gene areassociated with shorter PFS in resected breast cancer treated treated with neoadjuvant chemotherapy. Further studies are warranted to determine whether *TP53* ND mutations can be a prognostic marker of poor outcome in this setting.

1043 Poster Session (Board #157), Sat, 8:00 AM-11:30 AM

A single institution experience of salvage therapy for locally advanced breast cancer: Treatments and trends. *First Author: Jacques Raphael, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada*

Background: Progression during neoadjuvant therapy (NAT) for LABC is uncommon. However, these patients often do poorly, and salvage treatment (ST) options are varied. Predictors of resistance or response to ST are not well defined. The goal of this study was to establish the characteristics of LABC patients requiring ST and potential predictors of response or progression after ST. **Methods:** A retrospective review was conducted using our LABC database. Survival outcomes were estimated using Kaplan-Meier. Fisher's exact test was used to estimate the probability of progression after ST. PFS1 represents the time between diagnosis and first progression (on NAT) and PFS2 the time between the first progression and the second progression (after ST), or the date of last follow up. **Results:** Eighteen patients out of 232 (8%) progressed on primary NAT. Median follow up was 23 months and the median age 51. The majority (72%) of these patients had T3/T4 disease and 56% were also N1. Tumors were mainly ductal carcinoma (89%), grade 3 (78%) and 72% had triple negative receptor phenotype (TN). Most patients (94%) had local tumor progression alone; the most commonly used ST (56%) was concurrent radiation and cisplatin (RT/CT); 69% of the TN patients had RT/CT. 93% of the patients had a clinical response to ST and 72% had mastectomy. One patient (TN) had a complete pathologic response (pCR) on surgery after RT/CT, and 10 patients (56%) had a recurrence after ST. PFS1 and PFS2 were 4.2 and 29 months respectively. Median overall survival for all patients was 37.3 months. Initial tumor size was the only variable predictive of progression after ST (p= 0.03). Patients who received concurrent RT/CT had a trend towards better PFS2 (p= 0.08). **Conclusions:** In this patient cohort, progression on NAT was comparable to the literature. Most tumors were TN and of these almost 70% received RT/CT as ST. These patients had a trend towards improved progression free survival after ST; one patient had a pCR. Ongoing work in this area is imperative; effective ST can have a significant impact on delaying disease progression. ST with RT/CT should especially be investigated further for TN LABC progressing on NAT.

1044 Poster Session (Board #158), Sat, 8:00 AM-11:30 AM

Gene expression of metastatic biopsies for prediction of response to palliative chemotherapy in breast cancer. *First Author: Theodoros Foukakis, Karolinska University Hospital, Stockholm, Sweden*

Background: To date, no clinically useful predictive tests for chemotherapy in breast cancer (BC) are available. Several studies have tried to identify predictive gene expression signatures in the neoadjuvant setting, but no data are available for metastatic BC. **Methods:** Patients with advanced breast cancer were treated with epirubicin and paclitaxel with or without capecitabine as first-line treatment in the Swedish Phase 3 TEX trial. For 111 patients, a metastatic biopsy was obtained at baseline for gene expression profiling (Affymetrix array GPL10379). PAM50 molecular subtypes and published gene modules related to immune response or proliferation were investigated as predictors of objective response to chemotherapy (by RECIST 1.0) and progression-free survival (PFS). **Results:** 102 patients were evaluated and 58 had an objective response. Table shows the PAM50 classification and the response within each subtype. Nine patients achieved a complete response, 6 of them were classified as basal-like and 3 as luminal B. Median PFS was significantly higher in luminal tumors than in non-luminal (16.5 vs. 8 months, hazard ratio = 2.2, 95% confidence interval (CI) = 1.4-3.4, $p < 0.001$ by log-rank test). A high immune response module was predictive of response to chemotherapy for the whole cohort (Odds ratio (OR) = 1.61, 95% CI 1.02-2.64) and for luminal tumors (OR = 2.91, 95% CI 1.32-7.75), but not for basal-like tumors (OR = 0.87, 95% CI 0.34-2.25). The PAM50 proliferation index was positively associated with response in patients with estrogen receptor (ER) negative tumors (OR = 2.58, 95% CI 1.06-7.83). **Conclusions:** A high immune gene module was predictive of chemotherapy response in metastatic breast cancer, but this was restricted to the subgroup of luminal tumors. ER negative tumors with high proliferation rate had a higher probability to respond to chemotherapy. Clinical trial information: nct01433614.

Objective responses within PAM50 molecular subtypes.

	Objective Response			
PAM50 subtype	**non-responders**		**responders**	
Basal-like	10	(40.0%)	15	(60.0%)
Her2 enriched	15	(51.7%)	14	(48.3%)
Luminal A	6	(60.0%)	4	(40.0%)
Luminal B	11	(34.4%)	21	(65.6%)
Normal-like	2	(33.3%)	4	(66.7%)

1045 Poster Session (Board #159), Sat, 8:00 AM-11:30 AM

Proteomic analysis of primary and metastatic breast cancers and expression of the folate receptor as a potential drug target. *First Author: Todd A. Hembrough, OncoPlex Diagnostics, Rockville, MD*

Background: The folate pathway is a critical nucleotide biosynthetic pathway in many tumor cells, and blockade of this pathway with antifolates has demonstrated clinical utility in NSCLC and mesothelioma. The folate receptor alpha (FRa) is reported to be highly expressed in triple negative breast cancer (TNBC). However, targeting this pathway with pemetrexed in metastatic breast cancer (MBC) has been a modest success (~20% response rate in unselected patients). We used multiplexed mass spectrometry (MS) to assess the expression of the FRa and other biomarkers in TNBC to identify patients who may be responsive to antifolate therapy. **Methods:** In our clinical lab, primary and metastatic BC tissues were microdissected, solubilized and enzymatically digested following CAP/CLIA guidelines. Archival BC tissues (n = 270) were analyzed following GLP protocols. Absolute quantitation of protein targets was performed using selected reaction monitoring (SRM) mass spectrometry **Results:** Using quantitative proteomic analysis, we found that ~40% of TNBC tumors express high levels of FRa. In contrast, among 247 hormone receptor-positive and HER2-positive tumors, only 8% expressed FRa. FRa showed a 10-fold range of expression in both sample sets; a range that is most likely indiscernible by IHC. Correlation analysis between FRa and several other markers of chemotherapy sensitivity in the TNBCs showed only weak correlations suggesting that the FRa pathway is not influenced by other known pathways. **Conclusions:** Multiplex MS data confirm that FRa expression is more common in TNBC than other BC subtypes, and demonstrate that there is a wide dynamic range of FRa expression Further analyses are warranted to identify a cutoff which predicts for antitumor activity of antifolate drugs. Proteomic screening should be performed to identify TNBCs which highly overexpress FRa to enrich for a population most likely to benefit from antifolate therapy. Prospective evaluation of pemetrexed and other FRa-targeted agents is warranted in metastatic TNBC pts whose cancers express high levels of FRa.

1046 Poster Session (Board #160), Sat, 8:00 AM-11:30 AM

Impact of systemic therapy on the outcomes of patients with metastatic breast cancer to brain: MD Anderson Cancer Center (MDACC) experience 1999-2012. *First Author: Diogo Bugano Diniz Gomes, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Management of metastatic breast cancer to the brain (MBC-B) is mainly surgery and/or radiation. The efficacy of systemic therapy remains controversial. **Methods:** Out of 1514 consecutive patients (pts) with MBC-B treated at MDACC October 1999-December 2012, 882 had complete data and were included in this retrospective study. We used a Cox multivariate model to identify the effect of any systemic therapy on time-to-progression in the brain (TTP-B) and overall survival (OS). **Results:** Disease subtypes: ER+/HER2- (26%) ER+/HER2+ (17%); ER-/HER2+ (20%); ER-/HER2- (33%), missing (4%). Number of brain metastasis (BM): 1 (24%), > 1 (67%), concurrent LMD (8%), missing (1%). Local treatment: metastasectomy (S) (5%), stereotactic radio-surgery (SRS) (14%), whole-brain radiation (WBRT) (58%), combination S/SRS with WBRT (12%); no treatment (11%). Subsequent systemic therapy was given to 679 pts (77%). Median OS was 9.7 months (m) (4.0-21.9). Systemic therapy prolonged OS (HR 0.44 CI 0.36-0.52 p < 0.001) for all subgroups: HER2+ (17.8 vs 3.3m); ER+/HER2- (10.7 vs 2.3m); ER-/HER2- (8.4 vs 2.4m). Other factors associated with OS: ER+, HER2+, age < 60, ECOG 0-1, single BM, controlled extra-cranial disease, local therapy to the brain, less than 3 lines of therapy prior to diagnosis of BM. Disease progression in the brain was documented in 359 pts (40.7%). Median TTP-B was 6.8m (3.7-12.1). Systemic therapy prolonged TTP-B (7 vs 4.5m; HR 0.58 CI 0.40-0.84 p = 0.005). Other factors associated with TTP-B: ER+, HER2+, single BM, and local therapy to the brain. In pts receiving anti-HER2 based therapy at diagnosis of BM, continuation of anti-HER2 agents prolonged TTP-B (HR 0.41 CI 0.23-0.72, p < 0.001) and OS (HR 0.41 CI 0.28-0.59, p < 0.001). Lapatinib-based was not superior to trastuzumab-based therapy and capecitabine was not superior to other cytotoxic agents. Pts who were on systemic therapy at diagnosis of BM and had controlled extra-cranial disease did not benefit from switching to non-cross-resistant agents. **Conclusions:** In patients with breast cancer metastatic to the brain, systemic chemotherapy was associated with better control in the brain and longer survival.

1047 Poster Session (Board #161), Sat, 8:00 AM-11:30 AM

Pre-treatment Near-Infrared Spectral Tomography (NIRST) to predict pathologic complete response to neoadjuvant chemotherapy (NAC) in women with locally advanced breast cancer (LABC). *First Author: Peter Kaufman, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: NIRST has a potential role for easily integrated monitoring and prediction of therapeutic response in women with LABC undergoing NAC. It captures biophysical changes in tissue occurring in the vascular as well as intra- and extra-cellular matrix compartments. **Methods:** 42 Women with LABC receiving NAC were enrolled in this pilot study to evaluate the role of NIRST, undergoing NIRST before, during, and after NAC. The NIRST imaging technology uses low intensity NIR light at 6 wavelengths (658-849nm) to assess total hemoglobin concentration (HbT), blood oxygen saturation (StO2), and water, at different time points. To normalize subject-specific variations of absolute HbT, StO2, and water in the tumor region, the ratios of these parameters to that of the baseline contralateral breast were used, to test the ability to differentiate patients having a pathologic complete response (pCR) versus lack of pCR. Additionally, whether the pre-treatment Dynamic Contrast MRI (CE-MRI) will improve the pre-treatment predication power was tested. A two-sample t-test was used to determine p-values for difference in mean between pCR and non pCR groups and Area Under the Receiver Operating Characteristic curve (AUC) was obtained to illustrate graphically. **Results:** The best NIRST predictor was tumor Hb_T change during the first cycle of NAC. The p-value and AUC were 0.001 and 1.0 between subjects with pCR and non pCR, respectively. A statistically-significant separation of *Pre-TX* Hb_Tbetween subjects with pCR and non pCR (p-value < 0.01, AUC = 0.92) was also found, suggesting that NIRST has the potential to differentiate between groups before NAC has begun. Additionally, by adding the delayed signal intensity enhancement of breast in pretreatment staging CE-MRI (relative to the contralateral breast), the AUC of differentiating pCR from non pCR can be raised to 0.94. **Conclusions:** Hb_T change subsequent to the first cycle of NAC and Pre-TX Hb_T correlate to response to NAC and may be predictive of pCR. These biomarker data could lead to image-based surrogates for pCR, and thus accelerate the validation of optimal NAC regimens.

1048 Poster Session (Board #162), Sat, 8:00 AM-11:30 AM

Impact of sequencing weekly paclitaxel (T) and dose-dense doxorubicin/cyclophosphamide (DDAC) on tolerability and relative dose intensity (RDI) in breast cancer (BC) patients (pts) receiving neoadjuvant chemotherapy (NAC). *First Author: Nicholas Martin LeCroy, Memorial Regional Hospital - Department of Pharmacy, Hollywood, FL*

Background: A preferred NAC regimen for HER2-negative BC is DDAC for 4 cycles followed by 12 weeks of T. RDI of 1 indicates that all intended doses are given at the scheduled interval. While large randomized studies are lacking, few studies indicated improved pCR and/or RDI when taxanes are given first. We hypothesize that tolerability and RDI are improved when T is given before DDAC. To our knowledge, this is the first study evaluating the impact of sequence on tolerability and RDI when using DDAC/weekly T. **Methods:** This IRB-approved, retrospective chart review included pts with stage II-III HER2-negative BC who received DDAC/weekly T NAC at our institution between August 2012 and May 2014. The sequence was based on physician preference. Conventional sequence group (CS) included pts who received weekly T after DDAC; reverse sequence group (RS) received T before DDAC. Our primary outcomes were rate of pCR and tolerability/RDI. **Results:** We identified 27 pts in CS and 29 pts in RS. No statistical differences between groups with respect to age, ethnicity or tumor characteristics (ER, PR, Ki67) were found. The RS had numerically more pts with stage III ($p = 0.054$). The table lists results relevant to the primary objectives. **Conclusions:** T before DDAC was associated with more pts tolerating the T maximum dose intensity (T-RDI = 1) without compromising DDAC-RDI or pCR. More pts experienced a T dose reduction (T-DR) in CS. The difference in tolerability of T cannot be explained by a specific toxicity but rather by a multitude of complications observed in CS. The most common reason for decreased T-RDI was peripheral neuropathy (PN) in both groups. Interestingly, significantly more pts in CS required pharmacologic intervention (Rx) for PN. Our study confirms the findings of others with respect to administering taxanes before antracyclines and provides specific evidence to support sequencing weekly T before DDAC.

Outcome, # (%)	CS (N = 27)	RS (N = 29)	p
T-RDI = 1	11 (40.7)	20 (69)	0.034
DDAC-RDI = 1	22 (81.5)	21 (72.4)	0.422
T-DR	11 (40.7)	5 (17.2)	0.049
pCR	5 (18.5)	5 (17.2)	0.587
Rx for PN	16 (59.3)	9 (31)	0.034

1049 Poster Session (Board #163), Sat, 8:00 AM-11:30 AM

Clinical evaluation of germline polymorphisms (SNPs) associated with capecitabine (C) toxicity (tox) in metastatic breast cancer (MBC). *First Author: Peter H. O'Donnell, The University of Chicago, Chicago, IL*

Background: C is associated with sometimes severe tox affecting patient (pt) adherence and quality of life, which can result in dose disruption/reduction potentially attenuating effectiveness. We sought to identify pharmacogenomic (PGx) markers of C tox using a novel prospective tox assessment method in a large, multi-institutional study of women with MBC. **Methods:** Pts were prospectively identified prior to C monotherapy initiation at 2000 mg/m^2/d, 14 d on/7 off. Pts completed in-person tox questionnaires (q) on d1 of each cycle (cy) and automated phone-in q on d8, d15 for 4 cy, but met study endpoint earlier if C was dose-reduced or suspended. Genetic analysis of 50 prespecified markers and a separate genome-wide association study (GWAS) were conducted with phenotypes immediate (cy 1) and overall diarrhea or hand-foot syndrome (HFS). **Results:** N = 259 pts enrolled from 14 institutions (median age 57 yrs, range 25-85). Pt adherence with tox reporting was robust, with 86% (cy 1) and 71% (cy 4) of q completed. Rates of any-grade diarrhea and HFS were 52% and 69%, respectively, including 17% reporting grade 3 diarrhea and 9% grade 3 HFS. Worst tox was identified solely via at-home phone reporting in 39% of pts. Only 29% of pts completed 4 cy without C interruption, dose change, or early discontinuation. In candidate PGx analysis, 3 SNPs associated with development of diarrhea: *DPYD*5* (OR 4.9; P = 0.0005, significant after multiple test correction), missense SNP in *MTHFR* (OR 3.3; P = 0.02), and upstream SNP of *MTRR* (OR 3.0; P = 0.03). For HFS, GWAS elucidated a novel SNP (OR 3.0; P = 0.0007) upstream of *TNFSF4*, a gene implicated in systemic sclerosis and graft-versus-host disease of skin, never before implicated in HFS. **Conclusions:** To our knowledge, this is the first PGx study to use phone-in pt self-reporting, permitting increased accuracy of tox-phenotype characterization. Three germline SNPs previously associated with fluorouracil sensitivity in preclinical/clinical models were identified, and a novel SNP having strong functional relevance was discovered. If further replicated, these markers could improve prediction of pts at highest risk for C tox, reducing morbidity and enhancing outcomes. Clinical trial information: NCT00977119.

1050 Poster Session (Board #164), Sat, 8:00 AM-11:30 AM

The role of LHRH agonists in ovarian function preservation in premenopausal women undergoing chemotherapy for early stage breast cancer: A systematic review and meta-analysis. *First Author: Rodrigo Ramella Munhoz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The risks of chemotherapy-induced ovarian dysfunction and fertility impairment remain a clinical challenge in the management of premenopausal women diagnosed with early breast cancer (EBC). For this subgroup of patients (pts) undergoing treatment with curative intent, careful consideration of techniques to minimize these risks should be given. In this setting, the role of gonadotropin-releasing hormone agonists (GnRHa) for protection of ovarian function is not fully resolved. **Methods:** We searchedPubMed, SCOPUS and Cochrane Central Register of Controlled Trials databases, as well as ASCO Annual Meeting and San Antonio Breast Cancer Symposium abstracts. Prospective, randomized trials investigating the effect of GnRHa administered concurrently with chemotherapy (CT) for ovarian function preservation were selected for data extraction. **Results:** Six placebo-controlled studies were included in the analysis, totaling 827 randomized pts (673 evaluable pts). GnRHa used for ovarian suppression included either goserelin or triptorelin. Anthracycline and cyclophosphamide-based regimens were administered to over 90% of the pts in the neo- or adjuvant setting; a smaller proportion received taxanes. The use of GnRHa was associated with statistically significant improvement in the rate of recovery of regular menses after 6 months (OR = 2.53; 95% CI 1.23-5.22; p = 0, 01) and at least 12 months (OR 1.76; 95% CI 1.17-2.64; p = 0,007) following last CT cycle among evaluable pts. A higher number of pregnancies occurred among pts treated with GnRHa in comparison to the control arms, however, the total number of attempted pregnancies was not uniformly reported and this was not statistically significant (OR 1.79; 95% IC 0.97-3.31). Additional analyzes addressing mean time to recovery of menses and changes in hormonal levels were hampered by incomplete data. **Conclusions:** This meta-analysis provides evidence to support the use of GnRHa as a tool to prevent chemotherapy-induced amenorrhea in young women undergoing treatment for EBC. Additional outcomes related to ovarian function and fertility need to be further investigated.

1051 Poster Session (Board #165), Sat, 8:00 AM-11:30 AM

FDG-PET/CT versus contrast enhanced CT for prediction of progression-free and disease-specific survival in stage IV breast cancer patients. *First Author: Christopher Riedl, Memorial Sloan-Kettering Cancer Center, Molecular Imaging and Therapy Service, New York, NY*

Background: To compare FDG PET/CT to contrast-enhanced CT (CECT) for the prediction of progression-free and disease-specific survival in stage IV breast cancer patients undergoing systemic therapy. **Methods:** The hospital database was searched for patients with stage IV breast cancer, who received first or second line systemic therapy in clinical trials from 2007-2012 and had received a (CECT)and a FDG PET/CT at baseline and within 3 months after therapy initiation. In the 71 evaluable patients identfied, response to treatment was evaluated by RECIST 1.1 for CT. For FDG PET/CT SUVmax of up to 5 FDG avid target lesions (SUVmax ≧4) was summed and response categorized by PERCIST criteria. If there was no FDG avid lesion (5 patients) response was assessed by RECIST 1.1. Response to treatment was correlated with progression-free (PFS) and disease-specific (DSS) survival. **Results:** All responders by RECIST (n = 24) were responders by PERCIST, but 43% (20/47) of the non-responders by RECIST were responders by PERCIST (Tab. 1). 2-year-PFS of responders and non-responders by RECIST was 39% and 19%, whereas 2-year PFS by PERCIST was 41% and 0%. 4-year-DSS of responders and non-responders by RECIST was 58% and 40%, whereas 4 year-DSS by PERCIST was 64% and 6% (Fig. 1). 4-year DSS of patients classified as non-responders by RECIST but as responders by PERCIST, was 72%. **Conclusions:** FDG PET/CT seems to improve prediction of PFS and DSS in stage IV breast cancer patients. Additional information gained with PET/CT, can change treatment in up 22% of patients. Prospective evaluation of FDG PET/CT for response assessment in randomized clinical trials is warranted.

		PET/CT				
		CR	**PR**	**SD**	**PD**	**Total**
CT						
	CR	2	0	0	0	2
	PR	8	14	0	0	22
	SD	5	12	8	6	31
	PD	3	0	1	12	16
	Total	18	26	9	18	71

1052 Poster Session (Board #166), Sat, 8:00 AM-11:30 AM

The early effect of breast density legislation on mammogram reporting. *First Author: Esther Jieun Lee, Loma Linda University School of Medicine, Loma Linda, CA*

Background: Federal legislation mandating mammographic breast density reporting to patients has been introduced to Congress. California enacted breast density notification legislation (SB1538) on April 1, 2013. What, if any, effect legislation has on mammogram reporting is unknown. We sought to determine the impact of legislation on mammographic density reporting. **Methods:** A retrospective review of consecutive patients undergoing mammography at a tertiary-care institution in California between March 1, 2013 and May 31, 2013 was conducted. Demographic variables and pre- and post- legislation mammogram results were analyzed. **Results:** Of 2,020 mammograms performed during the study period, 5.4% did not report breast density, leaving 1,911 cases for study. Median patient age was 58 (26-92). Dense breast tissue was reported in 72.3% of cases in the month prior to legislation, compared with 50.1% and 41.3% in the first and second months post-legislation respectively (p < 0.0001). On multivariable logistic regression analysis, dense breast tissue was independently associated with age < 50 (OR 2.42, 95%CI 1.82-3.20 vs ³50), Asian (OR 2.36, 95%CI 1.49-3.72) and Hispanic (OR 1.39, 95%CI 1.04-1.86) vs. white race/ethnicity, and lower BMI (< 25 OR 2.88, 95%CI 1.66-4.99, vs. ³30). Dense breast tissue was reported less frequently in the first month (April 2013, OR 0.65, 95%CI 0.42-1.00) and second month (May 2013, OR 0.30, 95%CI 0.17-0.52) post-legislation than pre-legislation (March 2013). **Conclusions:** Differences in breast density reporting pre- and post-legislation demonstrate the need for an objective measure of breast density. Breast density legislation has the potential to disproportionately target young, Asian, and Hispanic women. Health care providers, as well as legislators, should realize the full effects of this law on women undergoing mammograms who may have concerns regarding their results.

1053 Poster Session (Board #167), Sat, 8:00 AM-11:30 AM

Breast cancer with extensive regional lymph node involvement: Toward optimizing local management. *First Author: Lior Zvi Braunstein, Harvard Rad Onc Prog, Boston, MA*

Background: Extensive lymph node (LN) involvement portends significant risk for distant metastasis (DM) among breast cancer patients. As a result, local management may be of secondary import to systemic control in this population. We analyzed patients with ≥ 10 involved LNs (N3) to evaluate the outcomes of breast conserving surgery (BCS) vs modified radical mastectomy (MRM) in this high-risk cohort. **Methods**: From 1973-2011, 98 women with N3 disease were treated at our institution. Of these, 46 (46.9%) underwent BCS and 52 (53.1%) received MRM. Adjuvant chemotherapy was administered in 79 (80.1%) cases, and hormonal therapy in 56 (57.1%). Nearly all patients (92%) received comprehensive radiotherapy including axillary and supraclavicular fields. The Kaplan-Meier method was used to estimate local regional control (LRC), disease-free survival (DFS) and overall survival (OS). **Results:** At a median age of 51.5 years (range 26-82), 54% of patients had disease in 10-14 nodes, 26% in 15-19, and 20% had > 19 involved nodes. Median follow-up was 76 months, with a 5-year DFS of 64.9% and OS of 71.9% among the cohort. Multivariate Cox regression revealed that age < 50 years was unfavorable with regard to LRC ($p = 0.02$), although young age did not influence DFS ($p = 0.12$) or OS ($p = 0.31$). However, poorly differentiated ($p = 0.007$), ER-negative tumors (0.015) heralded adverse DFS outcomes. 10-year LRC was 91.4% following MRM and 89.3% following BCS ($p = 0.15$). Notably, treatment groups did not differ with regard to 10-year DFS (45.4% for MRM vs 57.6% for BCS; $p = 0.31$), or OS (61.4% vs 63.7%; $p = 0.79$). Though only 12 local regional recurrences were observed, 47 patients developed DM with a DM-free survival of 48.9% following MRM and 60.6% following BCS ($p = 0.19$). The use of contemporary chemotherapy improved 5-year OS (82.0% following doxorubicin, cyclophosphamide and taxol vs 61.3% for other regimens; $p = 0.04$). **Conclusions**: Patients with ≥ 10 involved LNs have similar outcomes following BCS or MRM, suggesting that radiotherapy may obviate the need for more-extensive surgery. While local regional control is comparably-favorable regardless of surgical approach, systemic control remains a challenge in this population.

1054 Poster Session (Board #168), Sat, 8:00 AM-11:30 AM

Risk of axillary node metastasis in Paget disease with invasive ductal carcinoma. *First Author: Stephanie M. Wong, Harvard School of Public Health, Boston, MA*

Background: Paget disease of the nipple is a rare manifestation of breast cancer that is associated with underlying invasive ductal carcinoma in approximately 60% of cases. The underlying pathology of patients with Paget disease and IDC is typically aggressive, with a tendency towards larger, high grade, hormone receptor-negative and HER2-positive tumors. Using population-based data, we sought to examine whether the presence of Paget disease was associated with increased risk of axillary node metastases in patients with underlying IDC. **Methods:** We identified women diagnosed with Paget disease and IDC (PD-IDC) or IDC alone and managed surgically from 2000 to 2011 using the Surveillance, Epidemiology and End Results database. We compared baseline patient demographic and tumor characteristics between the PD-IDC and IDC alone groups. We used multivariate logistic regression to examine the potential association of PD-IDC and axillary lymph node metastasis. **Results:** The study cohort consisted of 1,102 patients with PD-IDC, and 302,242 controls with IDC alone. The groups were similar with respect to patient demographics such as age (mean age 58.9 years PD-IDC vs. 58.6 years IDC, $p = 0.46$) and race distribution ($p = 0.12$). On analysis comparing characteristics of PD-IDC to IDC alone, tumors were more likely to be centrally located (26.9 vs. 5.5%, $p < 0.001$), high grade (63.5 vs. 40.3%, $p < 0.001$), larger than 2 cm (47.1 vs. 35.7%, $p < 0.001$), and estrogen/progesterone receptor-negative (45.2 vs. 22.1%, $p < 0.001$). In adjusted analysis controlling for patient age, tumor size, location, histologic grade, and hormone receptor status, PD-IDC had higher odds of axillary node metastasis (OR 1.83, $p < 0.001$) than IDC alone patients. **Conclusions:** In the context of invasive ductal carcinoma, the presence of Paget disease is independently associated with an increased risk of axillary lymph node metastasis compared with IDC alone.

1055 Poster Session (Board #169), Sat, 8:00 AM-11:30 AM

The efficacy and efficiency of half frozen section assessment of breast cancer sentinel lymph nodes: A retrospective analysis of 1116 cases. *First Author: Houpu Yang, Peking University People's Hospital, Beijing, China*

Background: Sentinel lymph node (SLN) biopsy became the standard of care for the staging of clinically negative axillary lymph node in patients with invasive breast cancer. Surgeons often request intra-operative frozen section assessment of SLN to guide treatment decision during the operation. This study was to assess whether this protocol was accurate and efficient. **Methods:** We retrospectively reviewed pathology records for consecutive breast cancer patients with frozen section of SLNB examined from 2012 to 2014. We defined paraffin section diagnosis as gold standard. Sensitivity, specificity, false negative rate, and false positive rate were calculated. The waiting time for frozen section analysis was record. **Results:** In total, 1116 cases involved frozen section evaluation of sentinel lymph nodes. The sensitivity, specificity of frozen section was 79.9%, 99.6% respectively. In 49 cases (20.1% of positive patients), the SLN was called negative during the intra-operative evaluation but positive on final examination (false negative). Furthermore, in another 3 patients, malignancy was only detected on frozen but not on paraffin sections (false positive). The waiting time for frozen diagnosis, unnecessary for true negative patients (77.8%), was 51±17 minutes, which is approximately 1.5 times the duration of a secondary axillary dissection (33±15). Only 17.4% patients from intra-operative half frozen section assessment. **Conclusions:** We do not recommend intra-operative frozen section to guide further axillary surgery, as the protocol of freezing half of SLN is not an accurate or an efficient method, with a relatively high false negative rate and some false positive cases which might make the axillary staging complicated.

1056 Poster Session (Board #170), Sat, 8:00 AM-11:30 AM

Cosmetic outcome after breast conserving surgery and either external beam or intraoperative radiotherapy for early breast cancer: Objective assessment of patients from a randomized controlled trial in Lublin, Poland. *First Author: Norman R. Williams, University College London, London, United Kingdom*

Background: The international randomised controlled TARGeted Intraoperative radioTherapy (TARGIT A) trial demonstrated non-inferiority between the technique of TARGIT (Intra-Operative RadioTherapy (IORT) with Intrabeam) and whole-breast external beam radiotherapy (EBRT) in women with early breast cancer. The aim of this study was to determine if the single high dose of TARGIT leads to impaired cosmesis in a group of patients in Lublin, Poland. **Methods:** Frontal digital photographs were taken of women participating in the TARGIT Trial at the Medical University in Lublin and analysed, blinded to treatment received, by BCCT.core software which produced overall Harris scores, and scores for various measures of symmetry, colour and scar. **Results:** 29 women (16 EBRT, 13 IORT), median age 56 years (range 49 to 79) had photographs taken at baseline (up to 2 days prior to surgery), then at 12m (median 364d). There were no differences in overall classification or measures of symmetry apparent between treatment groups. At 12m there was a significant difference in cEMDL, cEMDb and cX2b (see Table); these differences indicate more "redness" in the EBRT group compared with the IORT group. **Conclusions:** This objective assessment of aesthetic outcome in patients from a randomised trial demonstrates that "redness", a surrogate for radiation induced erythema grade I or II, is significantly worse in patients receiving EBRT compared with those receiving IORT. This study provides further evidence that the objective scoring of cosmesis using BCCT.core is feasible and may be an approach for standardisation, and confirms an early beneficial effect of TARGIT on cosmesis.

Median (first – third quartiles) of three measures of colour.

Measure	EBRT	IORT	p*
cEMDL	2.15 (1.54 - 3.48)	0.69 (0.43 - 1.10)	0.002
cEMDb	0.62 (0.37 - 0.92)	0.45 (0.15 - 0.57)	0.017
cX2b	0.22 (0.12 - 0.35)	0.13 (0.03 - 0.20)	0.037

* Wilcoxon Two-Sample test, 2-sided.

1057 Poster Session (Board #171), Sat, 8:00 AM-11:30 AM

Phase I dose escalation trial using stereotactic body radiation therapy (SBRT) for partial breast irradiation (PBI). *First Author: Asal Shoushtari Rahimi, Moncrief Rad Onc, Irving, TX*

Background: To evaluate tolerability of escalating doses of 5 fraction SBRT PBI in treating early stage breast cancer after partial mastectomy on a phase I dose escalation trial. The primary objective was to escalate the PBI dose utilizing a robotic stereotactic radiation system treating the lumpectomy cavity without exceeding the maximum tolerated dose (MTD). **Methods:** Eligible patients included DCIS or invasive ductal histologies, AJCC stage 0-II with tumor size $<$ 3cm, and margins $\geq$ 2mm. Prior to simulation 3-4 four gold fiducials were placed around the lumpectomy cavity for real-time respiratory tracking. Dose limiting toxicity (DLT) equaled grade $\geq$ 3 toxicity by CTCAE deemed definitely related to treatment for: skin, bone (fracture), pulmonary, neurological (intercostal or brachial plexus nerves) or any grade 4/ 5 toxicity definitely attributed to therapy. Both patients and physicians completed baseline and subsequent cosmesis questionnaires using a four point scale – excellent, good, fair, poor. Starting dose was 30 Gy in 5 fractions. Dose was escalated by 2.5 Gy total, provided 4 or fewer of 15 patients experienced a DLT within 90 days of treatment within each dose group. If more patients had DLT in a given dose cohort, the MTD would be exceeded. **Results:** 68 patients (15 per dose cohort (cohort 5 -8 patients)) enrolled with median age 62 years. Median follow-up for cohorts 1,2,3,4, and 5 were - 36.3, 26.4, 16, 8.8, and 2.3 months. The first 3 dose cohorts completed 90 day follow-up without DLTs. There was 1 focal grade 3 dermatitis DLT at 37.5 Gy. DLT follow-up is still ongoing in cohort 5. There were 72 grade 1 toxicity events, 2 grade 2 toxicities (rib fracture and breast pain), and 2 grade 3 radiation dermatitis toxicities. Physicians scored cosmesis as excellent or good in 94.9%, 100%, 97.7%, and 100% respectively ($p = 0.28$), at baseline, 6, 12, and 24 months post SBRT, while patients scored the same periods 82.7%, 96.2%, 95.4%, and 92.8% ($p = 0.04$). **Conclusions:** Dose is escalated to 37.5 Gy in 5 fractions without MTD thus far. Soon we are completing dose escalation for 40Gy in 5 fractions PBI, hoping to increase the likelihood of long term tumor control while evaluating toxicity and cosmesis of this innovative therapy. Clinical trial information: NCT01162200.

1058 Poster Session (Board #172), Sat, 8:00 AM-11:30 AM

Evaluation of the new Commission on Cancer Quality measure for post-mastectomy radiation treatment for breast cancer. *First Author: Christina Ahn Minami, Center for Healthcare Studies, Chicago, IL*

Background: Current National Comprehensive Cancer Network (NCCN) guidelines recommend post-mastectomy radiation therapy (PMRT) for patients with $\geq$ 4 positive lymph nodes and suggests strong consideration of PMRT in women with 1-3 positive nodes. These recommendations have been developed into a new Commission on Cancer (CoC) quality measure. Our aim was to describe the trends in the use of PMRT in breast cancer patients. **Methods:** From the National Cancer Data Base (NCDB), 268,557 mastectomies at 1123 hospitals were identified from 1998-2011. Changes in PMRT use over time were examined using random effects logistic regression analysis, adjusting for patient, tumor, and hospital characteristics. Analyses were stratified by having $\geq$ 4 nodes positive, 1-3 nodes positive, or node negative. **Results:** Overall, the proportion of patients receiving XRT increased from 1998 to 2011 ($\geq$ 4 positive nodes: 55.9% to 66.0%; 1-3 positive nodes: 25.9% to 38.0%; negative nodes: 7.9% to 8.9%, $p < 0.001$ for all), even after adjusting for differences in patient characteristics and tumor factors. When patients with T3 and T4 tumors were excluded, the proportion of patients receiving XRT similarly increased ($\geq$ 4 positive nodes: 55.1% to 66.6%; 1-3 positive nodes: 22.3% to 34.9%; negative nodes: 6.3% to 7.3%, $p < 0.001$ for all). In adjusted analyses, patients with $\geq$ 4 positive nodes were more likely to received PMRT if they had grade 3 or T3 tumors. Patients with 1-3 positive nodes were more likely to receive PMRT if they had higher grade or larger tumors. Irrespective of patients' nodal status, PMRT utilization rates decreased as age increased. **Conclusions:** Though PMRT rates increased over time in patients with $>$ 4 positive nodes and with 1-3 positive nodes, guideline-recommended use of PMRT in breast cancer patients with $\geq$ 4 positive nodes remains underutilized. Feedback to hospitals through the new CoC measure for patients with $\geq$ 4 positive nodes should help to improve adherence rates.

1059 Poster Session (Board #173), Sat, 8:00 AM-11:30 AM

Breast cancer brain metastases: Comprehensive review of tumor extent, histology and treatment on survival. *First Author: Jennifer A. Crozier, Mayo Clinic, Ponte Vedra Beach, FL*

Background: Breast cancer brain metastases (BCBM) are associated with poor overall survival (OS) and no treatment guidelines exist. Localized treatments include neurosurgery (ns), stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT). We studied the association of OS with tumor and patient (pt) characteristics, ns and radiation (rad). **Methods:** 196BCBM pts who received brain rad from 2009-2013 at three Mayo Clinic sites were retrospectively studied. Data included primary tumor histological subtype: ER+, HER2+, and triple negative (TN). ECOG status at BCBM diagnosis, number of brain lesions, ns and rad treatments were also studied. **Results:** In single variable analysis (Table), TN status had 1.8 fold ($p = 0.004$) increased hazard of death compared to ER+, while HER2+ had improved OS (HR 0.6, $p = 0.008$). Hazard of death in pts with leptomeningeal disease was 2.5 fold higher ($p = 0.003$) than pts with 1-3 brain lesions. Poor ECOG status was associated with poor OS. Pts who received WBRT and SRS had an improved OS (HR 0.37, $p < 0.001$) compared to WBRT alone. Combining ns, WBRT and SRS had better OS (HR 0.26, $p < 0.001$) than WBRT alone. **Conclusions:** In this large dataset,pts with the best OS had an ECOG score of 0, HER2+ disease, 1-3 brain lesions, and the combination of ns and rad.

OS analysis.

	Single variable analysis	
Variables	**HR (95% CI)**	**P-value**
ER+	1.0 (Ref)	
HER2+	0.61 (0.43, 0.88)	0.008
TN	1.76 (1.20, 2.58)	0.004
Number of BCBM		
1- 3	1.0 (Ref)	
0 (Leptomeningeal)	2.52 (1.38, 4.58)	0.003
≥ 4	1.41 (1.03, 1.95)	0.034
ECOG		
0	1.0 (Ref)	
1	1.53 (1.05, 2.23)	0.028
2	2.93 (1.64, 5.26)	< 0.001
3-4	6.79 (3.78, 12.19)	< 0.001
NS	0.44 (0.30, 0.63)	< 0.001
RAD		
WBRT	1.0 (Ref)	
SRS	0.78 (0.51, 1.19)	0.25
WBRT & SRS vs. WBRT as a ref	0.37 (0.26, 0.54)	< 0.001
WBRT & SRS vs. SRS as ref	0.48 (0.30, 0.77)	0.002
NS status & RAD combinations		
No NS, WBRT only (n = 87)	1.0 (Ref)	
No NS, SRS only (n = 29)	0.67 (0.42, 1.05)	0.082
No NS, WBRT and SRS both (n = 28)	0.32 (0.20, 0.51)	< 0.001
NS, WBRT only (n = 18)	0.29 (0.15, 0.57)	< 0.001
NS, SRS only (n = 7)	0.48 (0.19, 1.18)	0.11
NS, WBRT and SRS both (n = 27)	0.26 (0.16, 0.42)	< 0.001

Ref, reference; HR, hazard ratio; CI, confidence interval. Single variable Cox proportional hazard model was used for P-values.

1060 Poster Session (Board #174), Sat, 8:00 AM-11:30 AM

Effect of the use of immediate reconstruction on the rates of bilateral mastectomy and adjuvant radiation therapy use in women with node-positive breast cancer treated with neoadjuvant chemotherapy on ACOSOG Z1071 (Alliance). *First Author: Judy Caroline Boughey, Mayo Clinic, Rochester, MN*

Background: Each treatment decision can impact other multidisciplinary treatment recommendations. Herein we evaluate the interaction of surgery, reconstruction and radiation in node-positive breast cancer treated with neoadjuvant chemotherapy in a contemporary clinical trial. **Methods:** ACOSOG Z1071 (Alliance) was a prospective study evaluating sentinel node surgery after chemotherapy in patients with initial node-positive disease. We reviewed breast operation, use of immediate reconstruction and radiation on all patients who underwent mastectomy. Differences in proportions/rates were assessed with a chi-square test. **Results:** Of 686 eligible patients with data available, 409 underwent mastectomy (47% bilateral). Bilateral mastectomy rate was higher at 67% (117/176) in women undergoing immediate reconstruction compared to 33% (75/233) in women without reconstruction ($p < 0.0001$). Use of immediate reconstruction varied by clinical tumor stage at presentation, with reconstruction rates being higher in cT0-1 tumors, similar in T2 tumors and lower in cT3-4 disease ($p < 0.0001$) compared to no reconstruction. Immediate reconstruction did not vary by approximated tumor subtype, pathological tumor stage or nodal stage after chemotherapy. Adjuvant radiation was used less often in patients with immediate reconstruction (76% vs 88%, $p = 0.0002$) and those patients with pathologic complete response (72% vs 86%, $p = 0.002$). On multivariable analysis, use of immediate reconstruction was significantly associated with absence of adjuvant radiation ($p = 0.009$). **Conclusions:** A majority of node-positive patients treated with neoadjuvant chemotherapy undergoing mastectomy receive adjuvant radiation. Bilateral mastectomy rates are higher in women electing immediate reconstruction. We found that radiation therapy was less commonly used in patients with immediate reconstruction. Since radiation therapy in node-positive breast cancer may impact local control and survival, multidisciplinary input in surgical and reconstructive planning decisions is recommended. Clinical trial information: NCT00881361.

1061 Poster Session (Board #175), Sat, 8:00 AM-11:30 AM

Residual breast tissue after mastectomy in non high risk and BRCA mutated patients. *First Author: Georg Pfeiler, Med Univ of Vienna, Vienna, Austria*

Background: Skin sparing mastectomy (SSM) and nipple sparing mastectomy (NSM) and immediate reconstruction by an implant are widely used in patients with breast cancer and in high risk patients for prophylaxis. Surgical procedure is guided by oncological aspects on the one hand – meaning cutaneous/subcutaneous envelope as thin as possible – and by cosmetic aspects on the other hand – meaning envelope as thick as possible. Pre-operative MRI might help the surgeon to choose the right thickness of this envelope. In this retrospective analysis we investigated the presence of residual breast tissue and the thickness of the envelope after SSM and NSM. **Methods:** Patients treated with SSM or NSM for prophylaxis or after breast cancer at a single university hospital, who had at least one post-operative MRI, were included. MRI's were retrospectively analysed by two independent radiologists. Analyses included (a) the detection of residual breast tissue (yes/no) and (b) the maximum thickness of the envelope directly above the implant. **Results:** 39 patients of which 19 had bilateral SSM/NSM were included. 14 patients with BRCA 1/2 mutation had prophylactic bilateral SSM/NSM. Residual breast tissue could be detected in all 58 reconstructed breasts. The medium thickness of the envelope was 11.2mm (1-35mm). In patients with bilateral SSM/NSM, a strong correlation between the thickness of left and right breast envelope could be observed ($r = 0.79$, $p < 0.05$). **Conclusions:** Thickness of the envelope of the reconstructed breast does not appear to be the major determining factor of residual breast tissue.

1062 Poster Session (Board #176), Sat, 8:00 AM-11:30 AM

Detrimental effect of blood-product transfusion on survival for patients with breast cancer in Florida (1996-2007). *First Author: Hattan Alghamdi, University of Miami Hospital, Miami, FL*

Background: There has been a large body of evidence discussing the immunological effects of blood transfusion on survival in patients with a number of different types of cancers. However, few studies have examined the effect of blood transfusion on survival in breast cancer patients and these have had inconsistent results. **Methods:** Data from Florida Cancer Data System, Agency for Health Care Administration (AHCA), and the US Census were linked for female breast cancer patients in Florida (1996-2007) to understand the association of blood transfusion with female breast cancer patients' survival. Multivariate regression analyses for overall survival were adjusted for potential confounders related to blood transfusions, including age, gender, race, treatment received, and co-morbidities. **Results:** Among 120,940 patients identified, 17,686 (14.6%) received blood transfusion during the course of their treatment. The majority of patients were White (90.4%) and non-Hispanics (90.2%); most live in neighborhoods with middle-high (37.9%) and middle-low (29.2%) SES. Patients who had transfusion were older (mean = 66 years), with more advanced SEER stages (24.6% metastasis vs. 20% regional, direct extension±lymph nodes). Transfusion rates were higher in Blacks (18.8%) than in Whites (14.3%) and other races (8.2%). Medicare patients (18.1%) received more blood transfusion compared to private insurance and non-insured population (12%, both). Patients who received chemotherapy (16.8%) had higher rates of blood transfusion compared to the non-chemotherapy group (13.8%). Transfused patients had a shorter overall median survival time (7.7 years) compared to non-transfusion group (12.7 years). Among patients who received transfusion, Blacks, non-Hispanics, and patients with lower SES categories had lower overall median survival. Multivariate analysis indicated that blood transfusion is a significant independent predictor for survival (HR = 1.08;95%CI:1.03,1.13; $p < 0.001$) after adjusting demographic, clinical, and comorbid factors. **Conclusions:** Our study concludes that blood transfusion is a significant independent risk factor for survival in female breast cancer patients.

1063 Poster Session (Board #177), Sat, 8:00 AM-11:30 AM

Impact of neoadjuvant chemotherapy to surgery interval on survival outcomes in breast cancer patients. *First Author: Rachel Ann Sanford, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Retrospective analyses have sought to identify the optimal interval between surgery and initiation of adjuvant chemotherapy in breast cancer, with conflicting results. No studies have examined the impact of the interval from conclusion of neoadjuvant chemotherapy to surgery. We evaluated the relationship between survival outcomes and the time interval between neoadjuvant therapy and surgery. **Methods:** Retrospective review of the prospectively maintained Breast Medical Oncology Institutional database at The University of Texas MD Anderson Cancer Center identified 1101 women diagnosed with stage I-III breast cancer between June 1995 and April 2007 who received any neoadjuvant chemotherapy. We examined the effect of the interval from completion of neoadjuvant chemotherapy to surgery, defined as < 4 weeks, 4-6 weeks, or > 6 weeks, on survival outcomes. Descriptive statistics and Cox proportional hazards models were used. **Results:** Three hundred thirty five of 1101 patients (30.4%) had surgery within 4 weeks of their last dose of neoadjuvant chemotherapy, 524 (47.6%) within 4-6 weeks, and 242 (22%) after more than 6 weeks. Median age was 50 years, median time to surgery was 33 days (range 8-159 days) and median follow-up was 94 months (range 3-178 months). Patients whose interval was < 4 weeks were more likely to have more advanced stage ($p = 0.003$) and higher grade ($p = 0.04$) disease. The 5-year overall survival (OS) estimate was 79%, 87%, and 81% in patients who received surgery in 0-4, 4-6, and > 6 weeks after neoadjuvant chemotherapy, respectively ($p = 0.04$). The three groups did not differ in five-year locoregional recurrence-free survival (LRFS) or recurrence-free survival (RFS). In multivariate analysis adjusting for important clinical and pathologic characteristics, compared with an interval of < 4 weeks, patients who underwent surgery at 4-6 weeks or at > 6 weeks had equivalent OS (4-6 weeks HR = 0.88, 95% CI 0.68 – 1.16; > 6 weeks HR = 1.12, 95% CI 0.83 – 1.53), LRFS and RFS. **Conclusions:** Our results suggest no relationship between the neoadjuvant chemotherapy to surgery interval and overall survival, LRFS, or RFS. This data should prove reassuring to clinicians coping with ever-increasing patient volumes.

1064 Poster Session (Board #178), Sat, 8:00 AM-11:30 AM

Influence of marital status on tumor characteristics and survival in male breast cancer. *First Author: Shourya Tadisina, McLaren Flint, Flint, MI*

Background: The effect of marital status (MS) on survival varies according to cancer type and gender. To our knowledge there has been no report on the impact of MS on survival in male breast cancer (MBC). This study aims to determine the influence of MS on tumor characteristics at diagnosis and 5-year cancer specific survival (CSS) in MBC using the SEER database. **Methods**: We included patients (pts) with MBC ≥ 18 years of age in the SEER database from 1990 to 2011. Pts with unknown MS or survival data were excluded. Marital status was classified as married and unmarried (including single, divorced, separated, widowed and domestic partners). Kaplan-Meier method was used to estimate the 5-year CSS. Multivariate regression models were used to determine the independent covariates of cancer specific mortality and metastatic disease (stage IV) at diagnosis (Cox and logistic respectively). **Results**: We included 3,761 pts; 2,647 (70.4%) were married. Mean age was 64.9 years with no significant difference between the married and unmarried. Unmarried pts were more often diagnosed with advanced MBC (Stage III & IV) compared to married pts (33.3% vs. 22.1%, $p<0.0001$) but there was no significant difference in hormone receptor status, histologic grade or subtype. Unmarried pts were significantly less likely to undergo surgery compared to married pts (92.4% vs. 96.7%, $p<0.0001$). Overall unmarried pts with stage II, III & IV MBC have significantly worse 5-year CSS compared to married (Table). The survival difference between the two groups was significant only in MBC diagnosed after the year 1999. On multivariate analysis being unmarried was associated with increased hazard of death (HR=1.44, $p<0.0001$) and increased likelihood of metastatic disease at diagnosis (OR=1.95, $p<0.0001$). **Conclusions**: It is known that males with breast cancer (BC) have worse survival compared to females. Our study showed that unmarried males with BC are at an even greater risk for advanced disease at diagnosis and poorer outcomes compared to married males.

5-year cancer specific survival.

Stage	Married	Unmarried	p-value*
I	98%	96%	0.685
II	91%	86%	0.049
III	76%	71%	0.038
IV	31%	12%	0.002
Overall	88%	77%	< 0.0001

*Log rank test.

1065 Poster Session (Board #179), Sat, 8:00 AM-11:30 AM

Phase II study of panitumumab, nab-paclitaxel, and carboplatin followed by FEC neoadjuvant chemotherapy for patients with primary HER-2 negative inflammatory breast cancer. *First Author: Naoko Matsuda, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: EGFR overexpression is an independent poor prognostic factor in patients with inflammatory breast cancer (IBC). Our IBC animal model indicates that EGFR targeted therapy inhibited IBC tumor growth. It will reverse epithelial mesenchymal transition. Historically, the pathological complete response (pCR) rate in IBC has been 15%. We determined the effect of an anti-EGFR monoclonal antibody (panitumumab) of neoadjuvant chemotherapy by determining the pCR rate. **Methods:** In this single-arm, phase II prospective study, the patients received 4 cycles of combination panitumumab (2.5 mg/kg), nab-paclitaxel (100 mg/m^2), and carboplatin (AUC 2) on a weekly schedule (PNC). After the PNC regimen was completed, 4 cycles of FEC (5-fluorouracil, 500 mg/m^2; epirubicin, 100 mg/m^2; cyclophosphamide, 500 mg/m^2) was administered followed by surgical resection, radiation and hormonal therapy (ER+). The primary end point was the pCR rate. The secondary objectives were disease-free survival, safety and to identification of biomarkers. **Results:** We analyzed 25 IBC patients. Median age was 57 years (range 23-68 years). 15 were HR+/HER2- and 10 were HR-/HER2- (TNBC). The median follow-up time was 11.7 months (range, 8.7-33.9 months). The pCR rate was 36% (95% CI: 0.18-0.58). Six (60%) TNBC patients and 3 (20%) HR+/HER2- patients achieved pCR. Five patients experienced disease recurrence, and 4 died. The frequency of grade 3 or 4 hematological events was 18 (72%), grade 3 nonhematological adverse events were seen in 9 (36%) patients, (rash, n = 5; fatigue, n = 2; infection, n = 1; anorexia, n = 1; stomatitis, n = 1; pleuritic pain, n = 1) and grade 4 was 0 during the PNC regimen.The association between pCR and subtype has trending for significance (p = 0.087). There was no correlation between pCR and biomarker expression (EGFR, COX2, Nodal, E-Cadherin, Vimentin, ALDH1 expression) in 14 samples. **Conclusions:** Our data show that this novel treatment, based on the biological characteristics of IBC, produced unprecedentedly high pCR rates in TNBC. We plan to conduct a randomized study to determine the role of this regimen compared with standard regimens. Clinical trial information: NCT01036087.

1066 Poster Session (Board #180), Sat, 8:00 AM-11:30 AM

MHC II antigen presentation pathway expression in triple-negative breast cancer. *First Author: Andres Forero-Torres, University of Alabama at Birmingham, Birmingham, AL*

Background: The purpose of this study was to identify gene expression differences between triple negative breast cancer (TNBC) tumors from patients who did or did not have disease relapse. **Methods:** 47 snap frozen macro-dissected primary TNBC tumors from treatment-naïve patients, with an adequate follow up (greater than 24 months), were analyzed using RNA-seq to identify gene expression differences between patients with disease relapse and patients who did not relapse. In addition, archived de-identified primary TNBC tumors underwent standard immunohistochemical analysis with anti-CD74 and anti-HLA-DPB1 antibodies. **Results:** Database included 22 patients with disease relapse and 25 who did not relapse. 24 genes had significantly higher expression in tumor tissue from patients who did not relapse and 11 of these genes were integral members of the MHC II antigen presentation pathway. The 24 gene signature was significantly associated with progression free survival (PFS) (HR = 0.24; log rank p = 0.00016). Individually expression of CIITA and CD74, key components of the MHC II pathway, were significantly associated with PFS (HR values of 0.17 and 0.35; log rank p = 0.0002 and 0.0164. A large meta-analysis of microarray data from 199 patients with TNBC (Breast Cancer Res 2013; 140: 219) validated that 10 of the 24 genes (including 6 MHC II genes) were prognostic for PFS with a HR = 0.31; log rank p = 0.0000009 and CD74 alone was similarly prognostic with a HR = 0.31; log rank p = 0.0000019. Immunohistochemical analysis of patient primary tumors detected CD74 and HLA-DPB1 protein in TNBC tumor cells (greater than 20% of the cells), suggesting the MHC II pathway may be aberrantly expressed in tumor cells. The expression MHC II pathway genes correlated strongly with a tumor infiltrating lymphocyte gene signature. **Conclusions:** Tumor MHC II antigen presentation pathway is likely an important component of the anti-tumor immunity associated with good prognosis TNBC.

1067 Poster Session (Board #181), Sat, 8:00 AM-11:30 AM

A study of triple-negative breast cancer patients tested with a 25-gene panel of hereditary cancer genes. *First Author: John F. Sandbach, Texas Oncology Central Austin, Austin, TX*

Background: Although triple-negative breast cancer (TNBC) accounts for 15% to 20% of all breast cancers diagnosed in the US, its epidemiology is not well understood. Previous studies have shown a high incidence of *BRCA1* and, more recently, *BRCA2* mutations in patients with TNBC. As panel testing becomes more prevalent, these studies can be extended to other genes with a known breast cancer risk and improve understanding of the genetic origin of TNBC. Here we examined the gene distribution of mutations identified with a 25-gene hereditary cancer panel in patients with TNBC. **Methods:** We queried a commercial laboratory database for patients affected with breast cancer who were tested with a 25-gene panel of hereditary cancer genes from September 2013 through December 2014. Patients affected with TNBC were analyzed separately. All patient data was obtained by health care provider report on test requisition forms. **Results:** We identified 2,535 patients with a personal history of TNBC and 17,304 patients with a personal history of other breast cancers. Of the TNBC patients, 14.5% (367) were identified as having a pathogenic mutation, compared to only 8.8% (1,522) among patients with a personal history of other breast cancers. As previously reported, the TNBC mutation carriers were found to a have a higher occurrence of *BRCA1* mutations than patients with other breast cancers (47.5% and 18.1%, respectively). In line with more recent studies, we also found that 19.7% (74) of mutations in TNBC patients were in *BRCA2*. Additionally, patients with TNBC showed a marked shift in the mutation distribution in several genes relative to patients with other breast cancers. This included an enrichment in *RAD51C* (3.5%) and *PALB2* (10.9%) mutations, but a depletion in *ATM* (1.9%) and *CHEK2* (1.1%) mutations. **Conclusions:** This data confirms previous findings that patients with TNBC have a high incidence of *BRCA1* mutations. This study also shows that patients with TNBC have a different distribution of mutations compared to patients with other breast cancers. This data offers insight into the underlying genetic mutations that may drive the development of TNBC, which may allow affected patients to receive more appropriate medical management.

1068 Poster Session (Board #182), Sat, 8:00 AM-11:30 AM

Phase I dose-finding study of the gamma secretase inhibitor PF-03084014 (PF-4014) in combination with docetaxel in patients (pts) with advanced triple-negative breast cancer (TNBC). *First Author: Giuseppe Curigliano, Istituto Europeo di Oncologia, Milan, Italy*

Background: Gamma secretase is a key component of the Notch signaling pathway, which is involved in cancer cell biology and survival in various tumor types including breast cancer. PF-4014 demonstrated synergistic anti-tumor activity with docetaxel in preclinical models, supporting clinical development of this combination. **Methods:** Pts received PF-4014 orally, twice daily (BID) in combination with docetaxel Q3W, following a matrix design with the modified toxicity probability interval method. The purpose was to estimate the maximum tolerated dose (MTD); the primary endpoint was first-cycle dose-limiting toxicity (DLT). The MTD was defined as the highest, tested dose with a first-cycle DLT rate < 0.33. **Results:** In all, 22 female pts received treatment; mean age 50 yrs (27-76 yrs). The most common treatment-related adverse events (AEs) were neutropenia (91%), fatigue (77%), leukopenia (68%), nausea (64%), alopecia (59%), diarrhea (59%), and anemia (50%), which were generally mild to moderate in severity. We also noted G3 leukopenia (41%), hypophosphatemia (14%), and pneumonia (14%); and G4 neutropenia (82%), leukopenia (23%) and febrile neutropenia (FN) (18%). One G5 treatment-related AE, septic shock, occurred. DLTs are listed in the table, by treatment cohort. One pt, previously treated with paclitaxel, had a confirmed partial response in first-line treatment for advanced TNBC. Six pts had stable disease. PK and pharmacodynamic evaluations of pathway modulation in surrogate (blood) and tumor tissues are ongoing. Co-administration with PF-4014 did not affect exposure to docetaxel. **Conclusions:** The MTD estimated for the combination in pts with advanced TNBC was PF-4014 100 mg BID/docetaxel 75 mg/m^2. Antitumor activity will be assessed in an expansion cohort of pts with advanced TNBC (first-line setting). Clinical trial information: NCT01876251.

Cohort	PF-4014 100 mg BID/docetaxel 75 mg/m^2	PF-4014 150 mg BID/docetaxel 75 mg/m^2	PF-4014 100 mg BID/docetaxel 100 mg/m^2
Evaluable pts, n	8	11	3
DLT events, n (%)	1 (13) G3 diarrhea	4 (36) G3 dehydration, G3 nausea, G4 FN, G5 septic shock	1 (33) G3 diarrhea and G4 FN

1069 Poster Session (Board #183), Sat, 8:00 AM-11:30 AM

Lymphopenia after adjuvant radiotherapy (RT) to predict poor survival in triple-negative breast cancer (TNBC). *First Author: Anosheh Afghahi, Stanford Univ Med Ctr, Stanford, CA*

Background: The immune system is increasingly recognized as critical in cancer development, progression, and treatment response. Intense lymphocytic infiltration in pre-treatment biopsies predicts improved survival in TNBC; lymphopenia after RT correlates with poor prognosis in other solid tumors. We investigated the prognostic impact of RT-associated lymphopenia in early-stage TNBC. **Methods:** Diagnostic and treatment data from electronic medical records of Stanford University Hospital (SU) and Palo Alto Medical Foundation (PAMF), a nearby community practice, were linked at an individual patient level with demographic, staging and survival data from the California Cancer Registry. A Cox proportional hazards model (adjusted for patient age, race, insurance, marital and neighborhood socioeconomic status, and for tumor stage, grade, and chemotherapy receipt) was used to analyze the relationship between immunologic measures obtainable from complete blood counts (CBC) treated as continuous variables (minimum absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and white blood cell count [WBC]) and overall survival (OS). **Results:** 1211 TNBC patients (pts) seen at SU and/or PAMF were identified from 2000-2011; 218 pts with stage I-III TNBC received adjuvant RT and CBC within 12 months of starting radiation. 190 of these 218 pts (87.2%) received neoadjuvant or adjuvant chemotherapy. 58.3% of treated pts were lymphopenic (ALC $<$ 1.0 K/uL) with median ALC of 0.9 (interquartile range: 0.66-1.23). On multivariable analysis, lower ALC immediately after RT was strongly associated with worse OS (hazard ratio [HR] for death with an increase of 0.1 K/uL in ALC = 0.70, 95% confidence interval [CI]: 0.55–0.91); lower ANC (HR = 0.98, 95% CI: 0.95–1.01) and WBC (HR = 0.99, 95% CI: 0.97–1.00) were not associated with OS. **Conclusions:** Among curable TNBC pts, a low ALC after RT was independently associated with a substantial increase in the risk of death; no such effect was observed with other blood counts. These results build on tumor-based studies implicating lymphocyte function as a key determinant of treatment response and survival, and may guide development of targeted immunotherapies for TNBC.

1070 Poster Session (Board #184), Sat, 8:00 AM-11:30 AM

Masitinib plus carboplatin and gemcitabine for treatment of patients with advanced triple negative breast cancer: An open label phase Ib/II trial. *First Author: Mario Campone, Cancer Institute of the West (ICO), Nantes, France*

Background: Masitinib (MAS) is a selective inhibitor of c-Kit and mast cell function, both of which have been linked to disease progression and poor prognosis in triple negative breast cancer (TNBC). This trial evaluated MAS in combination with either carboplatin (C) and/or gemcitabine (G) as a treatment of advanced TNBC. We report here findings from the cohort receiving MAS plus CG. **Methods:** This dose-escalating phase I study assessed the safety and maximum tolerated dose of MAS plus C (AUC5) and G (1000 mg/m^{2}on days 1 and 8) over a 3 week cycle in patients (pts) with metastatic or locally advanced TNBC. Dose Limiting Toxicity (DLT) was defined as grade 3 for non-hematological adverse event (AE) or any grade 4 AE related to MAS. Phase II evaluated efficacy of the combination. **Results:** Twenty-one pts received MAS combined with CG. Reduction of dose was performed for MAS (from 9 to 6 mg/kg/day) and G (-25%) due to occurrence of DLT. In this cohort (n=13), 10/13 pts (77%) reported grade 3-4 AE (including neutropenia, 38% and thrombocytopenia, 38%); and 5/13 pts (38%) reported serious AE (including neutropenia, 15%). No treatment related deaths were reported. Overall, median OS was 10.2 months (95%CI [9.2;16.4]) and median PFS was 4.7 months (95%CI [2.1;10.8]). Objective response rate was 43%. **Conclusions:** The safety profile of MAS (6 mg/kg/day) plus C (AUC5) and G (750 mg/m^2) was acceptable, thereby defining the combination's MTD and recommended dose for further study. Efficacy findings seem to compare favorably against historic benchmarks (see table). MAS may therefore potentially offer patients a new active compound for treatment of metastatic or locally advanced TNBC. A confirmatory phase III trial evaluating MAS (6 mg/kg/day) in combination with C (AUC5) and G (750 mg/m^2) has been initiated.

	MAS + CG (n = 21)	*Benchmark CG (n = 62)
OS (months)	10.2	7.7
PFS (months)	4.7	3.6
Objective Response Rate	43%	32%
Complete	0%	2%
Partial	43%	31%

* O'Shaughnessy J, (2011) N Engl J Med 364:205.

1071 Poster Session (Board #185), Sat, 8:00 AM-11:30 AM

Enzalutamide: A new hormonal treatment for triple-negative breast cancer? *First Author: Francesco Caiazza, Education and Research Centre, St.Vincent's University Hospital and School of Medicine and Medical Science, University College Dublin, Dublin, Ireland*

Background: Like the estrogen receptor (ER), the androgen receptor (AR) is present in approximately 80% of invasive breast cancer. However, in contrast to the ER which is never expressed in triple-negative breast cancer (TNBC), the AR can be present in up to 30% of patients with this molecular subtype of breast cancer. The aim of this study was therefore to investigate the targeting of AR with the second generation anti-androgen enzalutamide as a possible new hormonal approach for the treatment of breast cancer. **Methods:** IC_{50}values for enzalutamide were determined for 14 breast cancer cell lines (8 TN; 6 non-TN), using the colony formation assay. AR was measured using both Western blotting and ELISA. Cell motility was determined using Boyden chamber assays in 4 TN cell lines. **Results:** enzalutamide IC_{50}values across 14 breast cancer cell lines varied from 4 μM to $>$ 50 μM. Response to the anti-growth activity of enzalutamide was similar in TN and non-TN cell lines but depended on the presence of AR. In addition to blocking cell growth, enzalutamide also inhibited cell migration and invasion in 3 out of 4 TN cell lines, again in an AR-dependent manner. Similar to enzalutamide, the first generation anti-androgen flutamide also blocked cell growth, migration and invasion in TNBC cell lines. The addition of doxorubicin to enzalutamide enhanced growth inhibition in 4 of 5 breast cancer cell lines investigated, including 2 TN cell lines. In contrast to doxorubicin, no enhancement of growth inhibition was found with cisplatin, carboplatin or 5-FU. **Conclusions:** We conclude that targeting AR with enzalutamide may represent a new approach to breast cancer treatment, especially for patients with AR-positive TN disease. The current availability of anti-androgens for the treatment of metastatic prostate cancer should facilitate their clinical investigation in TNBC. Finally, since the AR is expressed in several different types of cancer, targeting with enzalutamide may have wide application in cancer treatment.

1072 Poster Session (Board #186), Sat, 8:00 AM-11:30 AM

Prognostic significance of tumor subtypes in male breast cancer: A population-based study. *First Author: Jose Pablo Leone, University of Iowa, Iowa City, IA*

Background: Male breast cancer (MaBC) is an uncommon disease, information about prognostic factors is controversial and few reports have studied the role of tumor subtypes. The aim of this study was to analyze the characteristics of each tumor subtype in MaBC and its association with prognosis compared with other factors. **Methods:** We evaluated men with microscopically confirmed invasive breast cancer between 2010 and 2011 with known estrogen receptor (ER) and progesterone receptor (PR) (together hormone receptor [HR]) status and human epidermal growth factor receptor 2 (HER2) status reported to the Surveillance, Epidemiology, and End Results (SEER) program, which registers HER2 status since 2010. Patients (pts) with other primary either before or after breast cancer were excluded. Tumor subtypes were classified as: HR+/HER2-, HR+/HER2+, HR-/HER2+ and triple negative (TN). Pt characteristics were compared between tumor subtypes. Univariate and multivariate analyses were performed to determine the effect of each variable on overall survival (OS). **Results:** We included 657 pts. Median age was 65 years (range 29-97). Median follow-up was 10 months (range 0-23). At diagnosis 82.6% were ductal, 46.4% T1, 56.1% N0, 7.6% M1, 14% had breast conservation and 22% adjuvant radiotherapy. Tumor subtype distribution was: 84% HR+/HER2-, 12.2% HR+/HER2+, 1.2% HR-/HER2+ and 2.6% TN. Pts with TN tumors were younger (p = 0.007), had higher grade (p = 0.0001), presented with more advanced stage (p = 0.01), more likely to have mastectomy (p = 0.001) and to die from breast cancer (p = 0.0003). Univariate analysis showed that HER2+ was associated with shorter OS (p = 0.04) and TN pts had worse prognosis (p $<$ 0.0001). In multivariate analysis, pts who had no surgery, those with stage IV and those with TN tumors had significantly worse OS (table). **Conclusions:** In this cohort, we observed significant differences in pt characteristics according to tumor subtype. HER2+ and TN represented a small proportion of cases. In addition to stage and surgery, tumor subtype has clear influence on OS in MaBC.

	Univariate *p*	Multivariate *p*
Age	NS	
Race	NS	
Grade	NS	
ER	0.0004	
PR	0.0002	
HER2	0.04	
Stage	$<$ 0.0001	0.004
Surgery	$<$ 0.0001	0.007
Radiation	0.03	NS
Tumor subtype	$<$ 0.0001	0.001

1074 Poster Session (Board #188), Sat, 8:00 AM-11:30 AM

Neoadjuvant chemotherapy with dose-dense doxorubicin, cisplatin, and paclitaxel in patients with early triple-negative breast cancer (TNBC). *First Author: Mona Frolova, N.N. Blokhin Russian Cancer Research Center, Moscow, Russia*

Background: TNBC is characterized by aggressive behavior and poor prognosis. It has been shown that achievement of pathological complete regression (pCR) after neoadjuvant chemotherapy improved survival of patients (pts) with TNBC. Rates of pCR with standard antracycline- and taxanebased chemotherapy regimens don't exceed 20-27%. There are strong phenotypic and molecular similarities between BRCA1-related breast cancers and triple-negative sporadic tumors. Markers of BRCA1-dysfunction may predispose sensitivity to specific agents such as platinum salts. We performed a prospective trial to evaluate efficacy of dose-dense schedule of doxorubicin, cisplatin and paclitaxel in correlation with BRCA1-dysfunction in pts with early TNBC (NCT01672671). **Methods:** Pts with early TNBC (cT1-2N0-1M0) were treated with doxorubicin 25 mg/m2 iv weekly, cisplatin 30 mg/m2 iv weekly and paclitaxel 100 mg/m2 iv weekly for planned 8 weeks with G-CSF 300 mcg 2-4 days followed by surgery. Pathologic response was assessed in correlation with BRCA1-dysfunction in 17 pts. **Results:** Forty one pts were included in the study. Median agewas 44 years (23-72), 45% of pts had tumor Grade 3, Ki67 was $>$ 20% in 95% of cases. Forty pts completed chemotherapy (median treatment duration 8,9 weeks) and underwent surgery. Twenty-six pts (65%) achieved pCR. With median follow-up of 19,7 months, 3 pts had a disease progression and 2 pt died (one from disease progression and one from pulmonary embolism after 6 injections of chemotherapy). 1-year DFS was 95,1% and OS was 97,5%. The dose-limiting toxicities were neutropenia (53.7% grade 3-4) and mucositis (19.5% grade 3). In 8 pts treatment was discontinued early due to toxicity. Somatic BRCA1 5382insC mutation correlated with achievement of pCR ($p = 0.004$). All pts with somatic 185delAG and C61G mutations had residual disease ($p = 0,2$ and 0,2, accordingly). **Conclusions:** Dose-dense doxorubicin, cisplatin and paclitaxel regimen shows high activity as neoadjuvant treatment of early TNBC with acceptable toxicity. Somatic BRCA1 mutations may determine different responses to platinum-based chemotherapy. Clinical trial information: NCT01672671.

1075 Poster Session (Board #189), Sat, 8:00 AM-11:30 AM

Rampant centrosome amplification and aggressive disease course of triple-negative breast cancers. *First Author: Vaishali Pannu, Georgia State University, Atlanta, GA*

Background: Centrosome amplification (CA), a cell-biological trait characteristic of pre-neoplastic and pre-invasive lesions has empirically been associated with tumor aggressiveness suggesting an early and causal role of excess centrosomes in driving tumor progression. Recent studies provide convincing evidence that CA leads to malignant transformation and promotes invasion in mammary epithelial cells. Given that supernumerary centrosomes occur in ~80% of breast cancers, we hypothesize that CA can serve as a predictor of breast cancer aggressiveness. Triple (ER/PR/Her2) negative (TN) breast cancer, a histologically-aggressive breast cancer subtype, commonly afflicts African-American (AA) women and is characterized by high recurrence, metastases, and mortality rates. TN and non-TN breast tumors follow variable kinetics of metastatic progression, and thus constitute a test bed to explore if the severity and nature of CA can distinguish the two subtypes. **Methods:** Utilizing formalin-fixed paraffin-embedded and fresh-frozen breast cancer tissues, we quantitatively assessed extent of structural and numerical centrosomal aberrations for each patient sample in a large-cohort of grade-matched TNBC ($n = 30$) and non-TNBC ($n = 98$) cases employing multi-color immunofluorescence confocal imaging and immunoblotting. **Results:** Our data establish previously unrecognized differences in incidence and severity of CA between TNBC and non-TNBC cell lines and clinical specimens. We found strong correlation between CA and markers of aggressiveness associated with breast cancer metastasis in 20 pairs of grade-matched TNBC and non-TNBC clinical specimens ($p < 0.02$). Time-lapse imaging of MDA-MB-231 cells stably-transfected with GFP-tagged centrin harboring amplified centrosomes demonstrated that CA confers enhanced migratory ability. **Conclusions:** Our study reveals a causative link between CA and breast cancer aggressiveness. Organellar disparity between breast cancer subtypes harboring different metastatic potential has immense translational value as it may allow early-risk prediction and explain higher tumor aggressiveness in TNBC patients.

1076 Poster Session (Board #190), Sat, 8:00 AM-11:30 AM

Prognostic role of androgen receptor expression in triple-negative breast cancer. *First Author: Yanru Wang, Jinling Hospital, Southern Medical University, Nanjing, China*

Background: Expression of androgen receptor (AR) was reported to be associated with estrogen receptor (ER) expression and predict better disease-free survival (DFS) and overall survival (OS) in early breast cancer. The prognostic role of AR expression in triple-negative breast cancer (TNBC) is unclear. We performed a meta-analysis of published clinical studies to date. The Cancer Genome Atlas (TCGA) data was used to evaluate the association of AR expression with survival outcomes in TNBC. **Methods:** PubMed was searched for eligible clinical studies that investigated the association of AR expression with clinical outcomes (DFS and/or OS) of TNBC. Pooled hazards ratios (HRs) for survival outcomes with 95% confidence interval (CI) were calculated using Comprehensive MetaAnalysis (v2). AR mRNA expression, clinical information and survival data of breast cancer patients were extracted from the TCGA Data Portal. OS of TNBC patients with different levels of AR expression was compared using Cox-proportional hazards model and Kaplan-Meier method in Statistical Analysis System (SAS. v9.3). **Results:** Ten retrospective studies including 2463 patients were included in the meta-analysis. AR was expressed in 590 (24.1%) patients. Expression of AR was associated with significantly better DFS (HR = 0.70, 95% CI = 0.54-0.89, $P = 0.005$) in TNBC. Although there was a trend toward longer OS in TNBC patients with AR expression, it was not statistically significant (HR = 0.76, 95% CI = 0.56-1.04, $P = 0.083$). In the TCGA dataset, mRNA expression, clinical information and survival data were available for 971 female breast cancer patients. There were 149 TNBC cases for further analysis. AR expression was significantly lower in TNBC than adjacent normal tissue ($P = 0.001$). Again although there was a trend toward longer OS in cases with higher AR expression, the difference was not statistically significant (HR = 0.71 for $>$ 10% vs $\leq$ 10% AR expression, $P = 0.583$; HR = 0.66 for $>$ 15% vs $\leq$ 15% AR expression, $P = 0.470$; and HR = 0.70 for $>$ 50% vs $\leq$ 50% AR expression, $P = 0.452$). **Conclusions:** Expression of AR in TNBC is associated with better DFS. Though there is a trend for better OS in patients with high levels of AR expression, this requires validations by additional large studies.

1077 Poster Session (Board #191), Sat, 8:00 AM-11:30 AM

Measurement of nucleotide excision repair activity and correlation with cisplatin sensitivity. *First Author: Anne Calkins, University of Tennessee College of Medicine, Memphis, TN*

Background: Nucleotide excision repair (NER) of DNA is necessary for removal of crosslinks and other damage produced by UV light, genotoxins and chemotherapies. Germline NER deficiency causes Xeroderma Pigmentosum (XP) and inevitably leads to cancer. We explored the relationships between NER, breast cancer (BC), and cisplatin, a platinum-based chemotherapy. NER removes platinum-induced DNA crosslinks. Ergo, NER deficits may contribute to sensitivity to cisplatin-based chemotherapies. **Methods:** We assessed NER deficiency and sensitivity to cisplatin and UV in 40+ BC cell lines, including various subtypes as presented by published sources (COSMIC database from Forbes et al, 2014, and Neve et al Cancer Subtype Study, 2006). To monitor NER we measured removal of [6-4] photoproducts from UV-irradiated cells using a DDB2 proteo-probe (Dreze et al. 2014). Data analysis was based in Prism with t-tests and correlation studies. **Results:** The vast majority of tested cell lines, both cancerous and non-cancerous, exhibited more than 90% removal of [6-4] photoproducts 2 hours after UV damage. In general, UV damage persisted in triple negative (TN) cell lines compared to other BC, though not statistically significant (8% damage remaining vs 2%, $p > 0.05$). NER deficiency did not correlate with either cisplatin or UV sensitivity, while cisplatin and UV sensitivities correlated with each other. Fundamentally, intermediate steps exist between DNA deficiency and cell death in the majority of cell lines. However, one TN cell line, MDA-MB-468, showed extreme NER deficiency equivalent to XP cells (89% damage remaining). We did not identify mutations in NER genes but found reduced XP group F protein (XPF). Complementation with wildtype XPF cDNA rescued NER activity. This cell line may represent a new subtype of DNA repair-deficient breast cancer. In addition, BRCA1 and BRCA2 gene mutation status did not correlate with NER activity. **Conclusions:** We propose NER deficiency is present in DNA repair-deficient breast cancer, specifically in the TN subtype. NER deficiency is oncogenic and may be a driver of cancer. Measurement of NER in breast tumors may identify patients who benefit from platinum-based therapies.

1078 Poster Session (Board #192), Sat, 8:00 AM-11:30 AM

Nuclear HSET as a negative prognostic indicator and racial disparity biomarker in breast cancer patients. *First Author: Angela Ogden, Georgia State University, Atlanta, GA*

Background: The kinesin HSET (human spleen, embryo, and testes) is a negative prognostic indicator in cancer. Specifically, increased expression levels are associated with brain metastases in lung cancer, and increased nuclear levels are associated with worse overall and progression-free survival in breast cancer. HSET is overexpressed in triple-negative breast cancer, which is associated with African American (AA) race; however, a definitive role for HSET in health disparity has not been established. **Methods:** To probe associations between HSET levels, race, and prognosis, formalin-fixed paraffin-embedded breast tumor biopsies from 149 AA and 109 European American (EA) patients were immunostained for HSET. Staining intensity (0-3) and extent (0-100%) in nuclei and cytoplasms were determined by blinded pathologists. Weighted indices were calculated as the products of the staining intensity and extent and were stratified into low, moderate, and high groups. Associations of these groups with negative prognostic indicators and overall and progression-free survival were determined using Cox proportional hazards and Kaplan-Meier analyses. **Results:** High nuclear HSET was associated with more advanced grade and a higher percentage of Ki67-positive cells than low nuclear HSET regardless of race ($P < 0.05$ for all). However, high nuclear HSET was only associated with triple-negative receptor status ($P < 0.001$) and worse overall survival ($P = 0.02$) in AAs. In multivariate analysis, AA breast cancer patients with high nuclear HSET had a 5.05-fold increased risk of worse overall survival after adjusting for grade, stage, and triple-negative receptor status (95% CI = 1.77-14.40). They also had a 2.72-fold increased risk of worse progression-free survival in multivariate analysis (95% CI = 1.00-7.39). Cytoplasmic HSET was not significantly associated with survival in either race. **Conclusions:** These data suggest that nuclear HSET is a valuable negative prognostic biomarker in AA breast cancer patients. Determination of nuclear HSET levels may help to risk-stratify AAs with breast cancer, who suffer disproportionate disease-specific morbidity and mortality relative to their EA counterparts.

1079 Poster Session (Board #193), Sat, 8:00 AM-11:30 AM

DNA methylation signature to identify treatment response in triple negative breast cancer. *First Author: Begona Pineda, INCLIVA, Valencia, Spain*

Background: The triple negative breast cancer (TNBC) subtype is an aggressive phenotype with scarce treatment alternatives. Chemotherapy (CT) is only effective in about 40% of patients. DNA methylation could play a role in this differential response between TNBC. The objective of our work was to define a DNA methylation profile with potential to predict response to CT in TNBC patients. **Methods:** Tumor samples from patients diagnosed with a TNBC stage I to III and considered candidate for neoadjuvant CT with anthracycline and taxane were identified. DNA was extracted from FFPA samples obtained by pre-surgery biopsy. Patients were classified according to residual cancer burden (RCB) index in responders (RCB = 0, n = 10) *vs.* non-responders (RCB > 0, n = 14). DNA methylation was performed by the Infinium HumanMethylation450 array (Illumina) that allows interrogating more than 485,000 methylation CpG sites per sample. The selection criteria were: $p < 0.05$ and mean difference between methylation groups of $\geq 20\%$. The functions associated to genes were analyzed using the Gene Ontology FDR. **Results:** We identified 24 samples from TNBC patients. Median age was 58.4 (48.5-69.0) years. Most patients presented T1-2 tumors (72%), no axillar lymph involvement (53%). Proliferative scores were high with 53% of patients with ki67 > 60% and 88% of grade 3 tumors. We have detected 133 differentially methylated CpGs allowing clearly separate the responders from the non-responders. Thirty five were located at CpG islands (CGIs) or CGI shores at promoter regions. We selected 11 CpGs corresponding to 11 genes with the less variation intragroup (standard deviation $\leq 20\%$). Nine of them showed a consistent DNA methylation profile of consecutive CpGs. Of these, 5 genes (genes 1 to 5) increased and 4 genes (genes 6 to 9) decreased methylation in non-responding patients compared to those who responded to treatment. The increase ratio varies between 0.20 and 0.27, and the decrease ranges between -0.21 and -0.22. Some of these genes were related to Wnt and Hedgehog pathways, epithelial-mesenchymal transition and cell migration. **Conclusions:** DNA methylation profile is an interesting predictive tool for response to neoadjuvant CT in TNBC.

1080 Poster Session (Board #194), Sat, 8:00 AM-11:30 AM

A Phase II study of cabozantinib for metastatic triple-negative breast cancer (TNBC). *First Author: Sara M. Tolaney, Dana Farber Cancer Institute, Boston, MA*

Background: Data suggests that MET expression and activation are important for initiation and progression of TNBC. We evaluated the efficacy of cabozantinib (XL184), a novel inhibitor of multiple receptor tyrosine kinases, including MET and VEGFR2, in patients with metastatic TNBC. **Methods:** In this single-arm, two-stage Phase 2 study, patients with metastatic TNBC with measurable disease by RECIST v1.1 and up to 3 lines of prior chemotherapy in the metastatic setting received cabozantinib 60 mg daily on a 21-day cycle. Patients were restaged 6 weeks following treatment initiation and every 9 weeks thereafter. The primary endpoint was objective response rate (ORR). If $\geq 1/13$ pts responded at stage 1, 22 more will be enrolled. If $\geq 4/35$ responded, the null rate (5%) would be rejected in favor of a 20% rate of activity. Predefined secondary endpoints included progression free survival (PFS) and toxicity. **Results:** Thirty-five patients (median age 50 years, range 31-78) initiated protocol therapy and were included in this analysis. Patients had 0 (n = 6, 17%), 1 (n = 18, 51%), 2 (n = 4, 11%), or 3 (n = 7, 20%) prior lines of chemotherapy for metastatic disease. Two patients achieved confirmed PR (ORR 9% [95% CI 1-25%]) and 3 achieved unconfirmed PR; 18 patients (51%, 95% CI: 34-69%) had SD as their best response. The clinical benefit rate at 15 weeks was 31% (95% CI 17-49%) and the median PFS was 1.9 months (95% CI 1.3-3.3). The most common toxicities (all grades) were fatigue (77%), diarrhea (40%), mucositis (37%), and palmar-plantar erthrodysesthesia (PPE) (37%). There were no grade 4 toxicities. Twelve (34%) patients required dose reduction, 4 due to PPE and 8 due to other toxicities. Ongoing studies are exploring MET expression and amplification in archival tumor samples, MET amplification in circulating tumor cells, and plasma biomarkers of response to cabozantinib. **Conclusions:** In patients with metastatic TNBC, cabozantinib monotherapy showed evidence of antitumor activity. Adverse events requiring dose reduction occurred in about one-third of patients. Biomarker changes and their association with outcome will be presented at the meeting. Clinical trial information: NCT02260531.

1081 Poster Session (Board #195), Sat, 8:00 AM-11:30 AM

Contribution of immune system and tumor-related interferon signaling to epirubicin response in triple-negative (TN) breast cancers. *First Author: Giampaolo Bianchini, San Raffaele Scientific Institute, Milan, Italy*

Background: In HER2+ patients treated with HER2-targeted monoclonal antibodies in the NeoSphere trial, multivariate analysis showed a complex interplay between immune system and response (Gianni L SABCS 2012). High STAT1 and IGG metagens were associated with pCR, whereas high MHC1 and Interferon-inducible (IF.I) metagenes were associated with resistance. We sought to assess in TN tumors if there is a similar relationship between immune system and response to anthracyclines, which leads to immunogenic cell death **Methods:** We selected Affymetrix GEPs for 87 TN breast cancers (BCs) treated with neoadjuvant epirubicin monotherapy in the TOP trial (Desmedt C JCO 2011). Association between four previously define immune metagenes (IGG, STAT1, IF.I and MHC1), pCR and distant metastasis free survival (DMFS) were assessed. We assessed in 51 BC cell lines (25 TN) if isolated cells themselves also express those immune-related genes. **Results:** In TOP trial, immune metagenes were not associated with pCR in univariate analysis. In multivariate analysis, high STAT1 (OR 5.17 (1.66-16.1); $p = 0.004$) and low MHC1 (OR 0.19 (0.07-0.51); $p = 0.001$) were associated with pCR. Significance was retained when clinical variables and TOP2A amplification/deletion were included. In univariate analysis for DMFS, only high STAT1 was associated with lower risk of relapse (HR 0.62 (0.43-0.90); $p = 0.012$). In multivariate, high STAT1 (HR 0.26 (0.12-0.59); $p = 0.001$) and low IF.I (HR 2.75 (1.26-6.00); $p = 0.01$) were associated with lower risk of recurrence. Results were similar when only patients with residual disease were considered in the analysis. In BC cell lines, expression of MHC1-related genes was very heterogeneous from low to very high. A group of cell lines, TN and HER2+ in particular, expressed also some IF.I/STAT1 related genes. **Conclusions:** Multivariate analysis is needed to uncover the contribution of immune components to the response and prognosis of TN tumors treated with anthracyclines, which was similar to the involvement with response of HER2+ tumors to monoclonals. Interferon signaling, defined by STAT1 and IF.I metagenes, and MHC1 expression are related to both the immune system status and tumor cells.

1082 Poster Session (Board #196), Sat, 8:00 AM-11:30 AM

Cisplatin with or without rucaparib after preoperative chemotherapy in patients with triple negative breast cancer: Final efficacy results of Hoosier Oncology Group BRE09-146. *First Author: Kathy Miller, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Patients (pts) with triple negative breast cancer (TNBC) with residual disease after neoadjuvant therapy have a high risk of recurrence. **Methods:** Pts with BRCA mutations and/or TNBC with lymph node (LN) or > 2 cm of invasive disease after anthracycline (A) and/or taxane (T) neoadjuvant therapy were assigned 1:1 to cisplatin (C: 75 mg/m^{2}D1 q3 wks x 4) +/- rucaparib (R: 24-30 mg IV D1,2,3 q3 wks x 4 followed by R 30 mg IV or 100 mg orally wkly for 24 wks). BROCA analysis identified deleterious germline mutations. Pharmacokinetic sampling to assess R exposure was obtained during IV and oral dosing. The primary objective was 2-yr DFS. **Results:** From Feb 2010 to May 2013, 128 pts were enrolled. Median tumor size at surgery was 1.9 cm (0-11.5) with median LN involvement 1 (0-38); median Residual Cancer Burden (RCB) score was 2.6. Neoadjuvant therapy included A in 57% and T in 91%. 86.7% of pts received radiation therapy prior to entry. BROCA identified deleterious mutations (8 BRCA 1, 12 BRCA 2, 2 BRIP1) in 22/101 (22%) pts. 8 pts randomized to C and 1 to CR did not start therapy. Toxicity was similar in both arms. Despite frequent dose reductions (21% of pts.) and delays (43.8% of pts), 73% of pts completed planned C. R dose reduction was uncommon (6%). 11 pts (17.5%) assigned to CR did not begin R monotherapy; 51% of pts completed the planned 24 wks. Rucaparib exposure was limited with median(min,max) concentration 275(82,4694) ng/mL post-infusion on Day 3. Exposure was less during oral maintenance (median concentration 47(19,185) ng/mL two hours post-treatment). 2-yr DFS was similar in both arms (C-58.3%, CR-63.1%; p = 0.43). In an exploratory analysis of patients receiving A-containing neoadjuvant therapy, 2-year DFS was significantly improved with CR (55.9% vs. 69.9%; p = 0.04). Mutation status did not impact DFS. **Conclusions:** The addition of low dose R did not impact the toxicity of cisplatin or improve 2-yr DFS. The dose of R used in this study was substantially less than the current phase II monotherapy dose (600 mg orally twice daily) and may not have been sufficient to inhibit PARP activity. Clinical trial information: NCT01074970.

1083 Poster Session (Board #197), Sat, 8:00 AM-11:30 AM

A novel biomarker to predict sensitivity to enzalutamide (ENZA) in TNBC. *First Author: Joel S. Parker, UNC Chapel Hill, Chapel Hill, NC*

Background: TNBC is a heterogeneous disease with multiple subtypes and drivers. ENZA, a potent inhibitor of AR signaling, is being tested in patients (pts) whose TNBC expresses AR (> 0%) by IHC (NCT01889238). However, AR expression may not confer ENZA sensitivity. Gene profiling was therefore explored to determine whether this could be superior to IHC in predicting benefit from ENZA. **Methods:** Consent and tissue for AR testing was collected from 404 pts. Next-Gen RNA-sequencing analysis was performed on 175 tissue samples: 122 samples came from pts treated with ENZA (118 unique pts) (ITT); 55 were from untreated pts. A Training Set (TrS, n = 122); and a Validation Set (VS; n = 55) were created. TrS consisted of 80 samples from ENZA treated pts (77 unique pts) + 42 from untreated pts (29 AR = 0%; 13 AR > 0 %). VS consisted of 42 samples from ENZA treated pts (41 unique pts) + 13 from untreated pts (10 AR = 0%; 3 AR > 0 %). A gene expression model of biological subtype (GES) was built directly from the response data in the TrS. Model development utilized the elastic-net algorithm in the context of 500 rounds of Monte-Carlo cross-validation. Tuned parameters were used to validate the gene-expression model in the VS, outcomes were blinded during model validation. **Results:** The selected GES achieved 80% sensitivity and 65% specificity in prediction of 16 week clinical benefit (CBR16). Utilization of this model to define Diagnostic positive (Dx+) and Dx- populations showed the following results in pts treated with ENZA are shown in the Table. Highest accuracy was demonstrated in pts receiving ENZA as their 1st or 2nd line of therapy. **Conclusions:** A genomic signature, associated with androgen biology, has been identified that demonstrates the potential to predict clinical response to ENZA in pts with TNBC. Nearly half of the pts enrolled in the phase 2 were classified as Dx+, suggesting a reasonable prevalence of pts who may benefit from this hormonal therapy. This assay may be useful to select TNBC pts for future studies evaluating ENZA. Clinical trial information: NCT01889238.

	Training Set		Validation Set		ITT (both sets)	
	Dx+ (n=39)	Dx- (n=38)	Dx+ (n=17)	Dx- (n=24)	Dx+ (n=56)	Dx- (n=62)
CBR16 (% pts; 95% CI)	44 (29-60)	13 (5-27)	29 (12-54)	8 (2-26)	39 (27-53)	11 (5-21)
CBR24 (% pts; 95% CI)	39 (24-55)	10 (4-24)	29 (12-54)	0 (0-13)	36 (24-49)	6 (2-16)

1084 Poster Session (Board #198), Sat, 8:00 AM-11:30 AM

Rac1 inhibition to sensitize triple negative breast cancer to EGFR inhibition. *First Author: Georges Azzi, University Of Miami/Sylvester Cancer Ctr, Miami, FL*

Background: Triple Negative Breast Cancer (TNBC) a subtype of breast cancer with the poorest prognosis lacks expression of estrogen progesterone receptors and does not overexpress HER2. Currently, there are no effective targeted therapies. TNBC frequently overexpresses EGFR, a member of the ErbB family of transmembrane receptor tyrosine kinases. Although EGFR targeted therapies are approved and used widely in lung cancer and head and neck cancer, their use in breast cancer has not revealed significant activity. Previous studies in lung cancer have shown that Rac1 overexpression results in resistance to EGFR inhibition. Rac1, a Rho GTPase, is frequently overexpressed in breast cancer. We have previously reported that Rac inhibition may be an effective therapeutic strategy in breast cancer. Furthermore, we have previously shown that EGFR over-expression results in resistance to Rac inhibition in breast cancer. The aim of the current study was to assess the activity of gefitinib (an EGFR tyrosine kinase inhibitor) and a Rac inhibitor (EHT1864) alone or in combination in TNBC. **Methods:** Using proliferation and clonogenic assays we assessed the activity of gefitinib (2.5 μM) and EHT1864 (25 μM), and their use in combination on the growth of TNBC breast cancer cell lines (MDA 231, MDA 468, MDA 436, HS578T). We also confirmed the pharmacological effect of gefinitib on EGFR with molecular knockdown of EGFR in HS578T cells. **Results:** All 4 cell lines tested did not show any significant growth reduction or difference in colony formation with either agent alone but the combination was effective in significantly reducing both growth and colony formation potential in 2 of the TNBC cell lines (HS578T and MDA468). The combination of shEGFR knockdown and Rac inhibition phenocopied the results of pharmacological inhibition with gefitinib plus EHT1864. **Conclusions:** Our results suggest that Rac inhibition sensitizes a subset of TNBC to EGFR inhibition and the combination of Rac and EGFR inhibition is a promising therapeutic strategy for a subset of TNBC that warrants further studies.

1085 Poster Session (Board #199), Sat, 8:00 AM-11:30 AM

Protein activation mapping and exploratory predictive markers for pCR in triple-negative breast cancer patients treated with neratinib in the I-SPY 2 TRIAL. *First Author: Julia Dianne Wulfkuhle, George Mason Univ, Columbia, MD*

Background: In the I-SPY 2 trial, the pan-ERBB inhibitor, neratinib (N) arm was open to all HR/HER2 subtypes but graduated in the HR-/HER2+ signature. Exploratory analysis of protein signaling was performed to identify biomarker candidates correlated with pCR in the TN population. We evaluated 110 key signaling proteins using reverse phase protein microarray (RPPA) data from pre-treatment LCM purified tumor epithelium. **Methods:** Of 59 TN patients, 49 (N: 30, concurrent controls: 19) had RPPA and pCR data. RPPA data was correlated to pCR in both the treated and untreated patients using parametric (t-test) or non-parametric (Wilcoxon) statistical analysis, depending on data distribution. Only analytes whose levels were associated with response in the N but not the control arm were selected for further analysis. Markers are analyzed individually; p-values are descriptive and were not corrected for multiple comparisons. ROC analysis identified an optimal cut point and pCR rates of biomarker positive patients were assessed using that cut point. **Results:** Out of 110 analytes analyzed, only activation of HER2 Y1248, p = 0.03; EGFR Y1173, p = 0.009; were found to be positive predictors of pCR, and 3 proteins, TIE2 Y992, p = 0.02; LC3B, p = 0.02, and A-RAF S299, p = 0.0008, were found to be negative predictors of pCR. pCR rates in the biomarker positive group of 62.5% (10/16), 66% (11/16), 55%(10,/18), 67% (12/17). 61% (11/18) were determined for phospho- HER2, EGFR, TIE2, A-RAF and total LC3B, respectively, compared to a pCR rate of 40% ffor the IHC/FISH-based TN subgroup where RPPA data were available. **Conclusions:** Our sample size is too small to draw definitive conclusions. However, activation of HER2-EGFR in HER2- tumors may identify patients who respond to N. Low levels of activated A-RAF and LC3B also correlated with response. The results imply that there is a subset TN patients that paradoxically exhibit HER family signaling activation and may achieve clinical benefit with N. These findings merit future consideration as we develop trials for patients with suboptimal response to neoadjuvant therapy where biomarkers could be used as the basis for treatment reassignment. Clinical trial information: NCT01042379.

1086 Poster Session (Board #200), Sat, 8:00 AM-11:30 AM

Characterization of KCNK9 in The Cancer Genome Atlas breast cancer dataset. *First Author: Keith A. Dookeran, Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, IL*

Background: Background: KCNK9 is a maternally imprinted and functionally mono-allelic 2-pore domain K+ channel proto-oncogene. It has been posited that loss of KCNK9 methylation (LOM) is associated with more aggressive triple negative (TN) phenotype breast cancer. Epidemiologic data characterizing KCNK9 is sparse and was the rationale for this study. **Methods:** Publically available breast cancer data from The Cancer Genome Atlas on clinical factors and KCNK9 gene methylation (HM450 beta values), amplification (putative copy-number alterations (CNA) from GISTIC), and mRNA expression Z-scores (RSEM) was examined in 818 women. Multivariable (MV) logistic regression models with model-based standardization were used to estimate risk ratios (RRs) with 95% confidence intervals (CIs). **Results:** Overall, KCNK9 gene amplification was more common than deletion (58% vs. 6%, respectively). Bivariate results for KCNK9 LOM (highest tertile loss vs. others), gene amplification (CNA gain vs. normal), and mRNA expression (highest tertile vs. others) are provided in the table below. Median overall survival for women with gain was 103 vs. 140 months (log-rank test, p= 0.011), and 96 vs. 130 months for higher vs. lower expression (p=0.014), but was not different for LOM. **Conclusions:** KCNK9 gene LOM, amplification and higher mRNA expression occur more frequently in black women, and ER/PR-negative and TN disease, and amplification and expression are associated with worse survival outcome.

KCNK9	LOM			Amplification			mRNA expression		
Characteristic	RR	95% CI	p	RR	95% CI	p	RR	95% CI	P
Age at diagnosis (<50/50+)	1.21	0.94-1.56	0.148	1.01	0.81-1.27	0.902	1.25	1.01-1.55	0.044
Stage (1-2A/2B-4)	0.88	0.74-1.04	0.131	1.03	0.89-1.19	0.676	0.99	0.86-1.14	0.895
ER/PR status (-/+)	7.52	5.02-11.28	<0.001	2.54	1.79-3.61	<0.001	2.35	1.83-3.02	<0.001
HER2 status (+/-)	0.71	0.47-1.09	0.113	1.35	0.99-1.83	0.053	0.92	0.69-1.22	0.547
TN status (+/-)	9.96	5.9-16.82	<0.001	2.94	1.88-4.59	<0.001	2.87	2.09-3.92	<0.001
Race (black/white)	1.98	1.3-3.01	0.001	1.94	1.23-3.06	0.003	1.37	0.95-1.99	0.096
Ethnicity (Hispanic/white)	1.44	0.72-2.89	0.300	0.82	0.41-1.66	0.586	1.03	0.5-2.09	0.945

1087 Poster Session (Board #201), Sat, 8:00 AM-11:30 AM

Expression and significance of the co-regulatory ligands B7-H4 and PD-L1 in triple negative breast cancer. *First Author: Mehmet Altan, Yale Cancer Center/Yale School of Medicine, New Haven, CT*

Background: B7-H4 is a member of the CD28/B7 family of immune co-inhibitory molecules and is upregulated in various tumors. It has been postulated that it functions as a negative regulator of effector T-cells. Here, we measured the levels of B7-H4 and PD-L1 protein in triple negative breast cancers (TNBC) using objective methods and determined their relationship with tumor infiltrating lymphocytes (TILs) and patient outcome. **Methods:** We used automated quantitative immunofluorescence (QIF) to assess the levels of B7-H4 (clone D1M8I, CST) and PD-L1 (clone E1L3N, CST) in 96 stages I-IV TNBC represented in tissue microarray format [YTMA149]. B7-H4 and PD-L1 were measured in the tumor and stromal compartments by simultaneous staining of pancytokeratin (Dako) and DAPI. The proportion of stromal TILs was assessed in H&E stained preparations by a pathologist using 10% increments, as recently reported. Cases with more than 50% stromal TIL content were considered as lymphocyte predominant breast carcinomas (LPBC). **Results:** B7-H4 expression was detected in 83 % of cases (80/96) and PD-L1 in 9% (9/96). In samples with high B7-H4 levels, the signal was predominantly located in the tumor compartment. Elevated PD-L1 was seen both in tumor and stromal cells. LPBC corresponded to 28% of cases (26/96) and were significantly associated with tumor and stromal PD-L1 expression (Table). Expression of B7-H4 was not associated with LPBC or PD-L1 positivity. Regression analysis of PD-L1 and B7H4 is suggestive of an inverse relationship. In univariable survival analysis expression of B7-H4 and PD-L1 were not significantly associated with overall survival. **Conclusions:** B7-H4 is expressed in the majority (~80%) of TNBC, but is not associated with the lymphocyte infiltrates. PD-L1 expression occurs in a lower proportion of TNBC (~10%) and shows strong association with LPBC. Most cases that are high for B7H4 are low for PD-L1, suggesting that expression of these checkpoints may be specific to tumor regions or types. Futures studies are required to better understand the relationship between these two immune checkpoints.

Protein Expression	High TILs	Low TILs	P value
Tumor stroma PD-L1	194 ± 18	324 ± 28	<0.0005
Tumor PD-L1	219 ± 15	299 ± 30	<0.012

1088 Poster Session (Board #202), Sat, 8:00 AM-11:30 AM

Clinical utility of in depth RNA sequencing for non-metastatic triple negative breast cancers. *First Author: Benoit Thouvenot, GENCLIS, Vandoeuvre-Les-Nancy, France*

Background: Triple negative breast cancers (TNBC), that represent the most severe form of the disease, are not amenable to current targeted therapies. RNA DNA divergences (RDD) reflect changes in RNA sequences not present at the DNA level. **Methods:** DNA and RNA from fresh frozen samples collected from 65 patients diagnosed with non metastatic TNBC before the age of 65 Y were sequenced with Illumina. The cohort was divided in a training set (n = 20) -9 alive after 2500 days of follow up and 11 dead within 1000 days following diagnosis- and a blind replication set (n = 45). **Results:** On the training set, sparse PLS discriminant analysis identified 5 transcripts with statistically significant different RDD rate that, when combined, separated patients with good and poor outcome with greater than 90 % accuracy after cross validation. Kaplan-Meier analysis showed that application of the RDD based algorithm to 45 unknown samples was highly predictive of clinical outcome ($p < 10^{-4}$). Most importantly, RDD algorithm accurately predicted outcome of patients with in situ, stage I and II TNBC (n = 53), 36 were predicted with good outcome and all are alive at the last follow-up irrespective of chemotherapy (n = 10 received no post-surgery treatment). RDD algorithm performances were not affected by patients ethnic origin, recruitment centers (n = 11), BRAC mutation, nor menopausal status. Neither positive lymph node (p = 0.09), nor tumor size (p = 0.89), nor Ki67 (p = 0.84), nor an expression-based model (p = 0.82) were statistically significant predictors of TNBC clinical outcome. **Conclusions:** RDD are previously unsuspected molecular events strongly associated with TNBC severity. The most immediate clinical application of the finding is to eliminate the need for conventional and potentially harmful chemotherapy for patients with predicted good outcome. Patients included in the current analysis were mostly from the USA. Therefore, a larger retrospective study based on an european cohort (Patients and Methods of the PATH Biobank – A Resource for Breast Cancer research; Waldmann A et al. Geburtshilfe Frauenheilkd. 2014 Apr;74(4):361-369) and powered to statistically ascertain the accuracy of the test, is currently undergoing in depth RNA sequencing.

1089 Poster Session (Board #203), Sat, 8:00 AM-11:30 AM

Prognostic markers in triple-negative breast cancer (TNBC): The role of androgen receptor, e-cadherin, and Ki67. *First Author: Giuseppina Rosaria Rita Ricciardi, Medical Oncology Unit AOOR Papardo-Piemonte, Department of Human Pathology, University of Messina, Messina, Italy*

Background: TNBC represents a group of tumors with poor prognosis owing to aggressive tumor biology and lack of targeted therapies. However, TNBC is clinically and biologically heterogeneous and no clear prognostic biomarker has been identified. We evaluated the prognostic value of various clinical-pathological variables, including androgen receptor (AR), E-cadherin (CDH1) and Ki67. **Methods:** This is an observational, retrospective study of 99 patients (pts) with TNBC diagnosed during 2000-2010 in two Italian hospitals. All pts received neo/adjuvant chemotherapy (mostly anthracycline/taxane-based). Immunohistochemistry (IHC) of the primary tumors was performed in formalin-fixed paraffin-embedded primary tumor samples. CDH1 expression was considered positive as ≥ 30% of the membrane cells staining. AR positivity was defined as > 10% of positive tumor cells. High Ki67 was defined as > 14% positive tumor cells. Cox proportional hazard univariate and multivariable models were used to evaluate the associations of each variable with relapse-free survival (RFS) and overall survival (OS). Distribution of samples within groups was compared using a Chi-square test. **Results:** Median age was 61 years (range 33-83). The majority of tumors were ductal (n = 85, 85.8%), node-negative (n = 49, 58.3%), grade 3 (n = 66, 66.7%) and showed high Ki67 (n = 74, 74.7%). The distribution of tumor stage was I (n = 32, 32.3%), II (n = 37, 37.4%), III (n = 30, 30.3%). AR, CDH1 expression was found in 17.1% and 50.5% of the cases. Only 26.6% of AR-positive cases were grade 3 compared with 68.2% of grade 3 in AR-negative cases (p =0.01). At median follow-up of 62.0 months (range 3.0-118.0), 95 pts were evaluable for RFS and OS. Univariate analyses showed that lack of expression of CDH1, tumor size and nodal status were significantly associated with worse RFS and OS (p< 0.05). AR expression and low Ki67 showed a trend towards better RFS and OS. Multivariate analysis showed an independent association between CDH1 expression and better RFS and OS (p< 0.05) beyond tumor size, nodal status and grade. **Conclusions:** Our findings support the potential prognostic value of molecular biomarkers such as CDH1 that might be useful to classify subgroups of TNBC.

1090 Poster Session (Board #204), Sat, 8:00 AM-11:30 AM

Programmed cell death 1 (PD-1) receptor and programmed death ligand 1 (PD-L1) expression in primary breast cancer (BC); correlations with clinical characteristics and patient outcomes. *First Author: Neelima Vidula, UC San Francisco, San Francisco, CA*

Background: The interaction of the PD-1 receptor on tumor infiltrating lymphocytes and PD-L1 on tumor cells dampens antitumor immunity. Two phase I trials suggested efficacy of anti-PD-1/PD-L1 antibodies in triple negative (TN) BC. This study investigated associations between primary BC PD-1 and PD-L1 expression, clinical characteristics, and patient outcomes in publically available databases. **Methods:** We evaluated PD-1 and PD-L1 expression using microarray data from the neoadjuvant I-SPY 1 study (n = 149). Associations with clinical features and chemotherapy response were assessed by Kruskal-Wallis and Wilcoxon rank sum tests, respectively. Recurrence free survival (RFS) associations were assessed by the Cox proportional hazard model. Pearson correlations between PD-1 and expression of PD-L1, HAVCR2, STAT5A, FOXP3, MYC, and ESR1 were determined in I-SPY 1 and 2 other datasets: METABRIC (n = 1992) and TCGA (n = 817). **Results:** In I-SPY 1, PD-1 expression was significantly higher in HER2+ and TNBC (p = 0.003), and in grade 2/3 tumors (p = 0.043); this association was also seen in METABRIC. PD-1 expression was associated with pathologic complete response (p = 0.006) but not with tumor stage, nodal status, lymphovascular invasion or RFS. While PD-L1 did not correlate with tumor features, patients with PD-L1 expression in the lowest quintile had worse RFS, even after subtype adjustment (HR 2.33, p = 0.01). In all 3 datasets, PD-1 significantly correlated with PD-L1, HAVCR2, and STAT5A, and inversely with ESR1. In the TN subset of TCGA and METABRIC, PD-1 significantly correlated with PD-L1, HAVCR2, and STAT5A. In TCGA and METABRIC, PD-L1 significantly correlated with HAVCR2 and STAT5A, and this was also seen in the TN subset. In TCGA alone, PD-1 and PD-L1 significantly correlated with FOXP3, and PD-1 with MYC. **Conclusions:** PD-1 expression is higher in TN and other aggressive BC subtypes. PD-1 and PD-L1 correlate with immune related genes HAVCR2 and STAT5A. Low PD-L1 expression may be an adverse prognostic factor. Trials are underway to investigate the activity of anti-PD-1/PD-L1 antibodies in TNBC and to elucidate markers of response.

1091 Poster Session (Board #205), Sat, 8:00 AM-11:30 AM

Reproducibility of homologous recombination deficiency (HRD) scores in biopsies of triple negative breast cancer (TNBC) tumors. *First Author: Kirsten Timms, Myriad Genetics, Inc., Salt Lake City, UT*

Background: The HRD score is the sum of three previously described (Abkevich et al, Birkbak et al, Popova et al) metrics that quantitate genomic rearrangements. The HRD score is significantly associated with both tumor *BRCA1/2* mutations (tmBRCA) and response to DNA damaging agents in TNBC. This study assesses the consistency of the HRD score in multiple biopsies obtained from the same cancer to examine the impact of spatial heterogeneity and sampling on the results. **Methods:** HRD scores, tmBRCA, and *BRCA1* promoter methylation were assessed in 96 samples from 32 surgically resected, stage II-III breast cancers; each cancer was biopsied in three distinct areas. HR deficiency was defined as having either high HRD score ($\geq$ 42) or tmBRCA positive. **Results:** A total of 81 samples (31 tumors) yielded DNA for sequencing and generated 81 tmBRCA calls and 76 BRCA1 methylation values passing QC metrics. HRD scores were obtained for 70 (86%) samples, leaving 16 triplets and 7 duplicates available for reproducibility analysis, and 8 singles. High HRD scores were observed in all biopsies that were tmBRCA positive (3 triplets; 1 single) or *BRCA1* methylation positive (2 triplets). *BRCA1/2* mutation and *BRCA1* methylation were consistent within all replicates. *BRCA1/2* wild type tumors without *BRCA1*methylation had high HRD scores in 4 tumor sets (1 triplet; 3 pairs). The average standard deviation (SD) within replicates was 2.6 with a coefficient of variation (CV) of 9%. SD was slightly higher in samples with higher scores but the difference between low and high HRD scores was not significant (Wilcoxon p = 0.18). HR deficiency status was the same in different biopsies from each of the 31 tumors; however, observable differences were apparent between the genomic profiles. **Conclusions:** All HRD metrics examined were consistent across the multiple repeat biopsies from different regions of the same cancer. While observable changes in the genomic profiles of matched samples were noted indicating subtle within-tumor spatial genomic heterogeneity, the HRD scores were highly conserved.

1092 Poster Session (Board #206), Sat, 8:00 AM-11:30 AM

Outcomes with neoadjuvant versus adjuvant chemotherapy for T1-2 node negative triple negative breast cancer. *First Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS*

Background: Randomized studies have demonstrated that Neoadjuvant Chemotherapy (NAC) is equivalent to adjuvant chemotherapy (AdjC) in operable breast cancer (BC). However, the differential impact of NAC vs AdjC on outcomes in various BS subtypes is not known. Specifically, the impact of AdjC vs NAC BC outcomes in small (T1-2) clinically node negative (NN) triple negative breast cancer (TNBC) is not known. Aim: To evaluate the impact of NAC vs. AdjC on BC recurrence and RFS in NN T1-2 TNBC utilizing data from a prospective registry. **Methods:** 316 stage I-III TNBC patients enrolled in a multisite IRB approved registry between 2011 and 2014. Clinical, demographic, chemotherapy and recurrence information was collected. This study was restricted to analysis of registry participants with T1-2, NN disease. RFS was estimated according to the Kaplan-Meier method and compared among groups with log-rank statistic. **Results:** 146 patients with NN T1-2 TNBC enrolled on the registry since 2011. Patients underwent either NAC (67/146, 46%) or AdjC (79/146, 54%) at the discretion of treating physician. For the 146 eligible patients, median age was 55 yrs (range 24-80), 14%: African American, 49% had T1 and 51% had T2 disease. Almost all patients received Anthracyline and/or taxane containing chemotherapy (AdjC: 95%, NAC: 100%). Compared to AdjC patients, NAC patients were younger (median age 52 vs 58 yrs, p = 0.015), more likely to have T2 tumors (76% vs 29%, p < 0.001), more likely to be treated at academic center (91% vs 24%; p < 0.001) and more likely to have received > 4 cycles of chemotherapy (85% vs 53%; p = 0.001). PCR was observed in 55% of NAC cohort (37/67). Overall, at a median follow of 37 months (6-89) there have been 8 (5%) recurrences (1/67 in NAC group & 7/79 in AdjC group). RFS in NAC group was 98% vs. 91% in AdjC group (p = 0.07). On multivariate Cox regression analysis, AdjC (compared to NAC) was the only factor demonstrating a trend towards worse RFS (p = 0.080). **Conclusions:** Patients with NN, T1-2 TNBC demonstrate excellent outcome when treated with NAC (98% RFS). Compared to AdjC, NAC was associated with a trend towards better RFS in NN T1-2 TNBC. In patients with clinically node negative TNBC, NAC should be compared to AdjC prospectively.

1093 Poster Session (Board #207), Sat, 8:00 AM-11:30 AM

Transcriptomic and protein expression analysis of helicase antigen (HAGE) in triple negative breast cancer (TNBC) as a novel prognostic and predictive biomarker. *First Author: Tarek M. A. Abdel-Fatah, Nottingham University City Hospital NHS Trust, Nottingham, United Kingdom*

Background: We recently provided evidences that HAGE is immunogenic. In current study, the expression of HAGE as a prognostic and predictive tool was assessed in 1079 TNBC patients. **Methods:** HAGE protein and mRNA expressions were investigated in two cohorts of BC who received adjuvant chemotherapy (CT) with 10 year median follow up: (1) early primary TNBC (EP TNBC; n = 520) and (2) the METABRIC TNBC (n = 317) cohorts, respectively. The relationship between HAGE protein and mRNA expressions and response to CT was explored in two TNBC cohorts in whom pathological complete response (pCR) was the endpoint: (3) the multicentre phase II clinical trial cohort (NCT00455533; n = 132) received doxorubicin/cyclophosphamide neoadjuvant-CT (Neo-ACT), followed by 1:1 randomisation to ixabepilone (n = 68) or paclitaxel (n = 64) and (4) a locally advanced primary TNBC cohort (LAP TNBC, n = 110) received anthracycline-based Neo-ACT (AC-Neo-ACT), respectively. To investigate HAGE interactome in TNBC, a non-linear, artificial neural network (ANN) modelling based, data mining approach was applied. **Results:** In CT naïve EP TNBC, high (+) HAGE protein expression had a higher risk of death compared to low (-) HAGE expression (HR (95% CI) = 1.4 (1.2-1.7, p = 0.0000004). While in EP TNBC patients who received adjuvant CT, HAGE mRNA+ level exhibited lower risk of death compared to HAGE mRNA- (HR (95% CI) = 0.56 (0.36-0.86), p = 0.0.008). In LAP TNBC received AC-Neo-ACT, pre CT HAGE+ expression was: linked to tumour infiltration lymphocytes (TILs, p < 0.001), found to be independent predictor for pCR [OR (95%CI) = 5.1 (1.2-22.4), p = 0.03] and significantly associated with prolonged survival (HR (95% CI) = 0.54 (0.41-0.85), p = 0.0.005). Following AC-Neo-ACT, loss of HAGE protein expression was found (p = 0.002) and patients with HAGE+ residual disease exhibited no TILs and had two fold increase in the risk of death (HR (95% CI) = 1.66 (1.10-2.52), p = 0.0.018) compared to HAGE- residual tumours. HAGE interactome included genes that involved in protein degradation and antigen presentation **Conclusions:** The expression of HAGE is a potential prognostic marker and a predictor of response to AC CT in TNBC.

1094 Poster Session (Board #208), Sat, 8:00 AM-11:30 AM

Association of tumor BRCA1 reversion mutation arising during neoadjuvant platinum-based therapy in breast cancer (BC) with therapy resistance. *First Author: Anosheh Afghahi, Stanford University School of Medicine, Stanford, CA*

Background: In germline BRCA1 or BRCA2 mutation carriers, restoration of tumor BRCA1/2 function by a secondary mutation in these genes has been recognized as a mechanism of acquired resistance to platinum and PARP inhibitors, primarily in ovarian cancer. We set out to evaluate this mechanism of resistance in newly diagnosed BRCA1/2-mutant BC patients (pts) with a poor response to platinum-based therapy. **Methods**: PrECOG 0105 was a single-arm phase II study in pts with clinical stage I-IIIA triple-negative (TN) or BRCA1/2 mutation-associated BC. Pts received neoadjuvant therapy with gemcitabine, carboplatin and iniparib every 21 days for 6 cycles (n = 80). The primary endpoint was pathologic complete response, defined as no invasive carcinoma in the breast and axilla. In addition to comprehensive germline BRCA1/2 testing, all pts underwent tumor BRCA1/2 genotyping using pre-treatment biopsies. For mutation carriers with unfavorable response (moderate or extensive residual disease at surgery), tumor BRCA1/2 status was re-sequenced in the residual surgical tissue. All testing was performed at Myriad Genetics. **Results**: 19 pts had a deleterious germline BRCA1/2 mutation, and of these 4 had moderate residual disease at surgery. BRCA1/2 sequencing of residual tissue was available in 2 of 4 pts (no consent in 1 case; inadequate DNA extraction in 1 case). These 2 pts had BRCA1 1479delAG and W1712X mutations with LOH at these loci in the pre-treatment tumor. In the first case, a new BRCA1 mutation (a 42 base pair [bp] deletion that overlapped with the original 2 bp deletion) was detected in the residual tissue. This resulted in a 14 amino acid deletion and restoration of the BRCA1 reading frame. A relapse biopsy 4 months later revealed the identical reversion mutation and the pt subsequently died of metastatic TNBC. No reversion mutation was observed in the residual tissue of the second BRCA1 carrier, who notably had ER/PR+ BC. **Conclusions**: We report a BRCA1 reversion mutation in a newly diagnosed TNBC pt that developed over the course of 18 weeks of platinum-based neoadjuvant therapy. This was associated with poor neoadjuvant therapy response, early relapse and death from metastatic BC.

1095 Poster Session (Board #209), Sat, 8:00 AM-11:30 AM

Evaluation of local and distant recurrences pattern in patients with triple negative breast cancer according to age. *First Author: Julia Caroline Radosa, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Triple negative breast cancer (TNBC) and young patient age are both associated with an increased risk of local (LR) and distant recurrence (DR). In young women with TNBC it is unclear whether age or subtype is driving prognosis. Here we examine outcomes in a large population of patients with TNBC according to age. **Methods:** Our prospectively maintained database was reviewed to identify all patients treated for primary TNBC from 1998 to 2011. Clinical data and outcomes were abstracted from medical records. Comparisons were made between patients < 40 and ≥ 40 years of age at diagnosis and multivariate models adjusted for disease stage, grade and treatment were used to identify factors independently associated with LR and DR. Cumulative incidence of LR and DR and disease free survival (DFS) were compared using competing risks methodology and log-rank tests. **Results:** Among 1930 patients with TNBC, 289 (15%) were < 40 and 1641 (85 %) were ≥ 40 years of age at diagnosis. Younger patients were more likely to have larger tumors (median 2.0 cm vs 1.7 cm, $p = 0.001$), positive nodes (47% vs 36%, $p = 0.022$), to receive mastectomy (61 % vs 42 %, $p < 0.0001$) and adjuvant chemotherapy (91 % vs 81 %, $p < 0.0001$). On univariate analysis there was no difference in LR by age (5 yr LR = 6% in both groups), although in the subset (n = 1066) treated with breast conserving therapy (BCT), patients < 40 had higher rates of LR (5 yr LR = 10% vs 6%, $p = 0.03$). Cumulative incidence of DR was higher for younger patients (5 yr DR = 20% vs 14%, $p = 0.04$). At a median followup of 74 months (0-201) there was no difference in DFS by age (6-yr DFS = 74% under 40 vs 75% ≥ 40). On multivariate analysis, BCT, nodal positivity, larger tumor size and no chemotherapy were associated with increased risk of LR. Larger tumor size, LVI and nodal positivity were associated with increased risk of DR. Age was not associated with either LR or DR. **Conclusions:** In this large population of women with TNBC treated at a single institution, younger patients were more likely to present with higher stage disease and experienced higher rates of LR when treated with BCT. However, after adjusting for stage, grade and treatment young age was not associated with an increased risk of local or distant recurrence.

1096 Poster Session (Board #210), Sat, 8:00 AM-11:30 AM

Effect of the anti-Warburg agent BPM 31510 on TAC therapy synergy and survival in a xenograft model of triple-negative breast cancer (TNBC). *First Author: Niven R. Narain, Berg, Framingham, MA*

Background: High glycolytic metabolism in breast cancer is known to support tumor progression and metastasis, and a unique glycolysis signature has been identified in ER- and triple-negative (TNBC) breast tumors. Here, the therapeutic effect of the anti-Warburg agent BPM 31510 (in clinical trials for solid tumors) was investigated alone and in combination with standard-of-care chemotherapy in a murine xenograft model of TNBC. **Methods:** Treatment cycles included TAC (5mg/kg docetaxel, 1 mg/kg doxorubicin, 35 mg/kg cyclophosphamide, 1x week) and/or BPM 31510 (75 mg/kg, IV 1x day) administered in cycles (3 weeks on, 1 week off) to MDA-MB231 tumor-bearing mice. Survival was assessed. A subset of tumors were analyzed histologically after 2 cycles of treatment. *In vitro* models were used to define mechanistic underpinnings. **Results:** BPM 31510 or chemotherapy alone improved survival; however, BPM 31510 monotherapy was associated with more than a 6 week increase in survival compared to TAC alone. BPM 31510 in combination with chemotherapy further attenuated tumor growth and enhanced survival compared to either treatment alone. Cleaved caspase 3 levels were higher in tumors from BPM 31510-treated mice, demonstrating activation of apoptosis in response to this treatment. A panel of primary, non-tumorigenic, and breast cancer cells was used to determine IC_{50} values for BPM 31510 *in vitro*. At doses comparable to circulating levels achieved *in vivo*, BPM 31510 exposure was selectively cytotoxic in cancer cells with the triple-negative MDA-MB231 cells demonstrating maximal sensitivity to cell death. Interestingly, although cellular proliferation rate was not predictive of anti-cancer responses to BPM 31510, a bioenergetic signature characterized by high glycolytic flux and low mitochondrial respiration was highly correlated with sensitivity to BPM 31510-induced cell death. **Conclusions:** These data demonstrate that BPM 31510 is effective as a single agent in breast cancer. When used in combination with chemotherapy, BPM 31510 augments survival, particularly in distinctly glycolytic TNBC, a sub-type for which prognosis is poor and few therapeutic options exist.

1097 Poster Session (Board #211), Sat, 8:00 AM-11:30 AM

A 3-gene expression score as prognostic factor in triple negative and basal breast tumors with residual disease. *First Author: Joseph A. Pinto, División de Investigación, Oncosalud, Auna, Lima, Peru*

Background: Residual disease after neoadjuvant chemotherapy (NAC) in triple negative breast cancer (TNBC) represents poor prognosis. Identification of genes involved in prognosis could lead to a better stratification of patients and better design of therapeutic strategies. Our aim was to identify gene signatures related to the recurrence free survival (RFS) in this subset of patients. **Methods:** We quantified expression for 450 genes by Nanostring in 82 triple negative residual tumors after NAC (discovery group). Levels of gene expression were normalized to spike controls then log2 transformed and median centered. The validation group consisted in 117 basal breast tumors with residual disease (from the public dataset GSE25066) profiled with the U133A microarray. Samples in this dataset were evaluated before NAC. **Results:** An univariate Cox regression identify 7 genes significantly related with the RFS (CCL5, CYBB, DDIT4, GTPBP4, KRT6B, PALMD and POLR1C). A stepwise multivariate analysis selected to CCL5, DDIT4 and POLR1C as independent factors for RFS. Using the regression coefficient for each gene we constructed a score (-0.393*CCL5 + 0.443*DDIT4 + 0.490*POLR1C). The median of score was 0.1494. The CoxPH show an HR = 2.72 per unit of change ($P < 0.001$; CI95%: 1.72-4.28). The median score in the validation set was -0.036 and the score was significant related with the RFS with an HR = 15.86 per unit of change ($P < 0.045$; CI95%: 1.06-237.11). Using the logrank test and the median scores as cutoff (for each group), it was possible identifies two subgroups with different RFS ($P < 0.001$ in the discovery group and $P < 0.003$ in the validation group). **Conclusions:** We could identify a prognostic score based in CCL5, DDIT4 and POLR1C expression related with the recurrence free survival. A deep evaluation of the molecular mechanisms of these genes in resistance to chemotherapy should be done.

1098 Poster Session (Board #212), Sat, 8:00 AM-11:30 AM

TOP2A-based prognostication in triple negative breast cancer and correlation with basal phenotype. *First Author: Benjamin C. Calhoun, Cleveland Clinic Foundation, Cleveland, OH*

Background: Patients with triple-negative breast cancer (TNBC) are ineligible for endocrine and HER2-trageted therapy and remain at high risk for relapse after treatment. Most TNBC are basal-like (BL) but recent studies identified additional subtypes of TNBC. Immunohistochemistry (IHC) for various markers has been reported to correlate with clinical outcomes, but many studies are based on relatively limited IHC panels. We applied a large IHC-based marker set in a TNBC cohort to evaluate their potential for prognostic and predictive modeling **Methods:** Archived tissue samples from a prospectively maintained registry of 145 TNBC patients (mean age 57.2 years; median follow up 3.8 years) were used to investigate associations between marker expression and time-to-progression. Progression was defined as local, regional, or distant recurrence. IHC for EGFR, HMWCK (high molecular weight cytokeratin), TOP2A, BCL2, and AR was performed. Simple data imputation was used for missing protein data as complete case analysis (no missing data) resulted in a sample size of 82. Positive was defined as $>$ 10% for AR and $>$ 0% (any staining) for EGFR and HMWCK.TOP2A and bcl2 staining was recorded in 5% increments and optimal cut-points relative to time-to-progression were used to define positivity and negativity. Cox proportional hazard models were used to examine associations between expression and progression. A random forest classification tree approach was used to identify potential co-expression between proteins **Results:** TNBC expressed HMWCK, EGFR, AR, TOP2A, and BLC2 in 76.6, 86.2, 13.1, 58.6, and 12.4% of cases, respectively. With an optimal derived cutoff of 40%, TOP2A expression was associated with shorter time to progression (HR = 2.01; p = 0.059) while the expression of BCL2 (optimal cut-off: 60%) was not (HR = 0.18; p = 0.087). Sixty-seven (46.2%) cases showed co-expression of HMWCK, EGFR, and TOP2A. TOP2A was consistently correlated with HMWCK (66% agreement in positivity) and c-MET (43% agreement in positivity) per the classification tree **Conclusions:** Results indicate a potential correlation of TOP2A with the BL phenotype of TNBC and provide a rationale for further investigation into tailored therapy for TNBC.

1099 Poster Session (Board #213), Sat, 8:00 AM-11:30 AM

Neratinib to inhibit the growth of triple-negative breast cancer cells. *First Author: Maeve Mullooly, Education and Research Centre, St.Vincent's University Hospital and School of Medicine and Medical Science, University College Dublin, Dublin, Ireland*

Background: An urgent problem in breast cancer treatment is the identification and validation of a targeted therapy for triple-negative breast cancer (TNBC), ie, breast cancer negative for ER, PR and HER2. Neratinib is a low molecular weight irreversible pan-HER inhibitor that selectively targets the tyrosine kinase activity of EGFR, HER2 and HER4. To-date, neratinib has been exclusively investigated in HER2-positive tumors. However, as neratinib also targets EGFR expression, we hypothesised that it may also have clinical efficacy in TNBC. **Methods:** The anti-proliferative effects of neratinib were investigated in 14 TNBC cell lines. To identify potential biomarkers of response, we examined the expression of baseline EGFR, HER2, HER3 and HER4 using reverse phase protein array (RPPA) analysis and flow cytometry analysis. **Results:** IC_{50} values for neratinib across the 14 TNBC cell lines ranged from 0.06 μM to 1.9 μM. However, basal A-type cells were significantly more sensitive to neratinib than basal B-type cells (p = 0.024). No relationship was observed between IC_{50} values for neratinib and levels of EGFR, phospho-EGFR, HER2 or phosphor-HER2. In contrast, a significant correlation was detected between response and HER3 levels (with flow cytometry, r = -0.612, p = 0.020; with reverse phase protein arrays, r = -0.55, p = 0.043), suggesting that levels of HER3 may identify response to neratinib in this subset. Using a larger panel of 35 breast cancer cell lines of all molecular subtype, we found a significant relationship between the IC_{50}values for neratinib and those previously reported for another pan-HER inhibitor, i.e., dacomitinib ($p < 0.001$; r = 0.65). **Conclusions:** Based on our findings *in vitro*, further studies are required to further investigate the clinical potential of neratinib treatment in TNBC. Acknowledgements: The authors wish to thank Science Foundation Ireland, Strategic Research Cluster Award (08/SRC/B1410) to MTCI and the Science Foundation Ireland Short Term Travel Fellowship Award for funding this work.

TPS1100 Poster Session (Board #214a), Sat, 8:00 AM-11:30 AM

Cardiac toxicity prevention in non-metastatic breast cancer patients treated with anthracycline-based chemotherapy: A randomized, placebo controlled, phase III trial—SAFE trial. *First Author: Icro Meattini, Florence University, Florence, Italy*

Background: Anthracyclines and trastuzumab play a key-role in preoperative and adjuvant breast cancer (BC) treatment, and showed a significant survival benefit in several trials. Although acute cardiac toxicity is infrequent and usually reversible in a dose-dependent manner, published data evidenced a clinically relevant early late cardiac toxicity, with a chronic progressive deterioration of left ventricular ejection fraction (LVEF), up to congestive heart failure (CHF). Late toxicity occurs in most cases within the first year following chemotherapy completion, but an echocardiographic monitoring is strongly recommended even after a longer time. Recent studies highlighted that the evaluation of myocardial strain could be a refined predictive marker of early cardiac dysfunction after anthracyclines exposure. The aim of our study is to find out the best approach as cardiac toxicity prevention in non-metastatic BC patients undergoing anthracycline-based chemotherapy, with or without subsequent anti-HER2 therapy. **Methods:** This is a randomized phase III, four-arm, single-blind, placebo-controlled study that aims to evaluate the effect of bisoprolol (5 mg, twice daily), ramipril (5 mg, twice daily), or both drugs, compared to placebo, on anthracycline therapy induced LVEF dysfunction for non-metastatic disease. Cardioprotection is administered for one year, or until the end of trastuzumab (if HER2 positive). All patients undergo cardiac surveillance with echocardiogram and speckle tracking strain at baseline and every three months, until 2 years. Primary endpoint is maximum change in LVEF. Assuming a cardiac toxicity incidence of 40%, with a 15% reduction in both arms to reach the outcome, a sample of 120 patients per arm provides a 90% statistical power, for a total of 480 enrolled patients. The analysis is based on intent-to-treat. Exclusion criteria are: history of CTCAE (v.4) grade $>$ 2 symptomatic CHF, previous myocardial infarction, significant symptoms (grade $>$ 2) relating to LVEF dysfunction, valvular disease, cardiac arrhythmia (grade $>$ 3). Clinical trial information: NCT2236806.

TPS1101 Poster Session (Board #214b), Sat, 8:00 AM-11:30 AM

A randomized phase III trial comparing two dose-dense, dose-intensified approaches (EPC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto). *First Author: Andreas Schneeweiss, Heidelberg University, Heidelberg, Germany*

Background: The sequential use of dose-dense, dose-intensified epirubicin, paclitaxel, and cyclophosphamide (EPC) (Möbus et al. J Clin Oncol 2010) as well as weekly treatment with paclitaxel/liposomal doxorubicin (plus carboplatin in triple negative disease, TNBC) (PM(Cb)) (von Minckwitz et al. Lancet Oncol 2014), both with dual HER2 blockade in HER2+ breast cancer (BC), are considered highly efficient regimens for high-risk early stage BC patients and will be compared in the GeparOcto study. **Methods:** GeparOcto (NCT02125344) will randomize patients to 18 weeks EPC (E 150mg/m^2 q2w for 3 cycles, P 225mg/m^2 q2w for 3 cycles, C 2000mg/m^2 q2w for 3 cycles) or PM(Cb) (P 80mg/m^2 q1w concomitantly with M 20mg/m^2 q1w and, in case of TNBC, Cb AUC 1.5 q1w). Patients with HER2+ BC will receive trastuzumab 6 (8) mg/kg q3w and pertuzumab 420 (840) mg q3w concomitantly with all P, C, and PM(Cb) cycles. Patients with untreated, histologically confirmed, cT1c - cT4a-d BC and central receptor assessment can be included. Patients with HER2+ or TNBC are eligible irrespective of nodal status, luminal B-like tumors only if pN+. Primary objective is to compare pCR rates (ypT0/is ypN0). Sample size calculations assumed a pCR rate of 50% for EPC and 60% for PM(Cb), requiring 950 patients to show superiority of PM(Cb). Secondary objectives are to compare pCR rates between treatment arms within the stratified subpopulations (BC subtype [HER2+ HR+/- vs HER2- HR+ vs HER2- HR-], Ki-67 [$\leq$ 20 vs $>$ 20%], lymphocyte-predominant BC [no vs yes]), amongst others. Due to a high risk of chemotherapy induced anemia in both regimens, patients are also randomized to parenteral ferric carboxymaltose or physician's choice for treatment of iron deficient patients. **Results:** Recruitment started in 12/2014 and is planned for 18 months at 80-100 sites in Germany. 65 patients were recruited by 1st Feb 2015. **Conclusions:** GeparOcto investigates the efficacy of dose-dense dose-intensified EPC compared to weekly PM(Cb), both with dual HER2-blockade in HER2+ BC, in high-risk early stage patients and compares anemia management strategies. Clinical trial information: NCT02125344.

TPS1102 Poster Session (Board #215a), Sat, 8:00 AM-11:30 AM

Phase 3 randomized, placebo-controlled trial of carboplatin (C) and paclitaxel (P) with/without veliparib (ABT-888) in HER2-*BRCA*-associated locally advanced or metastatic breast cancer (BC). *First Author: Shannon Puhalla, Magee-Womens Hospital of UPMC, Pittsburgh, PA*

Background: *BRCA*-mutated tumors are more susceptible to platinum therapy and PARP inhibitors due to underlying defects in homologous recombination repair of DNA damage. In preclinical models the potent oral PARP1/2 inhibitor veliparib was shown to enhance sensitivity to C and to have single-agent activity in *BRCA*+ cell lines. Phase 1 trials suggest promising antitumor activity and acceptable toxicity of veliparib plus C/P in triple-negative BC (Puhalla et al. *Cancer Res* 2012;72[24 suppl]:PD09-06) and single-agent activity of veliparib in *BRCA*+ BC (Somlo et al. *J Clin Oncol* 2014;32[15 suppl]:abstr. 1021). This phase 3 trial assesses efficacy and toxicity of veliparib plus C/P vs C/P alone in patients with HER2− *BRCA*-associated locally advanced or metastatic BC (NCT02163694). **Methods:** Phase 3 randomized, double-blind, placebo-controlled, multicenter trial. Eligible patients (female or male; $\geq$ 18 years) have HER2−metastatic/locally advanced unresectable BC with (suspected) deleterious *BRCA1/2* germline mutations and received 2 or fewer prior lines of DNA-damaging chemotherapy for metastatic BC. In addition, patients must have received $\leq$ 1 prior line of platinum therapy (any setting) without progression within 12 months of completing treatment. Patients are randomized 2:1 to C/P with veliparib or C/P with placebo, stratified by estrogen and/or progesterone receptor expression, prior platinum therapy, and central nervous system metastases. Veliparib (120 mg p.o. BID) or placebo will be given on Days −2 to 5, C (AUC 6 mg/mL/min i.v.) on Day 1, and P (80 mg/m^2 i.v.) on Days 1, 8, and 15 (21-day cycles). Treatment continues until unacceptable toxicity or progressive disease (PD). Patients in the placebo arm who discontinue due to PD are eligible for crossover to veliparib monotherapy. The primary objective is to assess if the addition of veliparib to C/P increases progression-free survival; additional objectives include evaluation of overall survival, clinical benefit rate, objective response rate, quality of life, and safety. Enrollment began in July 2014 with a planned sample size of 270 patients. Clinical trial information: NCT02163694.

TPS1103 Poster Session (Board #215b), Sat, 8:00 AM-11:30 AM

POSNOC: Positive sentinel node—Adjuvant therapy alone versus adjuvant therapy plus clearance or axillary radiotherapy: A randomised trial looking at axillary treatment in early breast cancer (ISRCTN54765244). *First Author: Amit Goyal, Royal Derby Hospital, Derby, United Kingdom*

Background: Women with early breast cancer that has spread to 1 or 2 sentinel nodes (SNs) undergo axillary node clearance (ANC) or axillary radiotherapy (ART). The publication of the Z11 trial challenged this practice. There are however concerns about this trial which may limit the interpretation and generalisability of its results. These issues include the proportion of patients with micrometastases, variability in radiotherapy and applicability in patients undergoing mastectomy. Therefore further randomized trials are needed to define the role of axillary treatment in patients with 1 or 2 SNs with macrometastases. The UK-ANZ POSNOC trial is asking this question and will provide a more solid evidence base to inform clinical practice. **Methods:** Trial design: A pragmatic, randomized, multicenter, non-inferiority trial. Interventions:All participants will receive systemic adjuvant therapy according to local guidelines and radiotherapy to breast or chest wall if indicated. Women in the intervention group will receive systemic adjuvant therapy alone, whereas those receiving standard care will receive adjuvant therapy plus ANC or ART. Study population: Women with unifocal or multifocal invasive breast cancer($\leq$ 5 cm) undergoing breast conserving surgery or mastectomy, node-negative by clinical and ultrasound examination, who have 1 or 2 nodes with macrometastases at SN biopsy and no extranodal extension. The sample size is 1900 women. All participants will be followed up for 5 years. Primary outcome: axillary recurrence at 5 years. Secondary outcomes: arm morbidity, quality of life, anxiety, loco-regional recurrence, distant metastasis; time to axillary recurrence, axillary recurrence-free survival, disease-free and overall survival, contralateral breast cancer, non-breast malignancy and economic evaluation. Key differences from Z11: a) stringent radiotherapy quality assurance program, b) prospective pathology reporting, b) axillary ultrasound is mandatory, b) mastectomy patients are eligible, c) axillary treatment in the standard group may be ANC or ART. Current enrollment: 35 patients. Clinical trial information: ISRCTN54765244.

TPS1104 Poster Session (Board #216a), Sat, 8:00 AM-11:30 AM

A phase 2 randomized, double-blind, placebo-controlled trial of hormone therapy (HT) ± radium-223 dichloride (Ra-223) in HER2$^-$ hormone receptor$^+$ breast cancer patients (pts) with bone metastases (mets). *First Author: Robert E. Coleman, University of Sheffield, Weston Park Hospital, Sheffield, United Kingdom*

Background: Treatment of bone-metastatic breast cancer (MBC) is limited. Multimodality therapy may improve symptom control and survival. In a phase 2a study of advanced breast cancer pts with bone-dominant and no visceral disease, Ra-223, a first-in-class α-emitter selectively targeting bone mets, reduced baseline bone biomarker levels with favorable safety (Coleman et al. *Breast Cancer Res Treat* 2014). This study (NCT02258464) evaluates Ra-223 efficacy and safety vs placebo (pbo) in HER2$^-$ hormone receptor$^+$ breast cancer pts with bone mets receiving single-agent HT. **Methods:** Pts receive (1:1) Ra-223 50 kBq/kg IV or pbo q 4 wk (6 cycles) + concurrent single-agent HT + best supportive care. Stratification is by geographic region, prior lines of HT for MBC, and number of prior skeletal events. Pts are assessed for efficacy and safety, and followed to symptomatic skeletal event (SSE), radiologic progression, death, or withdrawal. Primary endpoint is SSE-free survival. Eligible pts are pre- or postmenopausal with estrogen receptor$^+$, HER2$^-$, bone-dominant MBC with $\geq$ 2 bone mets and $\geq$ 1 or 2 prior SSEs (external beam radiotherapy for bone pain, pathologic bone fracture, spinal cord compression, orthopedic surgery). Pts had $\geq$ 1 line of HT for MBC; are taking bisphosphonates or denosumab for $\geq$ 1 month before study; are eligible for endocrine treatment; and have evaluable disease (RECIST 1.1), asymptomatic or mildly symptomatic bone disease (Brief Pain Inventory), ECOG score 0-1, and adequate hematologic, renal, and liver function. Pts may not have had visceral or brain mets or leptomeningeal disease, need for chemotherapy for mets, and untreated spinal cord compression. Assuming a 1-sided α of 0.1, power of 90%, ~ 119 SSEs are required for the analysis. Time-to-event variable analysis will use a log-rank test, accounting for stratification. Kaplan-Meier estimates and survival curves will be given for each treatment group. Safety analyses will be descriptive. Target enrollment is 227 pts. First pt first visit is expected in early 2015. Clinical trial information: NCT02258464.

TPS1105 Poster Session (Board #216b), Sat, 8:00 AM-11:30 AM

NRG BR002: A phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer. *First Author: Steven J. Chmura, The University of Chicago Hospitals, Chicago, IL*

Background: This is a randomized Phase II trial to evaluate if stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) of all metastatic sites in oligo-metastatic breast cancer who have received up to 6 months of first line systemic therapy without progression will significantly improve median progression free survival (PFS). If this aim is met the trial continues as a phase III to evaluate if SBRT/SR improves 5 year overall survival (OS). Secondary aims include local control in the metastatic site, distant metastatic rate, and technical quality. Translational primary endpoint is to determine whether $<$ 5 CTCs is an independent prognostic marker for improved PFS and OS. Predictive value of CTCs will be assessed. **Methods:** Women with pathologically confirmed metastatic breast cancer to $<$ / = 2 sites who have received up to 6 months of standard first line systemic therapy and the primary site disease is controlled are eligible. CNS metastases are ineligible. ER/PR and HER-2 neu is required on the primary or metastatic site. Site radiation credentialing with a facility questionnaire and a case benchmark is required. Randomization is to local radiotherapy/surgery for palliation only when necessary versus ablation of all metastases with SBRT and/or SR. Statistics: For the phase IIR portion to detect a signal for improved median PFS from 10.5 to 19 months with 95% power and accounting for ineligible/lost patients, 146 patients will be required. For the Phase III, an additional 246 patients will be required to definitively determine if ablative therapy improves 5-year OS from 28% to 42.5% (HR = 0.67), with 85% power and a one-sided type I error of 0.025. For the translational research, the number of patients accrued in Phase IIR and Phase III portions will provide sufficient power of at least 91% to detect whether $<$ 5 CTC's is a prognostic marker for improved PFS and OS. Contact Information: Protocol: CTSU member web site https://www.ctsu.org. Pt enrollment: OPEN at https://open.ctsu.orgor the OPEN tab on CTSU member web site. Support: NCI U10CA180868 and U10CA180822 Clinical trial information: Pending.

TPS1106 **Poster Session (Board #217a), Sat, 8:00 AM-11:30 AM**

Weekly *nab*-paclitaxel (*nab*-P) plus gemcitabine (gem) or carboplatin (carbo) vs gem/carbo as first-line treatment for metastatic triple-negative breast cancer (mTNBC) in a phase 2/3 trial (tnAcity). *First Author: Denise A. Yardley, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: Treatment of mTNBC is an unmet clinical need. First-line *nab*-P with gem or carbo/bevacizumab has demonstrated efficacy and safety in female patients (pts) with mTNBC. *nab*-P significantly improved pCR vs solvent based-paclitaxel in pts with early TNBC. The phase II/III tnAcity (triple-negative Albumin-bound paclitaxel combination international treatment study) trial will compare the efficacy and safety of 2 *nab*-P combination regimens (with gem or carbo) vs gem/carbo as a control as first-line treatment for mTNBC. **Methods:** 790 female pts $\geq$ 18 yrs with measurable mTNBC will be enrolled at $\approx$150 sites globally per major eligibility criteria (Table 1). In phase II, 240 pts will be randomized 1:1:1 to receive *nab*-P 125 mg/m^2 + gem 1000 mg/m^2 (arm A), *nab*-P 125 mg/m^2 + carbo area under the curve (AUC) 2 (arm B), or gem 1000 mg/m^2 + carbo AUC 2 (arm C), given D 1 and 8 q3w. Pts will be treated until disease progression. Stratification factors are disease-free interval ($\leq$ 1 yr vs $>$ 1 yr) and prior taxane exposure (phase III only). A ranking algorithm of 5 efficacy and safety parameters will be used to identify the *nab*-P combination for the phase III portion in which 550 pts will be randomized 1:1 to receive the selected *nab*-P regimen (arm A or B) or gem/carbo. Pts in phase II will not be in the phase III population. The phase III primary endpoint is PFS by independent radiological assessment. Study design provides $\approx$ 90% power to detect an HR of 0.70 for PFS with a 2-sided 5% significance level. Secondary endpoints: ORR, OS, disease control rate, duration of response, and safety. Exploratory analyses include tumor biomarkers and circulating tumor cells analyses. Current enrollment as of submission: 128 pts. Clinical trial NCT01881230. Clinical trial information: NCT01881230.

Key eligibility criteria.

ER and PgR expression both < 1% of tumor cell nuclei

HER2 IHC 0 or 1+ or FISH−, or IHC 2+ and FISH−
ECOG PS 0-1
Peripheral neuropathy grade < 2
No prior chemo for metastatic disease
Prior adjuvant/neoadjuvant anthracycline treatment required unless contraindicated
Prior taxane, gem, or platinum treatment permitted if completed ≥12 months before randomization

TPS1107 **Poster Session (Board #217b), Sat, 8:00 AM-11:30 AM**

A phase 3, open-label, randomized, parallel, 2-arm international study of the oral PARP inhibitor talazoparib (BMN 673) in BRCA mutation subjects with locally advanced and/or metastatic breast cancer (EMBRACA). *First Author: Jennifer Keating Litton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Poly-ADP-ribose polymerase (PARP) represents a family of enzymes of which at least two (PARP1 and PARP2) play important roles in DNA repair. PARP inhibition induces synthetic lethality in tumor cells bearing deleterious mutations in the genes *BRCA1/2*. Talazoparib (BMN 673) is a novel, dual-mechanism PARP inhibitor that potently inhibits the PARP enzyme and effectively traps PARP on DNA [1]. In preclinical models, trapping PARP on DNA was more likely to induce cancer cell death than inhibition of PARP alone [1,2]. Talazoparib is the most potent preclinical PARP inhibitor described to date with the highest efficiency at trapping PARP-DNA complexes [1]. Talazoparib has shown promising single-agent anti-tumor efficacy in several solid tumor types and was generally well tolerated in a Phase 1/2 clinical study [3]. **Methods:** This international Phase 3 trial (EMBRACA) compares the safety and efficacy of talazoparib versus physician's choice (capecitabine, eribulin, gemcitabine or vinorelbine) in patients with advanced breast cancer. The primary objective is progression free survival (PFS). Secondary objectives include objective response rate (ORR), overall survival (OS), and safety. Exploratory objectives include duration of response (DOR) and health-related quality of life assessments. Subject eligibility includes $\geq$ 18 years, histologically/cytologically confirmed breast carcinoma, locally advanced and/or metastatic disease, germline *BRCA1/2* mutations, $\leq$ 2 prior chemotherapy-inclusive regimens, prior treatment with a taxane and/or anthracycline, and ECOG performance status $\leq$ 1. Subjects (n = 429) will be randomized 2:1 to receive either talazoparib oral capsules (1.0 mg/day, 21-day cycles) or physician's choice treatment. This trial is currently enrolling patients from the United States, Asia/Pacific, Europe, Israel, and South America (NCT01945775). [1] Murai J et al. *Mol Cancer Ther.* 2014;13:433-443. [2] Murai J et al. *Cancer Res.* 2012;72(21):5588-5599. [3] Wainberg ZA et al. *J Clin Oncol.* 2014;32(suppl):5; abstr 7522 Clinical trial information: NCT01945775.

TPS1108 **Poster Session (Board #218a), Sat, 8:00 AM-11:30 AM**

A phase 2 study (2-stage, 2-cohort) of the oral PARP inhibitor talazoparib (BMN 673) in patients with germline BRCA mutation and locally advanced and/or metastatic breast cancer (ABRAZO). *First Author: Nicholas C. Turner, Royal Marsden, London & Surrey, United Kingdom*

Background: Poly-ADP-ribose polymerase (PARP) represents a family of enzymes of which at least two (PARP1 and PARP2) play important roles in DNA repair. PARP inhibition induces synthetic lethality in tumor cells bearing deleterious mutations in the genes *BRCA1/2*. Talazoparib (BMN 673) is a novel, dual-mechanism PARP inhibitor that potently inhibits the PARP enzyme and effectively traps PARP on DNA [1]. In preclinical models, trapping PARP on DNA was more likely to induce cancer cell death than inhibition of PARP alone [1,2]. Talazoparib is the most potent preclinical PARP inhibitor described to date with the highest efficiency at trapping PARP-DNA complexes [1]. Talazoparib has shown promising single-agent anti-tumor efficacy in several solid tumor types and was generally well tolerated in a Phase 1/2 clinical study [3]. **Methods:** This Phase 2 trial (ABRAZO) evaluates the safety and efficacy of talazoparib in patients with locally advanced or metastatic breast cancer with a deleterious germline *BRCA 1* or *BRCA 2* mutation. Eligible subjects will be assigned to one of two cohorts: 1) Subjects (n = 70) previously responding to a platinum-containing regimen for metastatic disease (PR or CR) or 2) Subjects (n = 70) with $>$ 2 prior chemotherapy regimens in metastatic setting, no prior platinum therapy. The primary objective is objective response rate (ORR). Secondary objectives include clinical benefit rate (CBR), duration of response (DOR), progression free survival (PFS), and overall survival (OS). Health-related quality of life assessments are an exploratory objective. Patient eligibility includes $\geq$ 18 years, locally advanced and/or metastatic disease, deleterious *BRCA1/2* mutation, and ECOG performance status $\leq$ 1. Eligible patients will receive oral talazoparib (1.0 mg/day, 21-day cycles) until disease progression or unacceptable toxicity. This trial is enrolling patients in the United States, France, Germany, Spain, and the United Kingdom. (NCT02034916). [1] Murai J et al. *Cancer Res.* 2012;72(21):5588-5599. [2] Murai J et al. *Mol Cancer Ther.* 2014;13:433-443. [3] Wainberg ZA et al. *J Clin Oncol.* 2014; 32(suppl):5; abstr 7522 Clinical trial information: NCT02034916.

TPS1109 **Poster Session (Board #218b), Sat, 8:00 AM-11:30 AM**

OlympiA: A randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline *BRCA*1/2 mutation (g*BRCA*m). *First Author: Andrew Nicholas James Tutt, King's College London School of Medicine, London, United Kingdom*

Background: In a Phase II proof-of-concept study (NCT00494234), treatment with the PARP inhibitor olaparib (Lynparza; 400 mg twice daily [bid]; capsules) resulted in antitumor activity in patients (pts) with advanced BC harboring a gBRCAm (objective response rate: 41%; Tutt et al Lancet 2010). An AstraZeneca-sponsored Phase III trial (OlympiA; NCT02032823; coordinated by BIG, NRG Oncology, Frontier Science and AstraZeneca) of olaparib as adjuvant monotherapy has been initiated in pts with gBRCAm-associated triple negative BC (TNBC) who have completed local treatment and neoadjuvant or adjuvant chemotherapy (CT). **Methods:** OlympiA is a double-blind trial in which pts with TNBC at high risk of recurrence are currently randomized (1:1) to receive treatment with olaparib (300 mg tablets bid [2 x 150 mg]) or placebo for a maximum of 12 months. Eligible pts must have completed definitive local treatment and at least 6 cycles of either neoadjuvant CT (without a pathological complete response) or adjuvant CT. Pts must also have a known or suspected deleterious gBRCAm, which will be retrospectively confirmed by Integrated BRACAnalysis (Myriad Genetic Laboratories) before entering the trial. Stratification factors include prior neoadjuvant versus adjuvant CT, and whether pts have received prior platinum therapy for current BC. The primary objective is invasive disease-free survival (IDFS). Efficacy assessments will be made by mammograms/breast MRI scans annually for 10 years, beginning 6 months from randomization, and by medical history/physical examination from randomization every 3 months for 2 years, then every 6 months for a further 3 years and annually thereafter. Secondary objectives include overall survival, distant DFS, incidence of new cancers, HRQoL, safety and tolerability. The primary IDFS analysis will be performed after 330 IDFS events (25% maturity) using a stratified log-rank test. Patient enrollment began in April 2014. The target number for randomization is ~1320 patients across ~550 sites and ~25 countries worldwide. Support: U10CA12027,-69651,-37377,-69974,-180868,-180822,-189867; AstraZeneca Clinical trial information: NCT02032823.

TPS1110 **Poster Session (Board #219a), Sat, 8:00 AM-11:30 AM**

METRIC: A randomized international study of the antibody-drug conjugate glembatumumab vedotin (GV or CDX-011) in patients (pts) with metastatic gpNMB-overexpressing triple-negative breast cancer (TNBC). *First Author: Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: The internalizable transmembrane glycoprotein NMB (gpNMB) is overexpressed in 20% of BC, including 40% of TNBC (Yardley JCO, in press), where it is a poor prognostic marker (Rose CCR 2010). gpNMB enhances tumor invasion and metastasis and promotes angiogenesis in preclinical models. GV is a novel antibody drug conjugate targeting the potent cytotoxin monomethylauristatin E (MMAE) to gpNMB+ tumor cells. In a Phase I/II study (Bendell JCO, 2014) and the Phase II "EMERGE" study (Yardley JCO, in press), GV demonstrated promising activity, particularly in pts with TNBC and gpNMB overexpression, and was well-tolerated (treatment related toxicities: rash, neutropenia and neuropathy). In subset analyses, for GV vs. "investigator's choice" (IC) single-agent chemotherapy, objective response rate (ORR) was 30% (7/23) vs. 9% (1/11) in pts with gpNMB overexpression (in $\geq$ 25% of tumor epithelium); 18% (5/28) vs. 0% (0/11) in TNBC; and 40% (4/10) vs. 0% (0/6) in gpNMB-overexpressing TNBC, with apparent improvements in progression-free survival (PFS; hazard ratio (HR) = 0.11) and overall survival (OS; HR = 0.14). **Methods:** The international (US, CA, Aus) "METRIC" study (NCT01997333) is recruiting up to 300 pts with metastatic, gpNMB-overexpressing TNBC. Eligibility criteria include: $\geq$ 25% of tumor epithelium gpNMB+ by central IHC prescreening of archival tissue; ER and PR $<$ 10% and HER2(-) [0-1+ IHC, or ISH copy number $<$ 4.0 / ratio $<$ 2.0] by local assessment; ECOG 0-1; taxane resistance; anthracycline exposure (if indicated); $\leq$ 2 chemotherapy regimens for advanced BC; measurable disease; no persistent Grade $\geq$ 2 toxicity; and capecitabine naive. Pts are randomized (2:1) to GV (1.88 mg/kg IV q 21 days) or capecitabine, a current standard for this population (2500 mg/m^2 daily for d1-14, q21 days) until progression or toxicity. Crossover is not permitted. Endpoints are PFS (primary), ORR, duration of response, OS, safety, PK, PD (immune dynamics) and quality of life. Imaging will be centrally assessed per RECIST 1.1. The trial has 85% power to detect a PFS HR of 0.64 with α = 0.05. Clinical trial information: NCT01997333.

TPS1111 **Poster Session (Board #219b), Sat, 8:00 AM-11:30 AM**

LOTUS: A randomized, phase II, multicenter, placebo-controlled study of ipatasertib (Ipat, GDC-0068), an inhibitor of Akt, in combination with paclitaxel (Pac) as front-line treatment for patients (pts) with metastatic triple-negative breast cancer (TNBC). *First Author: Sung-Bae Kim, Asan Medical Center, Seoul, South Korea*

Background: The PI3K/Akt pathway is often activated in TNBC through loss of PTEN expression, low INPP4B expression, and/or increased *AKT3* amplification. Activation of Akt may then lead to chemoresistance; thus, inhibition of Akt signaling may result in improved efficacy of chemotherapy in TNBC. Ipatasertib (GDC-0068) is an oral, potent ATP-competitive small molecule inhibitor of all three isoforms of Akt. In preclinical breast cancer models, the combination of Ipat with taxanes enhanced efficacy. In a Phase Ib clinical study, the combination of Ipat with Pac was well-tolerated; the most commonly reported adverse events associated with Ipat were Grade 1-2 diarrhea, nausea, fatigue, vomiting, decreased appetite, and rash. RECIST responses were seen with the combination, including pts with tumors having PI3K/Akt activation. **Methods:** LOTUS is a randomized, double-blind, placebo-controlled, global Phase II study designed to estimated the efficacy and safety profile of Pac plus Ipat versus Pac plus placebo in pts with inoperable locally advanced or metastatic TNBC not amenable to resection with curative intent. Approximately 120 pts with measurable TNBC will be randomized (1:1) and stratified by prior adjuvant/neoadjuvant treatment, disease free interval from last dose of chemotherapy, and tumor PTEN status. Pts will receive Ipat or placebo 400 mg orally once daily on Days 1 to 21 of each 28-day cycle with Pac 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle until disease progression, intolerable toxicity, withdrawal, or study completion. Pts will then be followed every 3 months for survival. The primary efficacy outcome is progression-free survival in all pts and in pts with PTEN-low tumors. Additional endpoints include overall survival, objective response rate, duration of response, safety, pharmacokinetics, patient-reported outcomes, and correlative biomarkers. The study is open for accrual.Clinical trial information: NCT02162719.

TPS1112 **Poster Session (Board #220a), Sat, 8:00 AM-11:30 AM**

FAIRLANE: A phase II randomized, double-blind, study of the Akt inhibitor ipatasertib (Ipat, GDC-0068) in combination with paclitaxel (Pac) as neoadjuvant treatment for early stage triple-negative breast cancer (TNBC). *First Author: Mafalda Oliveira, Vall d'Hebron University Hospital / VHIO, Barcelona, Spain*

Background: TNBC often exhibits activation of PI3K/Akt signaling, associated with loss of PTEN expression, low INPP4B expression, and/or increased *AKT3* amplification. Inhibition of the PI3K/Akt pathway in diverse cancers leads to radiosensitization and/or chemosensitization. Ipat is an oral, potent ATP-competitive small molecule inhibitor of all three isoforms of Akt. The combination of ipat with taxanes in preclinical models resulted in enhanced efficacy relative to either ipat or chemotherapy alone. In a Phase Ib clinical study, the combination of Ipat with diverse chemotherapy regimens was well-tolerated and resulted in RECIST responses, particularly pts with tumors having PI3K/Akt activation. **Methods:** FAIRLANE is a randomized, double-blind, placebo-controlled, multicenter, neoadjuvant Phase II study designed to estimate the efficacy of ipat combined with pac versus placebo combined with pac in women with Stage Ia - IIIa TNBC. Approximately 150 patients (Pts) will be enrolled, randomized in a 1:1 ratio, and stratified by PTEN status, node involvement, and tumor size. Pts will receive 3 cycles of Ipat or placebo 400 mg orally once daily on Days 1 to 21 of each 28-day cycle, along with pac 80 mg/m^2 every 7 days for a total of 12 doses. All patients will undergo pretreatment and Day 8 tumor tissue acquisition to evaluate pathway biomarkers. Following three cycles of treatment, patients will undergo surgery. The primary efficacy endpoint, pCR within the breast and axilla (ypT0/Tis ypN0) in all patients and in patients with PTEN-low tumors, will be assessed by local pathology evaluation following completion of neoadjuvant therapy and surgery. Additional endpoints include objective response rate, safety, BCS rate, pharmacokinetics, and pathway biomarkers. Following surgical resection of primary tumor, patients are expected to continue post-operative treatment with a standard adjuvant chemotherapy regimen at physician's discretion. The study is open for accrual. Clinical trial information: NCT02301988.

TPS1113 **Poster Session (Board #220b), Sat, 8:00 AM-11:30 AM**

Women's triple-negative, first-line treatment: Improving outcomes in triple-negative breast cancer (TNBC) using molecular triaging and diagnostic imaging to guide neoadjuvant therapy (NACT). *First Author: Stacy L. Moulder, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In TNBC, pathologic compete response (pCR/RCB-0) or minimal residual disease (RCB-I) to NACT is associated with a good prognosis while extensive residual disease (RCB-II-III) has a ~50% chance of recurrence. It is important to predict pCR, in order to direct responsive disease (RespD) toward standard NACT and non-responsive disease (NRD) to therapy on clinical trials. **Methods:** The use of genomic signatures (JAMA, 2011; 305:1873-81) and imaging to predict response to NACT will be validated and the impact of selecting pts for targeted therapy on clinical trial in predicted NRD will be determined. Pts will have primary tumor biopsy for molecular analyses and be randomized 2:1 to know results versus not (control). Pts will receive 4 cycles anthracycline-based NACT with imaging for response. Pts with molecular/imaging criteria for NRD will be offered a clinical trial based upon molecular profiling or based upon physician/patient choice (control). Pts having RespD in either arm receive taxane based NACT. INCLUSION: tumor size $>$ 1.5 cm diameter; TNBC by standard assays; $>$ 18 years of age; LVEF $>$ 50%; adequate organ and bone marrow function. EXCLUSION: Stage IV disease; invasive cancer within 5 years; excisional biopsy of the primary; features that limit response assessment by imaging; unfit for taxane and/or antracycline regimens; prior anthracycline therapy; $>$ grade II neuropathy; Zubrod performance status of $>$ 2; history of serious cardiac events. *Primary Aim:* prospectively determine the impact of a molecular diagnostic/imaging platform in pts with localized invasive TNBC. *Secondary Aims:* compare rates of clinical trial enrollment, compare DFS, integrated biomarker analyses, identify therapeutic targets for resistant disease. A maximum of 360 pts will be randomized (2:1)using a group sequential design with one-sided O'Brien-Fleming boundaries, with two equally spaced binding interim tests for futility and superiority and one final test, having an overall Type I error .05 and power .80 to detect an improvement in pCR/RCB-I from 50% to 64%.

1500 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Final updated results of the NRG Oncology/NSABP Protocol P-2: Study of Tamoxifen and Raloxifene (STAR) in preventing breast cancer. *First Author: Donald Lawrence Wickerham, NRG Oncology/NSABP, and Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA*

Background: NSABP P-2 (STAR) was a randomized, double-blinded trial of tamoxifen vs raloxifene for the reduction of breast cancer incidence. The initial report from 2006 found raloxifene to be as effective as tamoxifen in preventing invasive breast cancer, but with fewer associated toxicities. In 2010 updated results indicated that raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive breast cancer and remained less toxic. **Methods:** May 31, 2012, STAR was permanently closed to followup. This current and final update is based on data through the end of followup for invasive and noninvasive breast cancer, other cancers, vascular events, and deaths. The final analysis comprises the same 19,490 women (9736 in the tamoxifen group and 9754 in the raloxifene group) as the 2010 update report. The median time of followup as of May 31, 2012, was 9.7 yrs. **Results:** Similar to the previous update, raloxifene remains less effective in preventing invasive breast cancer than tamoxifen (RR = 1.19, 95% CI = 1.04–1.37). For noninvasive breast cancer, the borderline statistically significant difference between treatment groups seen in the original findings continues to decrease (RR = 1.09, 95% CI = 0.88–1.36). Raloxifene also continues to have a better profile than tamoxifen re thromboembolic events (RR = 0.80, 95% CI = 0.66–0.96) and uterine cancer (RR = 0.56, 95% CI = 0.40–0.79). There were no statistically significant differences between treatment groups for any other site of cancer. There was, however, a borderline statistically significant all-cause mortality difference between the treatment groups. The death rates per 1000 in the raloxifene and tamoxifen groups were 4.10 and 4.73, respectively (RR = 0.87, 95% CI = 0.75–1.00). **Conclusions:** Raloxifene has retained approximately 81% of the effectiveness of tamoxifen in preventing invasive breast cancer and continued to grow closer to tamoxifen in preventing noninvasive breast cancer. Raloxifene has also maintained a better profile with respect to uterine disease, thromboembolic events, and death. Support: U10CA37377, -69974; -180868 -180822; -189867; -44066; Elli Lilly and Company; AstraZeneca Clinical trial information: NCT00003906.

1501 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Vasomotor symptoms, BMI, and adherence to tamoxifen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1). *First Author: Farzana L Walcott, National Cancer Institute, Rockville, MD*

Background: Tamoxifen (T) is underutilized as a chemopreventive agent for breast cancer (BC), despite a 50% reduced risk of developing breast cancer in high risk women with use of T vs. placebo (P). Vasomotor symptoms (VS - hot flashes, night sweats, cold sweats) were the most frequently cited reasons for women stopping tamoxifen in the P-1 study and occurred most frequently in the T arm. BMI may modify experience of vasomotor symptoms in women, with higher BMI associated with worse symptoms. **Methods:** 13,388 women at high risk of BC were randomly assigned to T (20 mg/day) vs. P from June 1992 to September 1997. We analyzed data from 11,064 women enrolled at least 36 months before trial un-blinding in May 1998. Associations between VS and adherence to T: Stratifying on study arm (T vs. P) and 10 year age group, we used proportional hazards (Cox regression) models for time-to-first non-adherence. Covariates were VS, BMI, and breast cancer risk (Gail model). VS were coded on a 5-point scale ranging from 0 (no symptom/symptom not at all bothersome) to 4 (symptom extremely bothersome). BMI was categorized into: normal (< 25), overweight (25-30), and obese (≥ 30). Time-to-non-adherence was censored at 36 months. Associations between VS and BMI: logistic regression (LR) was used for each VS starting at month 3. Covariates were BMI, 10-year age group, and study arm. VS were coded on a 2-point scale (0 = no symptom/symptom not extremely bothersome, 1 = symptom extremely bothersome). **Results:** Time-to-non-adherence analysis: Estimated hazard ratios (HR) and 95% confidence intervals (CI): hot flashes= 1.35 (1.22, 1.50); night sweats = 1.43 (1.28, 1.60); cold sweats =1.49 (1.19, 1.87); BMI = 1.13 (1.05, 1.21) (normal vs. obese). LR: Estimated odds ratios (OR) for BMI (normal vs. obese): hot flashes = 1.57 (1.26, 1.95); night sweats = 1.50 (1.19, 1.90); cold sweats=1.64 (0.86, 3.10). **Conclusions:** Adherence to T was lower in obese women and those with severe VS. In addition, VS were more severe in obese women. In order to improve uptake and adherence to chemopreventive options such as T in healthy, high risk women, interventions targeting risk factors for non-adherence must be addressed. SUPPORT: CA180868, 180822, 189867

1502 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Estrogen alone and health outcomes in black women by African ancestry. *First Author: Rowan T. Chlebowski, Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA*

Background: Disparities are seen in breast cancer outcome in black compared to white women. However, in black women in the Women's Health Initiative (WHI) randomized trial, estrogen alone significantly reduced breast cancer incidence, but its comprehensive influence on health outcomes in black women in this trial has not been reported. Therefore we examined, in post-hoc analyses, the risks and benefits for estrogen alone use in black women in the WHI randomized trial overall and by African ancestry. **Methods:** Of 10,729 postmenopausal women with prior hysterectomy randomized at 40 US centers, 1,616 were black, including 1,061 with % African ancestry determined using information from 656,852 single nucleotide polymorphisms. Participants received daily conjugated equine estrogen (CEE 0.625 mg) or placebo for 7.2 years (median intervention) with 13 years cumulative follow-up. Coronary heart disease (CHD) and breast cancer were primary efficacy and safety outcomes. A global index of outcomes under potential hormone influence also included stroke, colorectal cancer, hip fracture, pulmonary embolism and death. **Results:** At entry, black women had more diabetes, hypertension, and prior myocardial infarctions compared to white women. Black women in the estrogen alone compared to the placebo group had fewer breast cancers (17 vs. 40, hazard ratio [HR] 0.47 95% confidence interval [CI] 0.26-0.82) and somewhat fewer thromboembolism events (23 vs. 40, HR 0.63 95% CI 0.38-1.06, interaction p = 0.049 vs. effect in white women). All other outcomes including CHD, stroke, overall survival and the global index (HR 0.95 95% CI 0.77-1.17) were null without racial differences. In women with > 80% African ancestry, breast cancer HR was lower (0.32 95% CI 0.12-0.86, trend p = 0.04 for effect modification by ancestry). In black women, the estrogen global index effect was more favorable in younger (50-59 years) (HR 0.65 95% CI 0.43-0.98) than in older women. **Conclusions:** In black postmenopausal women with prior hysterectomy, estrogen alone significantly reduced breast cancers with no apparent adverse influence on CHD, stroke, or mortality. Favorable estrogen alone effects on the global index in younger Black women warrant further study. FUNDING: National Institutes of Health. Clinical trial information: NCT00000611.

1503 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Predisposing germline mutations in high grade ER+HER2- breast cancer (BC) patients diagnosed (Dx). *First Author: Judy Ellen Garber, Dana-Farber Cancer Institute, Boston, MA*

Background: Evaluation of women with triple negative BC for germline *BRCA1/2* mutations has become standard of care due to its impact on management and 11% mutation prevalence. Approximately 70% of *BRCA2*-associated BC is high grade ER+/HER2-, but the prevalence of *BRCA1/2* mutations has not been assessed. **Methods:** Blood samples from BC patients age <50 at the Dana-Farber Cancer Institute with grade III ER+/HER2- invasive BC who consented to research were identified in the Dana-Farber/Harvard SPORE biobank. DNA mutations in 25 cancer genes were identified using a next generation sequencing based panel. Germline sequence variations and large rearrangements were classified for pathogenicity. **Results:** 104 samples from eligible subjects were included. Mutations were found in 11 (10.6%) women [95% CI 5.4-18.1%]). *BRCA1/2* mutations were found in 6.7% [95% CI 2.7-13.4%]. Mutation frequencies were higher among Ashkenazim (p=0.02), women with PR negative tumors (p<0.01) and women who had undergone prior clinical testing (p=0.01). 3/11 mutation carriers had BC age 45-49. Family hx of BC/ovarian cancer (OC) in 1st or 2nd degree relatives (FDR/SDR) was not associated with mutation status. Among 49 women with no FDR/SDR with BC/OC, 5 (10.2%) had a mutation. Two mutations (1 *BRCA2*, 1 *PALB2*) were found in 56 women who had not undergone previous clinical testing. **Conclusions**: Approximately 10% of women with high grade BC ER+/HER2- diagnosed age <50 carry a germline mutation in a BC-associated gene. The frequency of *BRCA1* mutations is notable. Expanded testing in women with Grade III ER+/HER2- BC age <50 will find mutation carriers, which can impact management decisions. Examination of women diagnosed age >50 will be important.

Gene	Frequency	Percent	BC Dx Age	Ashkenazim	Family Hx**
BRCA1	4	3.85%	28,38,41,46	Y,Y,N,N	Y,Y,Y,Y
BRCA2	3*	2.88%	37,39*,42	Y,N,N	Y,N,N
PALB2	2	1.92%	25,43	N,N	N,N
CHEK2	1	0.96%	49	N	Y
ATM	2*	1.92%	39*,47	N,N	N,N

*1 patient with *BRCA2* and *ATM*. **FDR or SDR with BC or OC.

1504 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Uterine cancer (Ut Ca) following risk-reducing salpingo-oophorectomy (RRSO) in women with *BRCA* mutations (*BRCA*+): A multicenter, prospective study. *First Author: Catherine A. Shu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: While RRSO is key in management for *BRCA*+ women, concomitant hysterectomy is not standard. Here we estimate the risk of Ut Ca in *BRCA*+ women following RRSO and examine the distribution of specific histologic subtypes. **Methods:** *BRCA*+ women from 9 centers who underwent RRSO with retention of the uterus were prospectively followed from latest of ascertainment, *BRCA* testing, or RRSO. Censoring occurred at hysterectomy, Ut Ca diagnosis, last follow-up or death. Expected cancer incidence was determined using age and race specific SEER data, adjusted for prevalence of hysterectomy. Ut Ca were categorized into endometrioid endometrial cancer (E-EC) [e.g. endometrioid, adenocarcinoma NOS], serous endometrial cancer (S-EC) [e.g. serous, undifferentiated], and sarcoma. The observed-to-expected (Obs/Exp) ratios and lower limit of 97.5% CI were analyzed using 1-sided Poisson distribution test. **Results:** 1083 *BRCA*+ women were followed for a median 5.2 years. 8 incident Ut Ca were observed [4.2 Exp; Obs/Exp = 1.9, p = 0.06]. When stratified by subtype, there was no increased risk of E-EC [2 Obs vs 3.7 Exp; p = 0.29] or sarcoma [1 Obs vs 0.14 Exp; p = 0.13]. 5 S-EC were observed 7.2 – 12.9 yrs after RRSO [0.33 Exp; Obs/Exp = 15.2, p < 0.0001]. Tumor tissue was available from 4 *BRCA1*+ women. LOH and/or IHC analyses confirmed loss of *BRCA1* function in 3 of 3 S-EC. In the sarcoma, *BRCA1* function was retained. Analyses for S-EC stratified by prior breast cancer or tamoxifen use are below. **Conclusions:** While the overall risk of Ut Ca following RRSO does not appear to be increased, there is a small absolute increased risk of more aggressive S-EC (≈ 1.1% at 10 yrs in *BRCA1*+ women). Further studies are needed to define the risk/benefit of hysterectomy at time of RRSO.

Obs/Exp Rates for S-EC

	Exp	Obs	F/U (Women-Yrs)	Obs/Exp	1p*	Lower 97.5% CI* of Obs/Exp
All (n=1083)	0.33	5	6385	15.2	< 0.0001	4.9
***BRCA1* (627)**	0.18	4	3790	22.6	< 0.0001	6.2
***BRCA2* (453)**	0.15	1	2580	6.5	0.14	0.2
Br Ca						
Y (727)	0.25	4	4435	15.9	0.0001	4.4
N (356)	0.08	1	1950	12.7	0.08	0.3
Tam						
Y (273)	0.12	3	1879	24.8	0.0003	5.1
N (810)	0.21	2	4506	9.5	0.02	1.2

*1-sided values are reported because with small expected values, the Poisson distribution is markedly skewed.

1505 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Initial results of a prospective, multicenter trial to study inherited lung cancer risk associated with germline EGFR T790M: INHERIT EGFR. *First Author: Geoffrey R. Oxnard, Dana-Farber Cancer Institute, Boston, MA*

Background: EGFR T790M is most commonly seen as a somatic mutation in NSCLC following resistance to EGFR targeted therapies. Rarely EGFR T790M can be seen as a germline mutation where, in case reports, it has been associated with inherited lung cancer risk. The INHERIT study (INvestigating HEreditary RIsk from T790M, NCT01754025) is designed to prospectively identify and study individuals with this rare germline mutation. **Methods**: Subjects were eligible if they had EGFR T790M identified on routine cancer genotyping (excluding acquired T790M after therapy), or if they or a relative had already been found to carry a germline EGFR mutation. Subjects could participate in-person at 3 ALCMI sites or remotely via phone & mail. All subjects provided consent, filled out a questionnaire, and submitted a specimen for germline testing in a CLIA lab. Those interested in learning germline results were first provided counseling, and if positive could invite relatives to participate. **Results**: 46 subjects enrolled between 12/12 and 12/14; 22 in-person and 24 remotely (from 21 US states total); including 16 probands (NSCLC, germline pos), 23 relatives, and 6 germline neg patients with T790M-positive NSCLC (1 pending). Germline T790M prevalence: 16 of 22 patients with T790M-pos NSCLC (72%), 10 of 14 1st-degree relatives (71%). Among 12 total relatives with germline T790M, 1 had previously been diagnosed with NSCLC, 1 was diagnosed with NSCLC since germline testing, 4 have sub-cm lung nodules, 0 have negative CT scans, and 6 have not undergone CT imaging. In 18 germline carriers with NSCLC: median age at diagnosis was 56 (29-76), NSCLC stage was I-II in 2, III in 4, IV in 9. Pedigrees for 14 probands show 1-2 1st-degree relatives with NSCLC in 8, no 1st-degree relatives with NSCLC in 6. **Conclusions**: Using an innovative trial design including remote participation and germline testing based upon abnormal tumor genotyping, we have assembled the first multi-centered cohort of subjects with germline EGFR mutations. Penetrance is variable, but in some individuals germline T790M is associated with lung nodules or advanced NSCLC at a young age. Clinical trial information: NCT01754025.

1506 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Statin use and all-cancer mortality: Prospective results from the Women's Health Initiative. *First Author: Ange Wang, Stanford Univ School of Medcn, South Pasadena, CA*

Background: Statin medications are widely used for lipid lowering and heart disease prevention. Retrospective studies and basic scientific evidence have suggested that statins may also reduce cancer mortality. Data fromthe Women's Health Initiative Observational Study (WHI-OS) and Clinical Trial (WHI-CT) were used to investigate the association between statin use and all-cancer mortality in a prospective cohort of postmenopausal women. **Methods:** The WHI study enrolled women aged 50-79 from 1993-1998 at 40 U.S. clinical centers. Among 146,326 participants with median 14.6 follow-up years, 23,067 incident cancers and 3,152 cancer deaths were observed. Cox proportional hazards models were used to investigate the relationship between statin use (as a time-dependent exposure) and cancer mortality. Analyses were adjusted for age, race/ethnicity, education, smoking, body mass index, physical activity, family history of cancer, current health care provider, hormone use, age at menarche, solar irradiance, and history of heart disease/diabetes. **Results:** Compared with never users, current statin use was associated with significantly decreased cancer mortality (HR 0.78; 95% CI 0.71-0.86). Use of other lipid lowering medications was associated with a similar reduction in cancer deaths compared to monotherapy statin use (p-het = 0.57). The reduction in cancer death associated with statin use was not dependent on statin potency (p-het = 0.22), lipophilicity/hydrophilicity (p-het = 0.43), type (p-het = 0.34) or duration (p-het = 0.33). Current statin use was associated with significantly decreased mortality of multiple cancer types, including breast, colorectal, ovarian, digestive, and bone/connective tissue cancer deaths, but not lung cancer. However, past statin users were not at lower risk of cancer death compared to never users (HR 1.06; 95% CI, 0.85-1.33); additionally, statin use was not associated with a reduction in cancer incidence despite its effect on mortality (HR, 0.96; 95% CI: 0.92-1.001). **Conclusions:** In a cohort of postmenopausal women, regular use of statins or other lipid-lowering medications may decrease cancer mortality, regardless of the type, duration, or potency of statin medications used. Clinical trial information: NCT00000611.

1507 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Post-diagnosis BMI and physical activity in association with triple-negative breast cancer prognosis: Results from 5 prospective cohorts. *First Author: Sarah Jean Nechuta, Vanderbilt University Medical Center, Nashville, TN*

Background: Triple negative breast cancer (TNBC), defined as ER-/PR-/HER2-, has a poor prognosis and limited targeted treatment options. Modifiable lifestyle factors, including body mass index (BMI) and physical activity (PA), have been well-studied for overall breast cancer prognosis. However, no prospective study has investigated BMI and PA in TNBC prognosis; we conducted such an analysis using data from 5 breast cancer survivor cohorts in the US, UK, and China. **Methods:** The pooling project included 12,240 stage I-III breast cancer cases with known ER/PR/HER2 status from 5 cohorts, with 1,695 TNBC cases (13.9%). Clinical characteristics including treatment, and lifestyle factors collected on average 1.8 years after diagnosis, were pooled and harmonized. Self-reported recreational PA, summarized in MET-hours/week, was available for 4 cohorts; weight and height were available in all cohorts. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using delayed-entry Cox regression models, stratified by cohort and adjusted for known prognostic factors. Outcomes were breast cancer-specific survival (BCSS) and overall survival (OS). **Results:** Among TNBCs, mean follow-up was 9.5 years (401deaths). In adjusted models, increasing PA (MET-h/w) was associated with improved BCSS; HRs (95% CIs) by tertile (reference: < 4.1) were: 0.80(0.56-1.15) for 4.1-15.9 and 0.61(0.41-0.92) for ≥ 16.0; Ptrend = 0.02. Similar results were observed for OS (HRs (95% CIs): 0.86(0.64-1.15) for 4.1-15.9 and 0.63(0.45-0.88) for ≥ 16.0; Ptrend = 0.007). In adjusted models, a U-shaped association was observed for BMI (kg/m^2) and OS (ref. = 21.5-24.9). Only the HR for BMI < 21.5 was statistically significant, HR (95% CI): 1.60(1.10-2.32), however, the HR was no longer significant after exclusion of the Chinese cohort, HR (95% CI): 1.27(0.78-2.08). **Conclusions:** In this prospective evaluation of PA and BMI in TNBC, a trend for increasing PA and improved BCSS and OS was observed, which was significant only for high levels of PA (equivalent to ≥ 4 h of moderate intensity PA/wk). A U-shaped pattern was observed for BMI; however, obesity was not significantly associated with survival.

1508 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Alcohol consumption and prognosis in patients with stage III colon cancer: A correlative analysis of phase III trial NCCTG N0147 (Alliance). *First Author: Amanda I. Phipps, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Alcohol consumption is associated with a modest increased risk of colon cancer (CC). The relationship between alcohol and survival after CC, however, has not been well elucidated. Using data from N0147, a phase III randomized adjuvant trial in stage III CC, we assessed the association of alcohol consumption with CC outcomes. **Methods:** Patients completed a risk factor questionnaire before randomization to FOLFOX or FOLFOX + cetuximab (N = 1984). Information was collected on lifestyle factors, including smoking, physical activity, and the frequency and extent of alcohol consumption. Separate information was collected for different alcohol types. Multivariate Cox models assessed the association between alcohol consumption and outcomes of disease-free survival (DFS), time-to-recurrence (TTR) and overall survival (OS), adjusting for age, sex, study arm, body mass index, smoking, physical activity, and performance status. **Results:** Overall, 70% of patients had ever consumed alcohol regularly. There was no statistically significant difference in outcomes between ever and never drinkers in multivariate analyses [hazard ratio ($HR)_{DFS}$= 0.86, p = 0.11, HR_{TTR}= 0.87, p = 0.18, HR_{OS}= 0.86, p = 0.14]. However, when considering alcohol type, ever consumers of red wine (n = 639) had significantly better outcomes than never consumers (HR_{DFS}= 0.81, p = 0.01; HR_{TTR}= 0.81, p = 0.02; HR_{OS}= 0.78, p = 0.01). Favorable outcomes were confirmed in patients who consumed 1-30 glasses of red wine per month (n = 612, HR = 0.81 to 0.83, p = 0.03 to 0.048); there was a suggestion of more favorable (but not statistically significant) outcomes in patients who consumed > 30 glasses of red wine per month (n = 27, HR = 0.30 to 0.38, p = 0.05 to 0.06). For white wine, better OS was observed for patients who consumed 1-30 glasses/month (n = 538) compared to never consumers (HR = 0.75, p = 0.007), but no association was noted for other outcomes. Beer and liquor consumption were not associated with improved outcomes. **Conclusions:** Although alcohol consumption was not associated with CC outcomes overall, mild to moderate red wine consumption was suggestively associated with longer OS, DFS, and TTR in stage III CC patients.

1509 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Tumor relevant germline findings in targeted tumor sequencing using matched normal DNA of 1,570 unselected cases. *First Author: Kasmintan A Schrader, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor Sequencing (TS) can reveal presumed pathogenic germline variants (PPGV) that may be tumor-relevant (TR) and associated with tumorigenesis. Identification of PPGV may have significant implications for the individual and family. **Methods:** To estimate the burden of TR-PPGV identified in tumor-normal massively parallel sequencing, we analyzed 1,570 cases, unselected for cancer type or family history, that had undergone TS with matched normal DNA using a 341 gene panel employed at MSKCC (MSK-IMPACT). Subjects had provided IRB approved consent and anonymized analysis of the normal DNA samples was conducted under an IRB approved waiver. **Results:** Tumor phenotype was assessed for known genotype-phenotype correlations in cases harboring sequence PPGV in cancer-related genes of accepted clinical utility (ACMG gene list). Of 100 PPGV (98 cases, 2 cases had 2 PPGV each), 43 cases had expected tumor phenotypes. While 94 PPGV were retained in the tumor in 93 cases, in 24 cases we observed LOH/aberrant sequence of the other allele, suggesting possible involvement in pathogenesis. Eight out of 24 such cases were in tumors that do not typically trigger genetic evaluation for each corresponding syndrome; *BRCA1* (n = 2) in stomach adenocarcinomas; *BRCA2* (n = 2) in a neuroendocrine tumor and a pleomorphic sarcoma, *RET* (n = 1) in a colon cancer, *SDHC* (n=1) in a breast cancer and *MUTYH* (n = 2) in a breast cancer and Hurthle cell thyroid cancer. **Conclusions:** TR-PPGV can be estimated to occur in the matched normal DNA of up to 6% (93/1570) of unselected individuals undergoing TS. Correlation of the PPGV and tumor phenotype was seen in 44% (43/98) of cases, however 14% (8/56) of cases that had PPGV with non-conforming genotype-phenotypes showed evidence supportive of a role of the PPGV in tumorigenesis. These data indicate that phenotypes beyond those linked to known cancer syndromes may benefit from evaluation for TR-PPGV, which may also identify potentially aberrant pathways amenable to targeted therapeutic strategies.

1510 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Prevalence of incidental actionable germline mutations in 1,000 advanced cancer patients on a prospective somatic genomic profiling program. *First Author: Funda Meric-Bernstam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Next generation sequencing is increasingly used in cancer research and precision oncology. This practice may also reveal germline variants of potential clinical significance. We here report patient preferences for return of results as well as the prevalence of incidental deleterious germline mutations. **Methods:** Targeted exome sequencing of 202 genes was performed on tumor and normal DNA in a research laboratory. This panel included 18 genes for which return of incidental deleterious findings is recommended by The American College of Medical Genetics and Genomics. Mutations in these genes, as well as PALB2, were considered actionable. Results were confirmed with an orthogonal CLIA assay. A companion protocol determined patient preferences of return of incidental germline results. Return of results was initiated with genetic counseling and repeat CLIA testing. **Results:** Of 1,000 advanced cancer patients who underwent sequencing, 999 had at least one germline variant in one of the 19 "actionable" genes and 43 had likely pathogenic mutations: *BRCA1* (11*), BRCA2* (10), *TP53* (10), *MSH6* (4), *PALB2* (2), *PTEN* (2), *TSC2* (1), and *RB1* (1). Only 20 (49%) of 43 mutations were known based on clinical genetic testing. The ratio of somatic to pathogenic germline mutations differed by gene; for *TP53,* 375 patients had somatic mutations and 10 had pathogenic germline *TP53* mutations (38 to 1); for *BRCA1/2*, 106 patients had somatic mutations and 21 had pathogenic germline mutations (5 to 1). The 22 previously unrecognized mutations identified in the research environment were re-tested with an orthogonal CLIA platform with 100% concordance of mutation and interpretation. Of 1,167 patients who consented for a germline testing protocol, 1,157 (99%) stated they would like to be informed of incidental germline results. Initial experience with return of results will be presented. **Conclusions:** Most patients undergoing genomic testing are comfortable with germline testing and desire return of incidental results. A significant number may have unknown pathogenic mutations. Thus, genomic testing must be accompanied by a plan for return of germline results, in partnership with genetic counseling.

1511 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Characteristics of high risk breast cancer patients with mutations identified by multiplex panel testing. *First Author: Kara Noelle Maxwell, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: Multiplex panel testing studies evaluating cancer susceptibility in breast cancer (BC) patients suggest that between 4-11% of *BRCA1/2* negative individuals have a deleterious mutation in a high or moderate penetrance gene. The range in mutation positivity is likely due to heterogeneity of the studied patient populations. **Methods:** We performed targeted, massively parallel sequencing of 795 *BRCA1/2* negative BC patients in a research laboratory and analyzed 18 cancer susceptibility genes.Three high risk groups were studied: multiple primary cancers (MP, n = 315), early onset breast cancer (EOBC, n = 323), and familial breast cancer (FBC, n = 415). MP was defined as at least one BC and at least one other primary malignancy excluding non-melanoma skin cancer, EOBC was defined as BC under age 40, and FBC was defined as at least three first to third degree relatives with BC under age 75. **Results:** Overall, 78 patients (10%) were found to have a deleterious mutation. Mutations were found most commonly in *CHEK2* (n = 32, 4.0%), *ATM* (n = 14, 1.8%), *TP53* (n = 10, 1.3%), and *MSH6* (n = 4, 0.5%). One to two patients each had deleterious mutations in *BARD1*, *BRIP1*, *CDKN2A*, *MRE11A*, *MSH2*, *NBN*, *PALB2*, *PTEN*, *PMS2*, and *RAD50*; no mutations were identified in *CDH1*, *MLH1*, or *STK11*. Deleterious mutations were more common in MP patients versus FBC patients without MP (12% versus 7%, p = 0.04) but not EOBC patients without MP (10%, p = NS). *CHEK2* and *MSH6* mutations were more common in MP versus non-MP patients (6% vs 3% and 1.3% vs none, respectively, p = 0.05) whereas *ATM* mutations were more common in non-MP patients (0.6% vs 2.5%, p = 0.05). The most common cancers in mutation carriers were a second primary breast cancer, sarcoma, melanoma, hematological malignancies, ovarian, thyroid and uterine cancer. There was a similar distribution of malignancies in MP mutation carriers versus non-mutation carriers. Sequencing is ongoing for 276 additional MP patients to validate these findings. **Conclusions:** Our results indicate that multiplex panel testing may find a higher rate of mutations in patients with MP malignancies as compared to patients with FBC alone; however, the type of second primary malignancy may not be predictive of mutation status.

1512 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Identification of ERCC2 as novel susceptibility gene for hereditary breast and ovarian cancer. *First Author: Pauline Wimberger, University Hospital Carl Gustav Carus, Dresden, Germany*

Background: Breast and ovarian cancer (BC/OC) predisposition has been associated with several high-, moderate-, and low-penetrance susceptibility genes. Despite comprehensive testing by next-generation sequencing (NGS), there is still a large portion of high risk cases with absence of mutations in any of the known susceptibility loci. Therefore, it is essential to extend the diagnostic spectrum by screening novel candidate genes. **Methods:** Inclusion criteria for study patients (n = 717, German and Lithuanian) were defined by the German Consortium for Breast and Ovarian Cancer. NGS was performed on the Illumina MiSeq sequencer and with the TruSight cancer panel including 94 genes cancer associated genes. **Results:** In 19.7 % of the patients, BRCA1 or BRCA2 variations were found. These were either pathogenic loss-of-function mutations (43%) or rare unclassified missense variations with high probability of a deleterious effect (57%). In 17.9% of the patients we found null-mutations and rare unclassified missense variants in the acknowledged BC/OC susceptibility genes ATM, CDH1, CHEK2, NBN, PALB2, RAD51C/D and TP53. Analysis of the non-BC/OC genes on the NGS panel identified the "excision repair cross-complementing rodent repair deficiency, complementation group 2" gene (ERCC2 or XPD) as promising BC/OC predisposition candidate: we found 3 frame-shift mutations and 1 splice-site mutation in four independent BC/OC families. In all individuals tested so far, ERCC2 mutations co-segregate with the occurrence of BC and/or OC. Additionally, we found 20 rare unclassified ERCC2 sequence variations with a cumulative allele frequency of 2.9%, which is 14.5-fold overrepresented compared to the "exome aggregation consortium" (ExAC) cohort (61486 exomes). Functional testing of ERCC2 variants is still ongoing. Preliminary results show that at least some of the protein variants (e.g. NM_000400.3:p.Asp513Tyr) have lost their DNA repair ability. **Conclusions:** Our data suggest ERCC2 as a novel BC/OC susceptibility gene and provide clinical rationale for ERCC2-mutational analysis in high risk patients with confirmed absence of mutations in known BC/OC predisposition genes.

1513 Poster Discussion Session; Displayed in Poster Session (Board #336), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Clinical impact of multi-gene panel testing for hereditary breast and ovarian cancer risk assessment. *First Author: Leif W. Ellisen, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Genetic testing for hereditary breast and ovarian cancer is evolving with the recent introduction of multi-gene panels, although the clinical impact of such panels is as yet poorly defined. For patients without BRCA1/2 mutations management is guided by personal and family history, although additional (non-BRCA) mutations can contribute additional information regarding risk for both the patient and their family members. It is unknown how often finding such mutations, including those that lack gene-specific guidelines, will potentially alter clinical management. **Methods:** We used similar 25 or 29 gene panels to test 1112 patients enrolled prospectively as appropriate candidates for HBOC evaluation at three academic medical centers. We applied uniform criteria to analyze the clinical impact of the non-BRCA1/2 mutations observed in these patients and also in comparable patients at these centers. Primary outcome measures included the frequency and types of potential management changes based on each patient's gene-associated cancer risks given personal/family history and established risk-based practice standards. **Results:** The prevalence of BRCA (9.0%, CI 7.1-11.3%) and non-BRCA (3.9%, CI 2.7-5.6%) mutations was in line with previous studies and suggests that this was a representative population. The most common non-BRCA findings involved known breast/ovarian cancer genes (PALB2, ATM, and CHEK2) and Lynch syndrome genes. Among 61 patients in all groups with non-BRCA findings, the majority would result in consideration of additional disease-specific screening and/or prevention measures for the patient (56%, 34/61) or mutation-positive first-degree relatives (76%, 42/55). **Conclusions:** In appropriately-referred patients, multi-gene panel testing yields clinically relevant findings with potential management impact for substantially more patients than does BRCA1/2 testing alone. Thus, this approach may improve care for many mutation-affected individuals in the short term, and in the long term should lead to the development of additional evidence-based guidelines for at-risk individuals.

1514 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Assessment of the clinical presentation of patients with at least two deleterious mutations on multi-gene panel testing. *First Author: Jeffrey N. Weitzel, City of Hope, Duarte, CA*

Background: Technical advances have upended the established paradigm of testing high penetrance cancer predisposition genes based on syndromic features. National guidelines now include discussion of multi-gene panels. However, significant gaps in our knowledge of gene-specific phenotypes have been identified, and the effects of various gene combinations are unknown. **Methods:** We examined results from patients tested with a 25-hereditary cancer gene panel in a CLIA approved laboratory. Clinical history was obtained from test requisition forms. **Results:** Of 55,803 patients tested, 3,953 (7.1%) had a single deleterious mutation, and 106 (0.19%) had mutations in at least two genes. Breast or colon cancer was the most common diagnosis among the probands (42.8-46.8% and 10.4-12.9%, respectively for single and dual mutation carriers). There were 19 different genes among the dual mutation carriers; both were high penetrance in 47 cases, 42 were combinations of high with moderate and 17 were a combination of 2 moderate penetrance genes. The most common second mutations were in *MUTYH*, *ATM* and *CHEK2*. Of 20 patients with 2 *MUTYH* mutations, 4 did not report either CRC or a polyp history. Common combinations included 6 *BRCA2/PMS2,* and 5 each for *BRCA1/ATM*, *BRCA2/ATM* and *CHEK2/PALB2*. Of 27 patients with mutations in two high penetrance genes (*APC, BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, p16, PMS2, TP53*), 11/27 showed a mixed phenotype, consistent with both; 16/27 only reflected the phenotype of one of the two. There was no significant difference in age at cancer onset (< or > age 50 years) or probability of being unaffected; 23/89 (25.8%) dual mutation carriers vs.1205/3953 (30.5%) single mutation carriers (Chi-Square = 1.1941, p = .2745). **Conclusions:** Discovery of more than one deleterious mutation by multi-gene panel testing confounds accurate prediction of the phenotype or magnitude of risk. Despite a trend for more dual mutation carriers to be affected with cancer, the sample size was inadequate to reach statistical significance. Some cases with two high penetrance gene mutations only manifested one's phenotype. There is no obvious effect of low penetrance genes (e.g., *ATM*) on high penetrance gene phenotypes.

1515 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Outcomes of clinical testing for 50,000 patients utilizing a panel of 25 genes associated with increased risk for breast, ovarian, colorectal, endometrial, gastric, pancreatic, melanoma, and prostate cancers. *First Author: Eric T. Rosenthal, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

Background: Genetic assessment for inherited risk is a key tool for cancer prevention. Genetic testing strategies are evolving in response to expanding information about gene associations and available technologies for the cost-effective simultaneous screening of large numbers of genes. Here we provide outcomes data from clinical testing of a large, diverse cohort of US patients using a panel of 25 genes known to be associated with an increased risk for 8 common cancers with known genetic associations. **Methods:** Results are included from the first 50,000 patients tested with the 25-gene panel in a CLIA approved laboratory. All clinical information was obtained from test requisition forms completed by ordering healthcare providers. **Results:** 3750 (7.5 %) of tested patients were found to carry one or more pathogenic variants linked to an increased risk for cancer, distributed as shown in the table below. Clinical history review demonstrates that many patients had pathogenic variants in genes for which they most likely would not have been tested based on the reported personal/family history. Pathogenic variants in most genes were found in patients of all ancestries, indicating that the panel testing strategy can increase the sensitivity of testing in all populations. **Conclusions:** Testing with a 25 gene panel targeted at 8 common cancers significantly increases the number of patients identified as being at an increased cancer risk compared with testing targeted to a single gene or syndrome. This potentially benefits patients carrying pathogenic variants in genes for which testing was not widely available previously, and/or whose personal/family histories do not fit unambiguously with a single gene or syndrome.

Distribution of pathogenic variants detected.

Gene	Pathogenic Variants Detected
BRCA2	869
BRCA1	791
CHEK2	432
ATM	350
PALB2	255
PMS2	157
BRIP1	138
MSH6	124
MSH2	117
MLH1	83
NBN	91
RAD51C	80
BARD1	77
APC	73
TP53	43
CDKN2A (p16INK4A)	40
RAD51D	32
CDH1	28
MUTYH Biallelic	18
PTEN	14
EPCAM	8
STK11	6
SMAD4	5
BMPR1A	4
CDKN2A (p14ARF)	1
CDK4	0
Total	3854

1516 Poster Discussion Session; Displayed in Poster Session (Board #339), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Sarcoma: A Lynch syndrome (LS)-associated malignancy? *First Author: John M. Kaczmar, Temple Univ/Fox Chase Cancer Ctr, Philadelphia, PA*

Background: Lynch syndrome (LS) is a well characterized hereditary cancer syndrome caused by mismatch repair (MMR) deficiency of epithelial tumors. Uncertainty remains as to whether several less common non-epithelial cancers such as sarcomas may also be associated with LS. We sought to describe the incidence and characteristics of sarcomas within a sample of LS families assembled through a multi-institutional collaboration. **Methods:** Participating sites (n = 7) queried their databases for molecularly proven and clinical LS families with sarcoma reported in a close relative (1st, 2nd, 3rd-deg). Information on the familial underlying MMR gene mutation (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) was collected, as was age, sex, and tumor histology of all familial cancers from LS-sarcoma pedigrees (if available). Vague sarcoma diagnoses ("bone") were considered possible, while a documented category/histology ("rhabdosarcoma") was considered likely. **Results:** In total, from 958 LS families, 55 LS-sarcoma families (5.7%) contained 58 individuals with possible (n = 16) or likely (n = 42) sarcomas. Mean age of sarcoma diagnosis was 47.1 years (age range 4-87 years), with a 1:1 male to female ratio. Nearly two-thirds (62%, 36/58) of sarcomas were in *MSH2*+/*EPCAM*+ families, in contrast to the ~40% of all LS that are *MSH2*+. Other LS-sarcoma families were: *MLH1*+ (n = 12), *MSH6*+ (N = 3), *PMS2*+ (n = 3) and unknown (n = 4). Sarcoma histologies were diverse and included pleomorphic, synovial, myxofibroid, DFSP, liposarcoma, rhabdomyosarcoma, and osteosarcoma. Recurrent *MSH2* mutations in presumed unrelated LS-sarcoma families included 2 known founder mutations del exon 1-6 and c.942+3A > T as well as c.1216C > T, c.2135insT and c.1906G > C. Other pedigree findings included: Muir-Torre variant LS in 14/38 (37%) evaluable families, 7 thyroid cancers (2 early-onset, 29 and 31 yrs), an adult retinoblastoma, and an MSI-H thymoma in a 55 year-old woman with 2 soft tissue sarcomas. **Conclusions:** From a large sample of nearly 1000 LS families, our findings suggest sarcomas may be a rare manifestation of LS, especially *MSH2*+ LS. More research of genotype-phenotype correlations in LS is needed.

1517 Poster Discussion Session; Displayed in Poster Session (Board #340), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A comparison of ascertainment of Lynch syndrome in colorectal cancer patients via reflex testing vs. hereditary guideline-based testing. *First Author: Setareh Samimi, BCCA VC, Vancouver, BC, Canada*

Background: In accordance with The American College of Medical Genetics and Genomics (ACMG), many institutions including The Hereditary Cancer Program (HCP) of the B.C. Cancer Agency recommend initiating testing for Lynch Syndrome (LS) based on the Bethesda criteria and/or on an age threshold of less than 50 years. Reflex immunohistochemical (IHC) testing independent of family history to infer deficient Mismatch Repair (dMMR) status combined with mutant BRAF 600E (mBRAF) IHC assessment provides an alternative means of screening for LS. Although many centers have adapted a reflex approach to screening for LS, this approach is still not standard. This study compares the efficacy of the two methods. **Methods:** From January 2012 to July 2013, reflex IHC testing to detect dMMR and mBRAF was performed in all cases of resected CRC across different jurisdictions in the greater Vancouver catchment area. Additional characteristics such as age at diagnosis, personal history of cancer, family history of cancer, and status of referral to HCP were reviewed. **Results:** In total, 1458 CRC patients were analysed, of which 194 (13%) were dMMR. The dMMR subset comprised abnormal staining of hMLH1 (n = 162), hMSH2 (n = 18), hPMS2 (n = 7) and hMSH6 (n = 7). Of these 194 patients, 103 (53%) were mBRAF, 60 (31%) were BRAF Wt and in 31 (16%), results are unknown. Using dMMR and BRAF Wt combined testing results to initiate referral to the HCP, only 60 patients would require further genetic evaluation, obviating the need for assessment of 103 potentially unnecessary referrals if only dMMR IHC was considered. Of the 60 dMMR and BRAF Wt patients, 54 (90%) were older than 50 years of age and 35 (65%) did not meet Bethesda criteria on chart review. **Conclusions:** A significant number of potential cases of LS would not be identified using established guidelines. Conversely, using only MMR testing would lead to unnecessary referrals. The combination of MMR and BRAF IHC testing may serve as a simple cost efficient and time saving tool to identify patients at highest risk for LS, supporting the role of reflex IHC testing of MMR and BRAF in CRC.

1518 Poster Discussion Session; Displayed in Poster Session (Board #341), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Usefulness of the patient self-administered cancer family history questionnaire in identification of gynecological cancer patients suspected of Lynch syndrome: KCOG-G1302 study. *First Author: Ryutaro Nishikawa, Nagoya City University, Nagoya, Japan*

Background: Detailed family history collection is necessary to detect gynecological cancer patients suspected of Lynch syndrome (LS). However, clinicians have little time for family history interviews. In addition, there is a lack of genetic counselors in Japan. Therefore, information from medical records on the first visit (MR) is insufficient to determine if a patient may be at risk of LS. We showed that using the self-administered cancer family history questionnaire (SACFHQ) improves identification of patients suspected of LS. **Methods:** We recruited endometrial or ovarian cancer patients already diagnosed or newly diagnosed from research participating institutions. After consent was obtained, participants completed the questionnaire. By referring to the cancer family history obtained from MR and SACFHQ, we referred to cases that met the Amsterdam criteria II(AMSII), the SGO20-25% criteria (SGO20-25%), ACOG's clinical bulletin 2014 criteria (ACOG2014). **Results:** There was a total of 493 participants. 38 patients were excluded by exclusion criteria. Finally, 455 were eligible. Median age at diagnosis was 56 (range21-84). 243 participants were endometrial cancer patients, and 213 were ovarian cancer, including peritoneal and tubal cancer. 12 cases had either synchronous/metachronous endometrial and colorectal cancer. 4 cases had either synchronous/metachronous ovarian and colorectal cancer. Among these 16 cases, endometrial or ovarian cancer was sentinel in 8 cases. By using MR, 0/455 (0%), 4/455 (0.9%), and 170/455 (37%) cases met AMSII, SGO20-25%, ACOG2014 criteria, respectively. By using SACFHQ, 6/455 (1.3%), 9/455 (2.0%), and 217/455 (48%) cases met AMSII, SGO20-25%, ACOG2014 criteria, respectively. All 6 cases that met AMSII were endometrial cancer patients. 8 of 9 patients who met SGO20-25% were endometrial cancer patients, and one patient was ovarian cancer. **Conclusions:** Family cancer history obtained from MR was shown to be insufficient to identify individuals at risk of LS. SACFHQ improves identification of gynecological cancer patients suspected of LS. Clinical trial information: 000013192.

1519 Poster Discussion Session; Displayed in Poster Session (Board #342), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Recreational activity and sedentary behavior in relation to lung cancer incidence and mortality in the Women's Health Initiative. *First Author: Ange Wang, Stanford Univ School of Medcn, South Pasadena, CA*

Background: Studies have suggested that physical activity may decrease cancer incidence and mortality. Data fromthe Women's Health Initiative Observational Study (WHI-OS) and Clinical Trial (WHI-CT) were used to investigate this relationship in a prospective cohort of postmenopausal women. **Methods:** The WHI study enrolled women aged 50-79 years from 1993-1998 at 40 U.S. clinical centers. Among 134,058 participants, Cox proportional hazards models were used to assess the association between lung cancer incidence/mortality and physical activity levels at study baseline [MET-minutes/week: inactive < 100 (reference), low 100- < 500, medium 500- < 1200, high 1200+] and sedentary behavior (sitting time/day in WHI-OS). **Results:** Over 11.8 mean follow-up years, 2,229 total incident lung cancer cases and 1,427 lung cancer deaths were identified. Increased total physical activity at study entry was associated with significant decreases in both lung cancer incidence [p = 0.004; physical activity levels: low HR 0.86 (95% CI: 0.77-0.96), medium HR 0.81 (0.72-0.91), high HR 0.89 (0.78-1.01)] and mortality [p < 0.0001, low HR 0.80 (0.70-0.92), medium HR 0.68 (0.58-0.79), high HR 0.77 (0.65-0.91)]. BMI was found to be an effect modifier of the relationship between total physical activity and lung cancer incidence (p = 0.008), with reduced HRs found for increasing physical activity levels for BMI < 30. While smoking status was not a statistically significant effect modifier, former smokers > 10 pack-years and current smokers were estimated to have reduced lung cancer incidence and mortality HRs for increasing physical activity levels, when compared to inactive women with the same smoking status. In the subtype analysis, decreased lung cancer mortality was associated with increased total physical activity levels for both overall NSCLC and adenocarcinoma. No association was found for sedentary behavior and lung cancer incidence or mortality. **Conclusions:** In a cohort of postmenopausal women, physical activity prior to diagnosis may decrease lung cancer incidence and mortality. Physical activity may be particularly protective for women with BMIs under 30, and for current and heavy former smokers. Clinical trial information: NCT00000611.

1520 Poster Discussion Session; Displayed in Poster Session (Board #343), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Modifiable metabolic markers c-peptide (C-PEP), highly sensitive c-reactive protein (hsCRP), leptin (LEP)] and lung cancer (LC) risk: A matched case-control study nested in the prostate, lung, colorectal and ovarian (PLCO) cancer screening study. *First Author: Pamela Jean Goodwin, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada*

Background: LC is not associated with obesity; however, metabolic factors have been inconsistently associated with LC risk or death in previous small studies (involving < 100 LC cases). We investigated pre-diagnosis C-PEP, hsCRP and LEP and LC risk in EVER and NEVER smoking PLCO participants. **Methods:** 986 LC cases and 2054 controls [matched for age, gender, race/ethnicity, study center, duration in study, smoking status (never, former and current smoker)] provided non-fasting blood ≥ 2 years pre-diagnosis (≥ 3 yrs in 75%). After storage at -80°C, C-PEP, hsCRP and LEP were assayed using Luminex xMAP Multiplex immunoassays. Log transformed continuous blood markers were analyzed using multivariable conditional logistic regression [that included family history LC (FH), COPD, and smoking intensity, duration and quit-time]. 2-tail P ≤ 0.05 was considered significant. **Results:** Cases [854 NSCLC, 132 SCLC] and controls had similar age (64 yr) and ethnicity (90% white); cases had more smoking pack years (57.4 vs 39.6, p < 0.001). In EVER smokers (89.2% of total), LC cases (vs controls) had higher mean C-PEP (976.9 vs 939.4 pmol/L, p_{trend} = 0.02), hsCRP (22.6 vs 18.3 mg/L, p_{trend} < 0.001) and lower LEP (7.7 vs 8.1 ng/ml, p_{trend} < 0.001). Multivariably, higher C-PEP (p = 0.049) and hsCRP (p = 0.001) but lower LEP (p = 0.001) were associated with LC [Odds Ratios (OR) for upper vs lower quartiles 1.23, 1.54, 0.60 respectively]. FH (OR 1.75, p < 0.001), COPD (OR 1.38, p = 0.04), and extent of smoking were also associated with LC. When BMI was added to the model, it was inversely associated with LC (p = 0.003); C-PEP (p = 0.025) and hsCRP (p < 0.001) remained significant but LEP become non-significant. Metabolic markers were not associated with LC in NEVER smokers. **Conclusions:** In EVER smokers, higher pre-diagnosis C-PEP and hsCRP were associated with higher LC risk; inverse associations were seen for LEP and BMI. Future research should replicate our findings and investigate biologic mechanisms. Because these factors are potentially modifiable, intervention studies may be warranted.

1521 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Epidemiology and management of HIV-related non-Hodgkin lymphoma (NHL) in the United States (US): Analysis of the National Cancer Data Base (NCDB). *First Author: Adam J. Olszewski, Alpert Medical School of Brown University, Providence, RI*

Background: Antiviral therapy has altered the incidence and prognosis of NHL associated with human immunodeficiency virus infection (HIV+NHL). We analyzed recent trends in HIV+NHL presentation, management and overall survival (OS) using data from the NCDB—a registry capturing about 70% of US cancer cases. **Methods**: We extracted from the NCDB records of 364,422 NHL cases diagnosed in 2004-2012. HIV status was recorded for 57% of cases, identifying 11,409 HIV+ and 197,343 HIV- patients (pts). Trends and relative risks (RR) were evaluated by robust Poisson regression. **Results**: HIV+NHL pts were on average younger than HIV- (median age, 47 versus [*vs*] 67 years), more often male (77 *vs* 52%), black (33 *vs* 8%) or Hispanic (14 *vs* 5%). The histologies of HIV+NHL were: diffuse large B-cell (DLBCL)—46%, Burkitt (BL)—15%, primary central nervous system (PCNSL)—9%, primary effusion (PEL)—1%, indolent B-cell—10%, T-cell—5%, other/unknown—14%. Between 2003 and 2012, the proportion of black pts increased from 28% to 39% (*P*< .0001). The proportion of BL cases doubled among white pts (from 11 to 22%, *P*< .0001), but not for other races (from 14 to 16%, *P*= .06). The rate of chemotherapy (Ct) use increased from 69% to 78% (*P*< .0001). Ct was given to 80% of DLBCL, 90% of BL, 61% of PEL but only 34% of PCNSL pts. In a multivariable model, Ct use was significantly less common in black *vs* white pts (RR, 0.90, *P*< .0001), in facilities reporting ≤ 2 HIV+NHL cases per year (RR 0.92, *P*< .0001), and varied by insurance type. OS improved between 2004 and 2011 (log-rank *P*= .0004 for trend). OS at 3 years was 47% for DLBCL, 48% for BL, 26% for PCNSL, and 28% for PEL. Among pts who received Ct, 3-year OS was 53, 51, 45 and 29%, respectively, which was significantly lower than for HIV- pts (67% for DLBCL, 61% for BL and 47% for PCNSL; stratified log-rank *P*< .0001). **Conclusions**: Changes in the HIV+NHL demographics mirror the high rate of HIV infections among US black and Hispanic men. More HIV+NHL pts receive Ct, and their survival is improving, but disparities in Ct delivery exist that are related to socioeconomic factors and facility expertise. HIV+ DLBCL and BL have similar OS if Ct is given. In contrast, Ct does not alter the poor prognosis of PEL.

1522 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Family history of breast cancer in Hodgkin disease and future risk for breast cancer. *First Author: Sarah Violet Colonna, George E. Whalen VA, Salt Lake City, UT*

Background: Women with Hodgkin disease (HD) who undergo thoracic radiation have an extremely high risk of breast cancer (BC), up to 56x that of the average woman. The genetics underlying this increased BC risk is unclear, and we do not know if increased risk is observed in family members. We investigated BC risk among HD patients and relatives of women with HD. **Methods:** Using a genealogical database linked to Utah cancer data from 1966-2011, hazard ratios from Cox models were used to estimate BC risk among first-degree relatives (FDR) of women with HD. We compared female HD probands with BC (N=43) and HD probands without BC (N=837) to population controls age-matched 10:1. **Results:** The 'baseline' BC risk in FDR among BC patients in the Utah population (with no HD) is 1.8-fold (95%CI 1.7-1.8; *P*<0.0001). Among women with HD diagnosed before 2000 (higher radiation exposure) with subsequent BC, their FDRs are at 4-fold BC risk (95%CI 1.9-8.1; *P*<0.0001) compared to controls. Conversely, women with HD have markedly higher BC risk if they have FDR with BC compared to controls (HR=9.1, 95%CI 6.1-13.7; *P*<0.0001) and >2-fold BC risk compared to HD patients with no FDR with BC (95%CI 0.96-5.2; *P*=0.06). **Conclusions:** FDRs of women with HD and BC are at increased risk to develop BC beyond the general ~2-fold risk seen in FDRs of women with BC. Consistently, we found a very pronounced increase in BC among HD patients with FDRs with BC and 2x BC risk compared to HD patients with no BC in FDRs. This suggests an underlying genetic mechanism may predispose women with HD and their relatives to an increased risk for BC. Obtaining a BC family history at HD diagnosis may help personalize treatment around radiation therapy. Further investigation into HD treatment details related to familial and genetic for BC risk is warranted.

BC risk among relatives and HD probands vs. controls.

Relationship	HR	95%CI	P-value
BC in HD probands with BC in FDR	9.2	6.1-13.7	<0.0001
FDR of HD probands with BC (before 2000)	4.0	1.9-8.1	<0.0001
FDR of HD probands with BC	3.3	1.7-6.1	0.0002
HD probands w/BC in FDR vs. HD no BC in FDR (case-case comparison)	2.3	<1.0-5.2	0.06
BC in HD probands, no BC in FDR	2.2	1.4-3.3	0.0003
FDR of BC probands (no HD)	1.8	1.7-1.8	<0.0001
FDR of HD probands with no BC	0.9	0.7-1.2	0.81

1523 Poster Session (Board #347), Mon, 1:15 PM-4:45 PM

Hereditary implications of somatic tumor testing. *First Author: Pauline Funchain, Cleveland Clinic, Cleveland, OH*

Background: Approximately 5-10% of all cancers are due to hereditary causes. Panel testing for somatic alterations to identify therapeutic targets has gained widespread use. Germline (heritable) implications from such testing have not yet been explored. In a prospective cohort study of patients who underwent tumor profiling by next generation sequencing (NGS), we determined the prevalence of potentially germline (PG) alterations and the frequency of referral to genetics professionals. **Methods:** We prospectively accrued 250 patients to an IRB-approved protocol to undergo commercial tumor genomic profiling. Inclusion criteria included pathologic diagnosis of select solid tumor malignancies without a known curative option, age ≥ 18 years, and ECOG PS 0-2. Tumor samples underwent targeted NGS through the FoundationOne panel (Cambridge, MA). Genes captured by this test were classified as PG if the gene is known to cause hereditary predisposition to cancer and has available CAP/CLIA-certified germline testing. **Results:** Of 315 genes tested by tumor genomic sequencing, 41 genes were classified as PG. Alterations were found in 23 PG genes. Of 222 patients with resulted tumor sequencing, 179 (81%) were found to harbor >1 PG alteration. After exclusion of *TP53, APC,* and *CDKN2A*alterations, frequently somatically mutated in tumors, 91 (41%) were found to harbor any PG alteration. 34 patients harbored >1 hit in a single PG gene (e.g. "double mutants"). When considering the mean number of PG alterations found per patient, the top 4 cancer types were glioblastoma, colorectal, bladder, and breast. In this series of 222, 23 (10%) were evaluated by genetics professionals: 3 genetics referrals were a direct result of somatic panel testing, resulting in 1 (33%) previously unknown germline mutation. Germline testing has been completed in 19 patients, and revealed 4 germline mutations and 4 variants of unknown significance. Allelic fractions derived from tumor genomic profiling for these confirmed germline variants ranged between 35-72% (mean: 51%). **Conclusions:** Somatic screening of tumors has germline implications. Tumor and germline testing are not equivalent, and should be done separately. More extensive data are necessary to determine guidelines for genetics referrals.

1524 Poster Session (Board #348), Mon, 1:15 PM-4:45 PM

Clinical outcomes based on multigene profiling in metastatic breast cancer patients. *First Author: Reva Kakkar Basho, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Identifying the clinical impact of mutations in cancer-related genes can help define their role in cancer. Here, we aim to classify frequent hotspot mutations in metastatic breast cancer (MBC) patients and determine how they may affect clinical outcomes. **Methods:** Hotspot mutation testing was conducted in 500 MBC patients using an 11 gene Sequenom (N = 126) and/or 46 or 50 gene Ion AmpliSeq Panel (N = 391). Patients were stratified by hormone receptor (HR) and HER2 status, type of therapy (chemo, endocrine or targeted therapy) and line of therapy. Clinical outcomes including recurrence-free survival from diagnosis (RFS) and time to treatment failure due to progression (TTP) were retrospectively collected, and comparative analysis between patients who did and did not harbor mutations in certain genes was conducted. **Results:** The most frequent genes with hotspot mutations were *TP53* (30%), *PIK3CA* (26%) and *AKT1* (4%). Triple-negative breast cancer patients had the highest incidence of *TP53* (58%) and the lowest incidence of *PIK3CA* (8%) mutations. *TP53* mutation was associated with significantly shorter RFS (median 19 vs 41 months; $P < 0.001$), TTP with first-line (median 6 vs 12 months; $P < 0.001$) and second-line (median 4 vs 7 months; $P = 0.006$) therapy and TTP with chemotherapy (median 6 vs 8 months; $P = 0.005$) and targeted therapy (median 4 vs 14 months; $P = 0.009$) in the first-line setting. Conversely, presence of *PIK3CA* mutation did not significantly affect RFS or TTP with first-line therapy. In HR-positive patients, *TP53* mutation was associated with significantly shorter RFS (median 24 vs 46 months; $P < 0.001$), distant RFS (median 30 vs 46 months; $P = 0.002$) and local-regional RFS (median 51 vs 131 months; $P < 0.001$). However, there was no significant association between TTP and mutation status of *TP53*, *PIK3CA*, or *AKT1* in HR-positive patients treated with endocrine therapy in the first- or second-line setting. **Conclusions:** Correlating clinical outcomes with the presence of hotspot mutations in cancer-related genes can help define the clinical significance of these mutations. In this cohort of MBC patients, *TP53,* the most frequent hotspot mutation, was associated with worse clinical outcomes, both overall and in HR-positive patients. Clinical trial information: NCT01772771.

1525 Poster Session (Board #349), Mon, 1:15 PM-4:45 PM

Whole exome sequencing to identify potentially causative gene variants in hereditary gastric cancer. *First Author: Yiqing Huang, National University Cancer Institute Singapore, National University Hospital, Singapore, Singapore*

Background: Gastric cancer is the leading cause of death in Asia where a small proportion is hereditary. While some causative genes like CDH1 and mismatch repair genes have been well characterized, many remain unidentified. **Methods:** We performed whole exome sequencing on peripheral blood DNA of gastric cancer patients suspected to have an underlying hereditary predisposition, defined as young onset cancer diagnosed at or below age forty, and/or strong family history of cancers. Potentially causative mutations were identified using ANNOVAR, the CADD algorithm and HGMD database. Sanger sequencing was performed to confirm mutations identified. **Results:** Twenty subjects (18 Chinese and 2 Malays) were studied. 70% were males. Median age at cancer diagnosis was 36 (range 24-68). 75% had poorly differentiated adenocarcinomas and 50% had signet ring cells. 9 subjects had young onset cancer without family history, 6 had young onset cancer with family history and 5 had gastric cancer after age 40 but had family history of gastric or Lynch syndrome related cancers. Potentially deleterious germline mutations that may cause hereditary gastric cancer were identified in 9/20 (45%) of subjects. Seven subjects carried 8 deleterious mutations in genes known to cause familial gastric cancer, including CDH1 (n = 1: *c.1888C > G(L630V)*), MLH1 (n = 2: *428T > A(V143D)*, n = 1: *2101C > A(Q701K)*), MSH6 (n = 2: *c.4071_4072insGATT*, n = 1: *3205G > C(G1069R)*) and TP53 (n = 1: *679G > T(G227X)*). A probably deleterious mutation was identified in 1 novel gene, ABCA10 (*1328_1331del*), in 2 patients with young onset gastric cancer without family history; this variant is present in less than 1% of Asians. Five of the 7 distinct deleterious mutations identified were novel. In addition, 6 subjects carried two PLCE-1 variants (*T1469I*, *H1619R)*, while another 6 subjects carried a *MLL3 S3660L* variant, all of which have been reported to be possible low-penetrance variants that increase gastric cancer risk by 1.4 and 2.5 fold respectively. **Conclusions:** In this cohort of Asian gastric cancer patients suspected to have hereditary gastric cancer, potentially causative rare high penetrance and common low penetrance genetic variants were identified.

1526 Poster Session (Board #350), Mon, 1:15 PM-4:45 PM

Amplification of *CRKL* in human cancer: A rare event associated with potential sensitivity to targeted therapy. *First Author: Kai Wang, Foundation Medicine, Inc., Cambridge, MA*

Background: *CRKL* amplification (amp) has been linked to tumor progression and adverse prognosis in solid tumors. Recent evidence suggests that *CRKL* amp may mediate resistance to EGFR inhibitors and may be associated with exceptional tumor response to Src kinase inhibitors. **Methods:** Next generation sequencing based comprehensive genomic profiling (CGP) using hybridization capture of 236 cancer-related genes was applied to ≥ 50 ng of DNA extracted from 33,000 FFPE specimens and sequenced to high, uniform median coverage (> 600X) and assessed for base substitutions, INDELs, copy number alterations and rearrangements. Clinically relevant genomic alterations (CRGA) were defined as those for which anti-cancer drugs on the market or in registered clinical trials could be identified. **Results:** *CRKL* amps (> 6 copies) were identified in 274 (0.8%) patients of median age 62 years (range 19-92) with 137 females and 137 males. There were 18 distinct tumor types featuring *CRKL* amp as show in the table below. Co-existent CRGA associated with *CRKL* amp were *FGFR1* (7%), *RICTOR* (6%), *ERBB2* (6%), *KIT* (6%), *EGFR* (5%), *PTEN* (5%), *NF1* (5%) and *AKT2* (5%). In 3 (1%) cases *CRKL* amp was the only GA and in 41 (15%) *CRKL* amp was the only CRGA. Of 6 *CRKL* amp cases with *EGFR* substitutions, 5 (83%) were in NSCLC consistent with a potential resistance mechanism to anti-EGFR therapy. Case examples of unanticipated major responses of tumors with *CRKL* amp treated with targeted therapies will be presented. **Conclusions:** *CRKL* amp is widely distributed across diverse tumor types and frequently associated with other druggable CRGA. *CRKL* amp may be associated with EGFR TKI resistance in NSCLC. Tumors with *CRKL* amp targeted with Src kinase inhibitors may be responsible for examples of exceptional clinical responses of advanced cancers to this class of therapy.

Selected Tumor Types	# of *CRKL* amp	# of tumors analyzed	% of tumors with *CRKL* amp
Testis + mediastinum germ cell tumors	6	63	9.5%
Bladder	14	562	2.5%
Ovary	28	1464	1.9%
Lung	81	6068	1.3%
Unknown primary carcinoma	33	2779	1.2%
Melanoma	20	1880	1.1%
Liver + bile duct + gallbladder	7	675	1.0%
Soft tissue + bone	11	1088	1.0%
Uterus	7	717	1.0%
Pancreas	10	1215	0.8%
Gastrointestinal tract	23	4622	0.5%
Breast	16	3988	0.4%

1527 Poster Session (Board #351), Mon, 1:15 PM-4:45 PM

Germline testing in hereditary cancer genes subsequent to the identification of mutations in tumor specimens. *First Author: Virginia Speare, Ambry Genetics, Aliso Viejo, CA*

Background: Molecular profiling of tumors is crucial in identifying targeted therapies. Secondarily, tumor DNA sequencing has the potential to reveal germline mutations leading to the diagnosis of a hereditary cancer predisposition. We sought to determine the frequency and clinical significance of germline testing performed at one laboratory subsequent to tumor profiling. **Methods:** Retrospective review of a laboratory database revealed 74 germline test orders following identification of mutations in tumor specimens from 54 patients. Age at cancer diagnosis, family history and a description of the patient's tumor including associated somatic mutations were obtained from test requisitions. Germline targeted sequencing was performed with DNA isolated from blood or saliva. Pathogenic mutations identified in hereditary cancer predisposition genes were included for analysis. **Results:** Ten of 74 (13%) tumor mutations were confirmed in the germline. The remaining mutations are presumed to be somatic. Mutations were identified in 5 of 17 genes with the majority of germline findings in *BRCA1* (3) and *BRCA2* (4). Although *TP53* alterations were most frequently submitted for germline analysis, none were confirmed in the germline, despite 3/18 patients meeting National Comprehensive Cancer Network (NCCN) criteria for *TP53* germline testing. Based on available clinical history, 3 patients who did not meet NCCN testing criteria carried a *BRCA2* germline mutation. **Conclusions:** Patients with germline mutations who did not meet criteria for testing represent a portion of high-risk individuals who may not otherwise be identified in the absence of tumor profiling results. In addition, germline mutation detection varied between genes. These insights may prove useful in identification of patients appropriate for cancer predisposition evaluation.

Gene	# Mutations from Tumors	# Confirmed in Germline (% met testing criteria)
APC	3	0
ATM	2	0
BRCA1	4	3 (100%)
BRCA2	12	4 (25%)
CDH1	4	0
CDKN2A	3	0
CHEK2	1	1 (NC)
MEN1	6	0
MLH1	1	0
MSH2	2	0
MSH6	2	0
NF1	6	1 (100%)
PTEN	6	1 (100%)
RB1	2	0
STK11	1	0
TP53	18	0
VHL	1	0

NC = no criteria available

1528 Poster Session (Board #352), Mon, 1:15 PM-4:45 PM

Comparison of genotyping performance in DNA extracted from matched FFPE tumor, FFPE lymph node, and whole blood for pharmacogenetic analyses. *First Author: Daniel Louis Hertz, University of Michigan, Ann Arbor, MI*

Background: Pharmacogenetics requires genetic information from patients' germline DNA.There is concern that DNA extracted from formalin-fixed paraffin embedded (FFPE) tumors may not accurately represent germline DNA due to somatic genetic alterations and technical challenges. Our objective was to compare genotyping performance for DNA isolated from FFPE tumor (T), FFPE non-cancerous lymph node (LN), and whole blood (WB) to determine the extent and source of genotyping inaccuracy in FFPE tumor DNA. **Methods**: Single nucleotide polymorphisms (SNPs) from genes that affect drug elimination, efficacy, and toxicity were genotyped on Sequenom MassArrays using DNA isolated from matched T, LN, and WB samples obtained from patients with early stage breast cancer. The no-call rate was calculated for each tissue type and the discordant call rate was calculated for T and LN by comparison with the WB genotype. **Results**: After quality control, matched samples from 114 patients were genotyped for 247 SNPs in 80 genes. The no-call rate in T (4.3%) was greater than LN (3.0%) and both were greater than WB (0.5%). The discordant rate in T (1.1%) was greater than LN (0.3%). Samples with heterozygous genotypes were more likely to be no- or discordantly-called than homozygous samples (all $p < 0.001$, Table). **Conclusions**: FFPE T no- and discordant-call rates were acceptable (< 5%), though higher in heterozygous samples, suggesting that somatic genetic alterations and FFPE storage have minimal effect and/or FFPE T samples contain sufficient normal tissue for germline genotyping. FFPE T samples can be used in pharmacogenetic research, however, certain genes that are highly altered in somatic tissue require germline specimens and inaccurate genotyping of heterozygous samples precludes use of FFPE T for clinical pharmacogenetics.

No and discordant call rates in each sample type.

		T	LN	WB
No Calls	Overall	4.3% (1221/28158)	3.0% (843/28158)	0.5% (135/28158)
	Homozygous	1.8% (346/18900)	2.5% (468/18900)	-
	Heterozygous	9.5% (864/9123)	4.0% (363/9123)	-
Discordant Calls	Overall	1.1% (306/26824)	0.3% (84/27204)	-
	Hom.	0.2% (33/18554)	0.2% (32/18432)	-
	Het.	3.3% (273/8259)	0.6% (52/8760)	-

1529 Poster Session (Board #353), Mon, 1:15 PM-4:45 PM

Personalized Genomic Analyses for Cancer Mutation Discovery and Interpretation. *First Author: Valsamo Anagnostou, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: The anticipated widespread adoption of large scale genomic analyses in precision oncology mandates the development of a gene actionability framework. Previous efforts of clinical interpretation of genomic alterations mainly rely on expert opinion and manual curation of the primary literature. Furthermore, analytic challenges such as distinguishing somatic -driver- mutations from germline alterations have limited the interpretation of genomic information. **Methods:** We comprehensively evaluated 815 tumor-normal paired samples from 15 tumor types and identified genomic alterations using next generation sequencing of whole exomes or 111 targeted genes. Tumor and normal data were compared to identify somatic and germline alterations. We extracted information from consensus guidelines (fda.gov), the centralized registry of clinical trials (ClinicalTrials.gov) and published clinical trials to generate a database with actionable genes according to graded levels of evidence. **Results:** These analyses revealed an average of 140 and 4.3 somatic mutations per exome and targeted sequencing respectively. We identified at least one somatic alteration in genes with potentially actionable consequences in 77% of patients analyzed. Most of the actionable changes were associated with current clinical trials (67%) rather than established therapies (33%). More than 90% of genes with actionable alterations were mutated in < 5% of individual tumors. Analyses of matched normal DNA identified germline alterations in cancer predisposing genes in 3% of patients with apparently sporadic cancers. In contrast, a tumor-only sequencing approach followed by bioinformatic removal of common germline variants led to a 31% and 65% false discovery rate in alterations identified in targeted and exome analyses, respectively. **Conclusions:** Our comprehensive actionability framework was used to classify genomic alterations based on existing levels of evidence and could be used as a platform for clinical interpretation of somatic alterations. Our findings suggest that matched tumor-normal sequencing analyses are essential for precise identification of somatic alterations and have important implications in clinical decision making.

1530 Poster Session (Board #354), Mon, 1:15 PM-4:45 PM

The landscape for genetic eligibility to basket clinical trials. *First Author: Todd Cory Knepper, H Lee Moffitt Cancer Ctr, Tampa, FL*

Background: There is a movement toward basket trials, where eligibility is based on molecular aberrations rather than anatomical origin of a cancer. There is a paucity of information on how many cancer patients (pts) meet eligibility for basket trials. This study assessed the genetic eligibility of cancer pts seen at a large cancer center for the currently open basket trials. **Methods:** Moffitt's Clinical Genomic Action Committee (CGAC) database was used to assess 236 pts across 30 cancer types with targeted deep sequencing as part of clinical care between 1/1/2013 and 12/31/2014. Pts were screened for basic histologic and genetic eligibility on all basket trials open in North America in January, 2015 (Novartis Signature, NCI-MATCH, NCI-M-PACT). The trials included 23 different arms utilizing different agents based on 44 different molecular alterations; 11 of these alterations allowed eligibility into multiple trials. **Results:** Among the 236 evaluable pts, 83.5% met genetic eligibility for at least 1 of the arms examined with an average of 2.89 eligible arms per patient and a range of 0 to 15. The percentage of histologically eligible pts meeting genetic eligibility ranged from 0% (non-melanoma or colorectal BRAF V600 mutated solid or hematologic malignancy) to 50.0% (PARP1/2 or TP53 mutated solid tumor) across all treatment arms. Of 188 pts with solid malignancies, 93.6% met genetic eligibility for at least 1 of the trials vs. 45.8% of 48 pts with hematologic malignancies. **Conclusions:** The vast majority of pts within a clinical genetic database who received somatic tumor sequencing met genetic eligibility for at least one aberration-specific clinical trial; however 16.5% of pts overall and the majority of those with hematologic malignancies remained without basket trial options. These results highlight opportunities for enrollment in clinical trials given access to both tumor sequencing and next-generation clinical trials.

	All Pts (n = 236)	Solid Malignancies (n = 188)	Heme Malignancies (n=48)
Any Trial	197 (83.5%)	176 (93.6%)	22 (43.8%)
SIGNATURE	160 (67.8%)	139 (73.9%)	22 (43.8%)
NCI-MATCH	22 (41.9%)	97 (51.6%)	*Only lymphomas eligible (n = 6)* 2 (33.3%)
NCI-M-PACT	156 (66.1%)	156 (83.0%)	n/a

1531 Poster Session (Board #355), Mon, 1:15 PM-4:45 PM

Patient-reported outcomes associated with population-based Jewish genetic testing for BRCA1 and BRCA2. *First Author: Kelly A. Metcalfe, University of Toronto, Toronto, ON, Canada*

Background: Population based genetic testing for common Jewish mutations in BRCA1 and BRCA2 has been proposed, however it is unclear what the outcomes associated with population based testing are. **Methods:** 6108 unselected Jewish women in Ontario were offered genetic testing for three common Jewish BRCA mutations. Cancer-related distress was measured prior to testing, and at one and two years post-testing. Information on uptake of cancer risk reduction options was collected at two years post-testing. **Results:** Of the 6108 Jewish women tested, 1.1% were found to have BRCA mutation (0.4% BRCA1 and 0.7% BRCA2). None of these women had a previous cancer diagnosis and 62% of the women would not have been eligible for testing based on current criteria. Of the 68 women identified with a BRCA mutation, 3 breast cancers and 1 ovarian cancer were identified on first screenings. Within two years of testing, 28% of women had prophylactic mastectomy and 72% had a prophylactic oophorectomy. Cancer-related distress was significantly higher at one-year post-testing for those with a mutation (mean 20.0, SD = 15.3) compared to those without (mean 9.8, SD = 13.9) ($p < 0.0001$). For women with a BRCA mutation, cancer-related distress declined significantly from one year to two-years post genetic testing ($p = 0.01$). Satisfaction with population based genetic testing was high (mean 4.1; 1 = extremely dissatisfied to 5 = extremely satisfied). After identification of the 68 women with mutations, 128 first degree relatives were eligible for testing, of which 90 were tested (70%) and 32 additional BRCA carriers were identified. **Conclusions:** Population based Jewish genetic testing for BRCA1 and BRCA2 is effective at identifying unaffected women with mutations who otherwise would not be eligible for testing, in addition to their first degree relatives. The majority of women elect for risk reduction surgeries after learning of their BRCA mutations. Increased levels of cancer-related distress in BRCA carriers are transient and decline at two years post genetic testing. We propose that population based genetic testing for BRCA1 and BRCA2 be made available for Jewish individuals who wish to be tested.

1532 Poster Session (Board #356), Mon, 1:15 PM-4:45 PM

Somatic mutation profiling of advanced breast and ovarian cancers according to germline *BRCA1/2* mutation status. *First Author: Neda Stjepanovic, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: The risk of breast cancer (BC) and ovarian cancer (OC) is increased in germline *BRCA1/2* mutations carriers (BRCA+). We investigated the somatic mutation profile and clinical impact of targeted sequencing in advanced BC and OC patients (pts) according to germline *BRCA1/2* status. **Methods:** Targeted sequencing with Illumina MiSeq TruSeq Amplicon Cancer Panel (TSACP; 48 non-homologous DNA recombination genes, 212 amplicons, $\geq 500\times$ coverage) was performed using archival tumor and germline DNA from advanced BC and OC pts through an ongoing institutional molecular screening program (NCT01505400). Medical records were retrospectively reviewed for clinical, pathological and germline *BRCA1/2* testing results. **Results:** From May/13 to Oct/14, somatic TSACP testing was completed in 257 pts (106 BC and 151 OC). Germline *BRCA1/2* testing was performed in 118 pts (35 BC [33%] and 83 OC [55%]), primarily in those with family history and/or young age at diagnosis. Among these, 25 pts were BRCA+ (21%), including 4 BC (11%; 25% triple negative [TN]) and 21 OC (25%, all type 2) pts. The BRCA-/unknown group (BRCA-/UK) comprised 102 BC (24% TN and 76% non-TN) and 130 OC (31% type 1, 68% type 2) pts. Using the TSACP, 188 pts (73%) had $\geq$ 1 somatic hotspot mutation with no difference in the number of somatic mutations detected in BRCA+ vs BRCA-/UK (median 1, range 0-3; $p = 0.85$). More BRCA+ pts had *TP53* hotspot mutations compared with BRCA-/UK pts (76% vs 50%, $p = 0.01$). Somatic hotspot mutations in *PIK3CA* were more frequent in BRCA-/UK vs BRCA+ (22% vs 4%, $p = 0.04$). After a median follow up of 8 months, 12 BRCA-/UK pts vs no BRCA+ pts were enrolled in somatic genotype matched targeted clinical trials (5% vs 0%, $p = 0.62$). Seven BRCA+ pts received PARP inhibitors on clinical trials. **Conclusions:** In pts with BRCA+ BC and OC, *TP53* mutations are common while *PIK3CA* or other hotspot somatic mutations are rare. Whether the association between germline *BRCA1/2* and hotspot mutation status is causal or confounded by histological subtypes should be validated in larger cohorts. Broader genomic sequencing may further highlight biological differences amongst BRCA+ and BRCA- tumors and provide more opportunities for genotype-treatment matching.

1533 Poster Session (Board #357), Mon, 1:15 PM-4:45 PM

Multi-gene panel testing in an unselected endometrial cancer cohort. *First Author: Kari Lassen Ring, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Endometrial carcinoma (EC) is associated with multiple hereditary cancer genes including Lynch syndrome (LS) genes, which are estimated to account for 2-6% of all cases. The role of other cancer predisposition genes in EC is unclear. We aimed to determine in an unselected EC cohort the prevalence of germline mutations in LS and other cancer predisposition genes. **Methods:** The study cohort was 381 EC patients unselected for age of dx with banked blood samples available for testing. DNA mutations in 25 cancer genes were identified using a next generation sequencing based panel. Germline sequence variations and large rearrangements were classified for pathogenicity. Patients' clinical data, tumor testing with immunohistochemistry (IHC) for mismatch repair proteins, microsatellite instability, and MLH1 methylation, were abstracted from the medical record. All cases had germline genetic testing regardless of tumor testing status. **Results:** 35 patients (9.2%) had a deleterious mutation (DM). 22 patients (5.8%) had a DM in LS genes (3 *MLH1*, 5 *MSH2*, 2 *EPCAM*, 6 *MSH6*, 6 *PMS2*) and 13 patients (3.4%) had a DM in non-LS genes (4 *CHEK2*, 1 each in *APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, NBN, PTEN, RAD51C*). Compared to patients with no DM, patients with DM in LS genes were younger at diagnosis (mean 51.7 v 61.5, $p < 0.01$), less likely to be overweight (63.6% v 85.5%, $p = 0.01$), more likely to have a tumor in the lower uterine segment (30.0% v 7.5%, $p < 0.01$), and more likely to meet SGO guidelines for genetic assessment referral (59.1% v 24.3%, $p = 0.01$). 3 patients (13.6%) with DM in LS genes were diagnosed $>$ 60 years. Of 20 patients with DM in LS genes and available tumor results, 2 (10%) had a DM (1 *PMS2*, 1 *MSH6*) and IHC results suggestive of sporadic cancer. Patients with DM in non-LS genes were more likely to have serous histology (23.1% v 6.4%, $p = 0.02$) than those with no DM. 3 patients with non-LS DM and serous histology had mutations in *BRCA2, BRIP1*, and *RAD51C*, genes previously linked to hereditary ovarian cancer. **Conclusions:** Results for EC with DM in LS genes were similar to previous findings. Panel testing to include non-LS genes allowed for the identification of possibly novel genes that may be associated with serous-type EC, the most clinically aggressive form of this cancer.

1534 Poster Session (Board #358), Mon, 1:15 PM-4:45 PM

Evaluation of rapid whole-body magnetic resonance as screening strategy for early cancer detection in 57 Brazilian Li-Fraumeni syndrome patients. *First Author: Daniele Paixao, A.C. Camargo Cancer Center, Sao Paulo, Brazil*

Background: Li-Fraumeni Syndrome (LFS) is a rare autosomal dominant syndrome associated with germline mutations in *TP53* gene. Carriers have a high risk for developing multiple early onset cancers, most commonly breast cancer, sarcomas, brain and adrenocortical carcinomas. Screening strategies for early diagnosis in carriers constitute a major challenge due to the diverse spectrum and ages of onset of tumors. Rapid whole body MRI (RWB–MRI) has been proposed as a screening strategy. In Brazil, there is a high prevalence of a founder mutation (p.R337H *TP53*) present in 0.3% of the South/Southeastern Brazilian population. Due to genetic modifiers, tumors occur at a later age in p.R337H carriers. **Methods:** The aim of this study is to evaluate the efficacy of RWB–MRI as a screening strategy in p.R337H *TP53* carriers and in classical LFS mutation carriers. A total of 84 RWB–MRI were performed in 57 *TP53* germline mutation carriers (49 p.R337H *TP53*), including 27 patients who performed a second exam 12 months after the first RWB–MRI. **Results:** Two malignant lesions were detected by RWB–MRI: (1) in a 19–year old p.R337H female carrier RWB-MRI demonstrated bilateral renal cortical alterations, confirmed with abdominal MRI which showed an enhancing solid lesion in the right kidney. The lesion was surgically removed and pathological findings confirmed a papillary renal cell carcinoma; (2) in a 30 year old p.R337H female carrier, RWB–MRI detected a solid right breast nodule. Breast MRI detected two solid lesions. Biopsy of each lesion confirmed diagnoses of a ductal carcinoma in situ and benign phyllodes tumor, respectively. Incidental findings were detected in 26/57 patients and further imaging modalities were performed in 9/26 cases which ruled out malignancies and no unnecessary biopsies were performed. No malignant lesions were detected in 8 classical LFS patients. **Conclusions:** Preliminary results from this study demonstrate the feasibility and effectiveness of RWB–MRI in detecting malignant lesions among 49 p.R337H *TP53* mutation carriers.

1535 Poster Session (Board #359), Mon, 1:15 PM-4:45 PM

Comprehensive genomic profiling of advanced stage esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinomas (EAC). *First Author: Adrienne Johnson, Foundation Medicine, Inc., Cambridge, MA*

Background: Esophageal Squamous Cell Carcinomas (ESCC) and Esophageal Adenocarcinomas (EAC) account for $>$ 95% of esophageal malignancies. Using a sensitive sequencing assay, we compared the genomic profiles of ESCC and EAC focused on the ability to identify potential targets for therapy in the 2 diseases. **Methods:** DNA was extracted from 40u of FFPE sections from 71 clinically advanced ESCC and 231 EAC. Next generation sequencing based comprehensive genomic profiling (NGS) was performed on hybridization-captured, adaptor ligation based libraries to a median coverage depth of $>$ 650x for 236 cancer-related genes. The results were evaluated for all classes of genomic alterations (GA). Clinically relevant genomic alterations (CRGA) were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials. **Results:** There were no significant differences in the age range for ESCC and EAC (median: 63 vs. 60 years). All ESCC and EAC were at an advanced stage (Stage III/IV) at the time of sequencing. GA per sample on average in 71 ESCC and 231 EAC were 7.4 and 5.6 respectively. The frequency of CRGA in ESCC (2.6/sample; 94.4% of cases) and EAC (2.7/sample; 93.1% of cases) were similar. CRGA more frequently identified in ESCC than EAC included *PIK3CA* (24% vs 10%), *PTEN* (11% vs 4%), *CCND1* (42% vs 13%) and *NOTCH1* (17% vs 3%). CRGA more frequently altered in EAC than ESCC included *KRAS* (23% vs 6%) and *ERBB2* (23% vs 3%). Other GA that were significantly different in the 2 tumor types included *SMAD4* (1% ESCC vs 14% EAC), *SOX2* (18% ESCC vs 1% EAC) and *NFE2L2* (24% ESCC vs 1% EAC). *EGFR* was altered in 8% of ESCC and 15% of EAC. Clinical case examples of patient responses to targeted therapy will be presented. **Conclusions:** ESCC and EAC share common high frequencies of overall and clinically relevant GA. However, PI3K/mTOR (*PIK3CA* and *PTEN*) and Notch pathway genes were significantly enriched in ESCC, and RAS/MEK pathway genes (*ERBB2* and *KRAS*) were significantly enriched in EAC. Comprehensive genomic profiling shows significant promise to identify CRGA in both ESCC and EAC and lead to potential use of clinical outcome altering targeted therapies in both major types of esophageal cancer.

1536 Poster Session (Board #360), Mon, 1:15 PM-4:45 PM

Is there a role for multi-gene screening panels in patients who previously underwent noninformative genetic testing? *First Author: Melissa K Frey, New York University School of Medicine, New York, NY*

Background: The availability of next-generation sequencing coupled with the recent discovery of multiple cancer-related genes has caused a shift away from single gene testing towards multi-gene panel testing for familial cancer syndromes. However, the utility of multi-gene panels in individuals who previously underwent noninformative genetic screening has yet to be evaluated. We aim to evaluate the use of rescreening and results of multi-gene panels in this rescreened population. **Methods:** We reviewed all patients who had previously undergone genetic testing for familial cancer syndromes and then underwent multi-gene panel testing at a single institution between 9/2013-11/2014. **Results:** One hundred and twenty-four patients with prior non multi-gene panel testing underwent multi-gene panels. One hundred patients (81%) had a history of cancer and 115 patients (93%) had at least one family member with cancer. On primary testing, no deleterious mutations were identified and 11 variants of uncertain significance (VUS) were found in 10 patients (8%). On repeat multi-gene panel testing, 5 patients (4%) had a deleterious mutation, 54 (44%) had VUS and 4 (3%) had a mutation and VUS. Among patients with a VUS on rescreening, 14 (24%) had more than one VUS identified (range 2-4). Rescreening found a total of 9 deleterious mutations and 80 VUS and resulted in a change in mutation characterization for 9 patients and VUS characterization for 48 patients. **Conclusions:** Among patients with negative primary testing there was a 47% rate of change in result characterization with multi-gene panels. Our data suggest that patients with noninformative prior screening may benefit from rescreening with multi-gene panels. As more about mutations now classified as VUS is learned, the additional information offered by multi-gene panel testing may prove to be increasingly relevant.

Gene	Primary testing - VUS	Repeat multi-gene panel - VUS	Repeat multi-gene panel - Mutation
MUTYH	0	3	3
BRIP1	0	2	2
BRCA2	5	10	1
ATM	0	9	1
APC	0	3	1
RAD51D	1	1	1
MLH1	2	7	0
CHEK2	0	5	0
MSH6	0	5	0
RAD50	0	4	0
PALB2	0	4	0
BARD1	0	4	0
CDH1	1	3	0
PMS2	1	3	0
TP53	1	2	0
AXIN2	0	2	0
BRCA1	0	1	0
NF1	0	1	0
MSH2	0	1	0
CDKN2A	0	1	0
NBN	0	1	0
XRCC2	0	1	0
BMPR1A	0	1	0
SMAD4	0	1	0
BLM	0	1	0
EPCAM	0	1	0
MET	0	1	0
MRE11A	0	1	0
RAD51	0	1	0

1537 Poster Session (Board #361), Mon, 1:15 PM-4:45 PM

Do women with *BRCA1* or *BRCA2* mutations have reduced ovarian reserve? *First Author: Kelly-Anne Phillips, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia*

Background: It is uncertain whether mutations in the DNA repair genes, *BRCA1* or *BRCA2*, result in reduced ovarian reserve. AMH is a surrogate marker of ovarian reserve. This study examined AMH levels of *BRCA1* and *BRCA2* mutation carriers and their non-carrier blood relatives. **Methods:** Eligible women were from families segregating *BRCA1* or *BRCA2* mutations enrolled in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab). Each woman had been tested for the family mutation and had completed an epidemiological questionnaire and provided a blood sample at cohort entry. Women were aged 25-45 years, had no personal history of invasive cancer, had two intact ovaries and were not pregnant or breastfeeding at the time of blood draw. AMH was tested on stored plasma samples using an electrochemiluminescence immunoassay platform. Higher AMH levels are associated with greater ovarian reserve. Associations between AMH level and carrier status were tested by linear regression, using the natural logarithm of AMH as the outcome variable, carrier status as the explanatory variable, and adjusting for age at blood draw, oral contraceptive use, BMI and cigarette smoking. Robust standard errors were estimated to account for the inclusion of multiple members from the same family. **Results:** AMH level was measured for 172 carriers and 216 non-carriers from families carrying *BRCA1* mutations, and 147 carriers and 158 non-carriers from families carrying *BRCA2* mutations. Within both groups, mutation carriers were younger at blood draw than non-carriers ($p \leq 0.031$). Age was negatively associated with AMH level for carriers and non-carriers of *BRCA1* and *BRCA2* mutations ($p < 0.001$). *BRCA1* mutation carriers had, on average, 25% lower AMH levels than non-carriers ($p = 0.022$). There was no evidence of an association for *BRCA2* mutation carriers ($p = 0.94$). Results did not change substantially after excluding women who were post-menopausal or taking oral contraceptives at blood draw. **Conclusions:** This study suggests that women with a germline mutation in *BRCA1* have reduced ovarian reserve. This could have implications for their fertility and family planning.

1538 Poster Session (Board #362), Mon, 1:15 PM-4:45 PM

Predictors of BRCA mutation in male breast cancer. *First Author: Can Ardic, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Breast cancer is uncommon among men. Male breast cancer accounts for less than 1% of all male tumors. Among affected men, it is estimated that 10% have a genetic predisposition for the disease, most of which are determined by BRCA mutations. According to the NCCN guidelines, diagnosis of male breast cancer is sufficient to recommend BRCA genetic testing. In the present study, we evaluated other potential predictors having a BRCA mutation in male breast cancer patients. **Methods:** Men with a personal history breast cancer and who were referred for genetic testing were identified from a prospectively maintained database. Patient characteristics included personal history of other cancers, family history of breast and ovarian cancer, tumor type, estrogen (ER)/progesterone (PR) /Her2 receptor expression, nuclear grade, age of diagnosis, currently known risk factors for male breast cancer (liver cirrhosis, gynecomastia, radiation exposure, and Klinefelter's disease), any hormone replacement therapy, and BRCA results. Univariate and multivariate logistic regression analyses were used to determine predictive factors associated with BRCA mutation. **Results:** After excluding male breast cancer patients presenting for predictive testing, 67 male breast cancer patients were identified. Nine (13%) patients carried a BRCA mutation, all of which were BRCA2. Risk factors that showed significant associations with BRCA mutation included having 2nd degree relatives with breast cancer ($p = 0.0465$) and having first degree relatives with ovarian cancer ($p = 0.0304$). Known risk factors for male breast cancer, previous history of other cancers, tumor markers (ER/PR/Her2, nuclear grade, and tumor type), did not show any significant associations. In multivariate analysis, having first degree relatives with ovarian cancer were more likely to have a BRCA mutation ($p = 0.0251$). **Conclusions:** Factors associated with predicting a positive BRCA result in men with breast cancer include a family history of breast and ovarian cancer as well as radiation exposure. Further larger studies should evaluate whether having solely male breast cancer is a strong enough predictor for BRCA mutations in the absence of factors mentioned above.

1539 Poster Session (Board #363), Mon, 1:15 PM-4:45 PM

Solid tumor profiling via next-generation sequencing to identify tumor-specific actionable variants. *First Author: Sara E. Patterson, The Jackson Laboratory for Genomic Medicine, Farmington, CT*

Background: Different tumor types are often associated with reoccurring mutations. Performing detailed genetic profiling to identify the milieu of actionable gene variants characteristic of specific tumors may guide targeted approaches to treatment, as well as uncover new therapeutic targets. To this end, we used a next-generation sequencing approach to identify characteristic actionable variants across various solid tumor types. **Methods:** DNA from FFPE sections of 58 solid tumor samples (15 colon, 14 ovarian, 13 lung, 11 melanoma, and 5 squamous cell carcinoma) was sequenced using the Jackson Laboratory Cancer Treatment Profile, a 358-gene targeted panel and submitted to the Clinical Genomics Analytical (CGA) bioinformatics pipeline. Resultant variant calls were filtered based on impact and actionable variants (defined as those having therapeutic relevance) were identified through extensive literature review from in-house curation efforts. **Results:** Tumor profiling for actionable variants demonstrated genetic heterogeneity among solid tumor types. Colon tumors contained codon 12 or 13 variants in KRAS (47%; 7/15), and RET G691S (33%; 5/15); lung tumors contained frequent AURKA F31I (31%; 4/13), and KDR Q472H (69% 9/15) variants; melanomas contained BRAF V600 (91%; 10/11) and AURKA F31I (64%; 7/11) variants; squamous cell carcinomas contained frequent FGFR4 G388R (60%; 3/5), with high prevalence of AURKA F31I, RET G691S, and PIK3CA E542K (each 40%; 2/5). KRAS variants were identified in 80% (4/5) of mucinous ovarian tumor samples. Mucinous ovarian tumors were also associated with MET T1010I (29%; 2/5), which was not identified in any other analyzed tumor type. **Conclusions:** Somatic variant profiling in solid tumors is biologically heterogeneous but often results in clinically actionable genomic characteristics. In this survey of 5 different tumor types, we identified various genetic variants including a frequent occurrence of MET T1010I in mucinous ovarian tumors. MET T1010I is an activating mutation in MET that has been demonstrated to enhance tumor cell proliferation and migration, and represents a potential therapeutic target that has not been previously identified in ovarian cancer.

1540 Poster Session (Board #364), Mon, 1:15 PM-4:45 PM

Germline variation in *NFE2L2*/*CUL3*/*KEAP1* and risk of head and neck squamous cell carcinoma (HNSCC). *First Author: Siddharth Sheth, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) is a key transcription factor regulating oxidative stress. Activated NFE2L2 translocates to the nucleus and binds anti-oxidant response elements in the promoter regions of cytoprotective genes. It is negatively regulated by its protein complex partners, CUL3 and KEAP1. Recent HNSCC genome profiling studies identified *NFE2L2*, *CUL3* and *KEAP1* as recurrent somatically altered genes, suggesting an important role in HNSCC carcinogenesis. We hypothesized that germline variation in *NFE2L2*, *CUL3* and *KEAP1*affects risk of HNSCC. **Methods:** The study population consisted of 751 cases (459 oral cavity, 292 oropharynx; 69% smoker) and 862 controls (50% smoker) from the University of Pittsburgh HNSCC case-control study. Subjects were genotyped for 22 single nucleotide polymorphisms (SNPs) located in or near *NFE2L2* (10), *CUL3* (8) and *KEAP1*(4) using Sequenom's iPLEX assay. Odds ratios (OR) for HNSCC risk and corresponding 95% confidence intervals (CI) were calculated using logistic regression models. Additive and dominant genetic models were evaluated; common allele homozygotes were used as the reference group. All analyses were adjusted for age (continuous), sex (male, female), smoking status (never, ever) and alcohol use (never, ever). **Results:** Two SNPs in *NFE2L2* (rs13001694, rs6726395) and two SNPS in *CUL3* (rs1466723, rs3738952) were significantly associated with HNSCC risk in our study population ($P< 0.05$). The minor alleles of these SNPs were associated with increased risk of developing HNSCC (rs13001694, OR: 1.16, 95%CI: 1.00-1.35; rs6726395, OR: 1.17, 95%CI: 1.02-1.35; rs1466723, OR: 1.27, 95%CI: 1.03-1.56; and rs378952, OR: 1.54, 95%CI: 1.20-1.98). **Conclusions:** Our results suggest that germline variation in the *NFE2L2*/*CUL3*/*KEAP1*pathway affects risk of developing HNSCC. Improved understanding of the role of genetic variation in HNSCC carcinogenesis may aid the development of more effective, personalized prevention and diagnostic strategies.

1541 Poster Session (Board #365), Mon, 1:15 PM-4:45 PM

Genetic testing decisions of breast cancer patients: Results from the iCanCare study. *First Author: Reshma Jagsi, University of Michigan Health System, Ann Arbor, MI*

Background: Breast cancer pts at high risk for pathologic genetic mutations should consider testing. Even those without elevated risk may have concerns about genetic predisposition. Little is known about cancer pts' decisions to undergo genetic testing as access to multiple gene panels and rising awareness transforms the decision-making context. **Methods:** We surveyed a population-based sample of early-stage breast cancer pts diagnosed in 2013-14, identified by 2 SEER registries (Los Angeles and Georgia), about experiences with genetic testing after diagnosis. Surveys were completed about 6 months after dx. A "high risk" subgroup was determined based on age, family history, and ancestry, and receptor status. We evaluated patterns of receipt of counseling and correlates of testing in a preliminary sample (response rate 68%). **Results:** Among 2,051 pts analyzed, 728 (35%) were "high risk." Most high risk pts (67%) and half (50%) of others desired testing. Most high risk pts (63%) and 38% of others spoke to a physician or other health care professional about testing. Overall, 23% reported formal genetic counseling (34% of high risk pts, 18% of others), and 28% received testing (46% of high risk pts, 19% of others). On multivariable analysis, test receipt was more common in pts with high risk, invasive vs in situ disease, and higher education. Among high risk pts, non-receipt of testing was associated with in situ vs. invasive disease (OR 1.8, $p = .02$), no family hx of breast cancer(OR 2.4, $p = < .001$), older age (OR 1.9 for +5-yrs, $p < .001$), lower education (OR 1.6, $p = .05$), and Medicaid insurance (OR 2.0 vs private, $p = .03$). Of 362 high risk pts who did not get tested, 54% indicated their doctor didn't recommend it, 10% didn't want it, and 12% said it was too expensive. **Conclusions:** Most newly diagnosed breast cancer pts desire genetic testing, but many do not discuss it with providers. Most high risk pts do not report formal genetic counseling; a substantial number report no discussion of genetic risk at all. Test receipt is reassuringly correlated with risk but also with SES. Providers must ensure that breast cancer patients with interest in genetic risk have adequate discussion, especially as access to more expansive testing soars. Funding: P01-CA-163233.

1542 Poster Session (Board #366), Mon, 1:15 PM-4:45 PM

Assessment of functional impact of germline BRCA1/2 variants located in noncoding regions in families with breast-ovarian cancer predisposition. *First Author: Elizabeth Santana dos Santos, Hospital Sírio Libanês, São Paulo, Brazil*

Background: The molecular mechanism of cancer susceptibility remains unclear for the majority of breast and/or ovarian cancer patients. The screening of the key genes *BRCA1* and *BRCA2* identifies a causal mutation in less than 15% of the families tested. Even if some germline mutations in the regulatory non-coding regions of these genes have been described, their screening is still limited to the coding regions and intron-exon junctions. The aim of this study was to evaluate the potential contribution of non-coding variants on the *BRCA1/2* promoter activity and then in breast-ovarian cancer predisposition. **Methods:** The variants tested were selected from the ENIGMA database (Evidence based Network for the Interpretation of Germline Mutant Alleles) and from the screening of 2 cohorts of patients with *BRCA1/2* negative status and whose personal and/or family history were suggesting a breast-ovarian cancer predisposition. The latter was performed on 4 *BRCA1/2* non-coding regions (promoter regions and intronic regions). The impact of the variants on the *BRCA1/2* gene expression was tested *in vitro*, after transient transfection in MCF-7 and MDA-MB231 breast cancer cells, by Luciferase gene reporter assay. **Results:** A total of 12 *BRCA1* and 8 *BRCA2* variants were tested. We delimited a *BRCA1* promoter region with 3 functionally active variants with a clear repressor impact on the promoter activity. This DNA sequence region corresponds to a putative DP1/E2F1 transcription factor binding site, which has never been described. One *BRCA2* variant in the promoter also showed a significant reduction in the transcriptional level. Two *BRCA1* in the promoter and in intron 2 and two *BRCA2* variants in the promoter increased the promoter activity. All the others were shown to have no impact in our functional assay. **Conclusions:** Through Luciferase gene reporter assay, we identified 8 non-coding and rare variants with a significant impact on *BRCA1/2* promoter activity, 3 of them showing a significant reduction in the transcriptional levels. As further investigation is needed, this approach has helped us to prioritize the studies on those variants.

1543 Poster Session (Board #367), Mon, 1:15 PM-4:45 PM

Transgenerational genomic effect of chemotherapy exposure in testicular cancer survivors. *First Author: Eliezer Mendel Van Allen, Dana-Farber Cancer Institute, Boston, MA*

Background: Cancer survivors who receive chemotherapy express concern that these exposures may induce germ cell mutations that lead to transmissible genetic damage in post-treatment children. Preclinical models suggest these mutagenic exposures may result in considerable genomic alterations in post-exposure progeny (e.g. elevated mutation rates, chromosomal abnormalities). Epidemiological studies have not demonstrated a significant increase in congenital abnormalities or genetic syndromes in post-treatment children of cancer survivors, although comprehensive genomic assessments have not yet been performed in this patient population. **Methods:** We identified two testicular cancer survivors who were cured with chemotherapy (bleomycin, etoposide, cisplatin) and had children before and after therapy without cryopreserved sperm. We acquired saliva from patients and their families and performed whole genome sequencing (WGS) from extracted DNA. Genome analysis and de novo mutation discovery were performed using established methods. **Results:** Genomes were sequenced to 50X mean depth. There was no increase in the de novo mutation rate of post-exposure children compared to their pre-exposure counterparts (Table). In fact, post-exposure offspring born two years after treatment had fewer de novo mutations than pre-exposure counterparts. There were no differences in recombination frequency or rearrangements between offspring. **Conclusions:** In two families of male cancer survivors, there was no genomic alteration increase in post-exposure children. The lower de novo mutation rate in early post-treatment children may indicate heightened selective pressure, especially when accounting for increasing paternal age. This study provides possible reassuring evidence for patients undergoing chemotherapy who are unable to have pre-treatment sperm cryopreservation. Broadly, this study illustrates the potential for using WGS to identify environmental cancer treatment effects on the inherited genome.

Offspring data.

Family	Exposure status	Years before(-)/after(+) chemotherapy	*de novo* mutations	mutations/Mb
1	Pre	-3.8	148	0.08
1	Post	+2.2	126	0.07
2	Pre	-1.6	125	0.07
2	Post	+2.4	88	0.05
2	Post	+5	136	0.08

1544 Poster Session (Board #368), Mon, 1:15 PM-4:45 PM

Somatic mutations in Luminal HER2 negative tumors from young breast cancer patients. *First Author: Giselly Encinas, Departamento de Radiologia e Oncologia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*

Background: Early age patients less than 36 years represent 4% of breast cancer cases and have a higher probability of being *BRCA1/2* mutation carriers. There are indications that tumors from young patients are biologically distinct from older women, however, these tumors have been less studied. Our aim was to identify somatic mutations in luminal tumors from BRCA1/2 wild type young breast cancer patients. **Methods:** Seventy-nine unselected young patients were enrolled. *BRCA1/2* mutations were screened by Sanger sequencing and Multiplex Ligation-Dependent Probe amplification (MLPA). Tumor and blood samples from eight patients (hormone receptor positive, HER2 negative) were selected for whole exome sequencing using Nextera Rapid Capture Enrichment in an Illumina HiSeq 1000, analyzed through MuTect (v1.14), SomaticSniper (v1.0.2) and Strelka (v1.0.1.2). **Results:** Median age of the 79 patients was 32 years (22-35) and luminal subtype was the most frequent (63.1%). Deleterious mutation in *BRCA1/2* genes was detected in 13 patients (*BRCA1*, n = 4 and *BRCA2*, n = 9). One novel mutation was detected in *BRCA1* gene: a stop codon in exon 6 (c.483T > A; p.Cys161Ter). Somatic mutations were evaluated in eight luminal samples and a median of 60 alterations/tumor was detected, varying from 49 to 113. A total of 537 individual genomic alterations were found, comprising 77 non-synonymous and four nonsense base substitutions and 2 splice donor variants. Among these 83 mutations, 56 were detected in potentially driver genes, including genes involved in Hedgehog signaling pathway and GSK3B interactions. Five to ten driver genes were mutated per tumor sample. For non-synonymous point mutations, only *PIK3CA* was repeatedly mutated in three samples; *TP53* was mutated in one sample. **Conclusions:** Besides *PIK3CA* mutation, which is the most frequent alteration in luminal tumors, and *TP53* mutation, at least five other different driver genes may be mutated in tumors from young breast cancer patients.

1545 Poster Session (Board #369), Mon, 1:15 PM-4:45 PM

Patient interest and willingness-to-pay (WTP) out-of-pocket (OOP) for comprehensive tumor genetic profiling (CGP). *First Author: Julie Innocent, Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA*

Background: CGP via multiplex gene panels has emerged as a novel technology to identify mutations in pathologically relevant cancer genes for therapy targeting. While CGP is anticipated to alter the course of standard cancer care, its current clinical role remains ill-defined, and thus its perceived value for patients is unclear. In an effort to understand patient awareness and perceived value of CGP, we explored interest and WTP OOP for CGP among cancer patients receiving active treatment. **Methods:** Fox Chase patients were recruited to complete a 20 min survey. In addition to assessing demographics, cancer stage/treatment, and financial items (income, health insurance, co-pays), we queried awareness of CGP, and interest in CGP to guide therapy using items adapted from previous research by our group. We specifically assessed interest in CGP only if covered by insurance vs interest conditional on paying an OOP cost: (< \$200, \$500, and > \$1000). All p-values are significant at $\alpha = 0.05$ using two-sided Fisher's exact tests. **Results:** Participants were 88 patients of diverse cancer histology, time since diagnosis (51% > 2yrs), therapy line (60% > 2nd line) age (mean 58.9 yrs), sex (38% F), race/ethnicity (20% non-White), family structure (64% married; 21% no children), education [27% < high school (HS)], and financial status (37% income < \$50,000; 38% Medicare/8% Medicaid; 40% reporting difficulty paying co-pays). 61% were aware of CGP, and 67% believed it could improve their treatment. In total, 79% were interested in CGP, with interest higher in younger ($p = 0.005$) and privately insured ($p = 0.01$). Patients with < HS education were less WTP OOP for any costs for CGP beyond those covered by insurance ($p = 0.005$). Those with income > \$50K ($p = 0.06$) and private insurance ($p = 0.001$) were more WTP. Of those WTP OOP, 44% were WTP < \$200, while 24% were WTP \$500 and 32% WTP > \$1000. WTP \$500 or > \$1000 for CGP was associated with White race ($p = 0.05$), education > HS, income > \$50K, and private insurance (all $p \leq 0.001$). **Conclusions:** Patients are interested in CGP and believe it can improve their cancer treatment. Those with lower income, less education and non-private insurance may be less likely to pursue CGP if accompanied by OOP costs.

1546 Poster Session (Board #370), Mon, 1:15 PM-4:45 PM

Evaluation of family history in newly diagnosed children with cancer. *First Author: Kinley Garfield, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: The collection of cancer family history (FH) is a key component for risk assessment in adult cancer patients, but is not routine in pediatric oncology. We collected FH on all newly diagnosed pediatric cancer (PC) patients presenting at Primary Children's Hospital to determine the feasibility of routine FH collection and risk prevalence for hereditary cancer syndromes. **Methods:** Parents of newly diagnosed children (age 0 to 20) were approached for enrollment and given a FH questionnaire to complete and return by mail assessing FH in first- and second-degree relatives. A genetic counselor contacted all participants by phone to review the reported history or to obtain a FH from those who did not return the form. Criteria for genetics referral were based on NCCN or peer-reviewed criteria. **Results:** Of the 91 families that completed a FH, 24 (26%) were considered eligible for further genetic risk evaluation. 16 (17%) warranted referral based on the child's tumor type or personal/ FH criteria, 8 (9%) children did not meet criteria but had a first- or second-degree relative who met criteria for referral. 10 of 16 children meeting criteria were seen for genetic counseling. **Conclusions**: Collecting FH at the time of diagnosis is feasible and identifies at risk individuals for cancer predisposition. Approximately 30% of newly diagnosed PC patients meet criteria for further genetic risk evaluation. This is consistent with data from a survivorship clinic reported by Knapke et al. (2011), although our study enrollment occurred at diagnosis and is not biased by patient mortality. These findings support a high rate of genetic predisposition related to childhood cancer (at least 1 in 4), and highlight the importance of obtaining an accurate FH at the time of initial diagnosis.

Cancer Type	Patients (n)	Child's history + FH warranted evaluation	Child's history warranted evaluation	FH warranted evaluation	Total referrals warranted
All types	91	6	10	8	24
Brain	7	0	1	0	1
Colon	1	0	1	0	1
Ewing sarcoma	3	0	0	0	0
Hepatoblastoma	5	2	3	0	5
Leukemia/lymphoma	44	0	0	3	3
Melanoma	1	1	0	0	1
Neuroblastoma	8	0	0	3	3
Optic tumor	2	1	1	0	2
Osteosarcoma	6	0	0	1	1
Pleuropulmonary blastoma	1	1	0	0	1
Retinoblastoma	1	0	1	0	1
Rhabdoid tumor	1	1	0	0	1
Rhabdomyosarcoma	4	0	3	0	3
Sarcoma	4	0	0	0	0
Wilms tumor	2	0	0	1	1

1547 Poster Session (Board #371), Mon, 1:15 PM-4:45 PM

Missense variants in Lynch Syndrome genes in endometrial cancer patients characterized by The Cancer Genome Atlas (TCGA) project. *First Author: Christine S. Walsh, Cedars-Sinai Medcl Ctr, Los Angeles, CA*

Background: We sought to characterize the missense variants in the Lynch Syndrome genes in patients with endometrial cancer that had normal germline DNA characterized by TCGA. **Methods**: We obtained institutional IRB approval and approval from the National Center for Biotechnology Information Genotypes and Phenotypes Database (NCBI dbGaP) for data access to TCGA data files. We utilized Variant Call Format (VCF) files to annotate germline single nucleotide variants in exomic regions of the Lynch Syndrome genes (*MLH1, MSH2, MSH6, PMS2*) among 248 patients with endometrial cancer. We used the MetaLR composite score from Annovar, which combines data from SIFT, PolyPhen2, LRT, MutationTaster, MutationAssessor, FATHMM, GERP++, PhyloP and SiPhy for prediction of variant effects on protein function. **Results**: A total of 120 different missense variants from 248 patients were found in the Lynch Syndrome genes (8 in *MLH1*, 26 in *MSH2*, 41 in *MSH6*, 45 in *PMS2*). 82 (68%) of these variants were novel and were not annotated in dbSNP or in publically available databases of Lynch Syndrome variants. None of the 120 missense variants were previously reported deleterious mutations known to cause Lynch Syndrome. Eight variants had a MetaLR score of > 0.9, signifying the highest probability of the variant having a deleterious effect. Of these, the top six variants clustered in exon 4 of the PMS2 gene between codons 105 and 116. Other variants with high MetaLR scores clustered in exon 1 of MSH2. **Conclusions**: We identified a large number of novel missense variants in the MLH1, MSH2, MSH6 and PMS2 genes in patients with endometrial cancer characterized by the TCGA. The variants with the highest probability of having a deleterious effect clustered in exon 4 of *PMS2* and exon 1 of *MSH2*.

1548 Poster Session (Board #372), Mon, 1:15 PM-4:45 PM

Rare germline *TP53* variants in lung adenocarcinoma. *First Author: Erin Michelle Parry, Osler Medical Housestaff Training Program, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: *TP53* is one of the most commonly altered genes in lung adenocarcinoma, with as many as 50% of all cases possessing somatic inactivating mutations. Germline mutations in *TP53* predispose to a wide variety of cancers in Li-Fraumeni syndrome. While lung cancer is generally not considered a classic Li-Fraumeni malignancy, several studies have indicated it may appear at an earlier age in this cancer-prone syndrome. **Methods:** We tested the frequency of germline *TP53* mutations in an unselected cohort of lung adenocarcinoma cases sequenced as part of The Cancer Genome Atlas (TCGA) project. At the time of data access (October 1, 2014), germline exome and genome data were available for download from 531 subjects, and clinical information was available on 94% of these cases (n = 497). After Data Access Committee approval, we extracted raw bam files that included the *TP53* sequence, called and annotated the variants. We considered variants with high (greater than 20x) coverage, and then excluded those with a minor allele frequency of 0.005 or greater in control populations. Suspected pathogenic variants were then confirmed by examining the matched tumor sequence data or a replicate normal tissue sample using the same methods. **Results:** Four cases carried germline missense variants in *TP53* (0.8%), and all of them fell in the DNA binding domain. Three of the mutations were previously described in Li-Fraumeni syndrome and all of mutations have been reported as somatically mutated in various cancers. The mean age at lung cancer diagnosis was 58 years (range 41-73) and one individual was male. One of the cases was a never smoker (female), and another subject had a prior history of thymic carcinoma, a diagnosis that has been documented in Li-Fraumeni syndrome. **Conclusions:** Our data suggest that a subset of lung adenocarcinoma patients carry germline mutations in *TP53*, pointing to a role for inherited factors in lung cancer susceptibility. This diagnosis may be overlooked in cases where genomic data is filtered for background germline variants, and is relevant for genetic counseling and screening decisions.

1549 Poster Session (Board #373), Mon, 1:15 PM-4:45 PM

Women with breast and uterine cancer in relation to genetic mutation risk: A case-control analysis. *First Author: Michael R. Milam, Norton Cancer Inst, Louisville, KY*

Background: The purpose of this study is to explore the mutation spectrum and prevalence among women with breast and uterine cancer (BUC) who were clinician-referred for multi-gene panel testing. **Methods:** Clinical histories for patients who underwent multi-gene panel testing at a single commercial laboratory (Ambry Genetics, Aliso Viejo, CA) were retrospectively reviewed to select cases with a history of both breast and uterine cancer. Patients underwent comprehensive analysis of 6-28 genes, depending on the panel ordered. Gene-specific mutation frequencies were calculated and compared with age- and ethnicity-matched female controls with no reported personal cancer history that were also referred for multi-gene panel testing. Fisher's exact tests were used to compare categorical variables, and Wilcoxon rank-sum tests were used to compare continuous variables between the 2 groups. **Results:** 319 women with BUC were identified from March 2012 to June 2014. Approximately 13% (n=42) of BUC patients were found to have gene mutations. The majority of the patients were Caucasian (80.6%; 257/319). The average age at first breast cancer diagnosis was 54 years (range 22-82 years) and the average age at uterine cancer diagnosis was 56 years (range 24-87 years). Analysis of gene-specific mutation frequencies revealed that mutations in *BRCA2*, *MSH6,* and *PTEN* were more frequent among cases than controls. **Conclusions:** In this multi-gene panel testing analysis, women with BUC are at greater risk of mutations in genes associated with Lynch Syndrome, Cowden Syndrome, and Hereditary Breast and Ovarian Cancer Syndrome. Further study is needed to explore these potential links and expanded genetic testing of breast and uterine cancer patients should be considered.

	Mutation Frequency		Fisher's Exact Results		
Gene	**Cases**	**Controls**	**Odds Ratio (95% CI)**	**95% CI**	**P-value**
BRCA1	1.4%	1.4%	1.04	[0.2,3.46]	1
BRCA2	3.8%	1.0%	4.02	[1.48, 9.97]	0.003*
CDH1	0.4%	0.1%	3.83	[0.07,73.65]	0.31
MLH1	0.6%	0.1%	4.99	[0.06,391.67]	0.31
MSH2	0.6%	0.1%	4.99	[0.063,391.67]	0.31
MSH6	3.2%	0.4%	8.5	[1.63,55.30]	0.005*
PMS2	0.6%	0.4%	1.66	[0.03,20.84]	0.52
PTEN	1.8%	0.1%	18.62	[3.03,196.06]	0.0004*
TP53	0.4%	0.0%	7.5	[0.10,586.74]	0.22

1550 Poster Session (Board #374), Mon, 1:15 PM-4:45 PM

The impact of a molecular tumor board on treatment decisions for 35 patients: The Dartmouth experience. *First Author: Laura J. Tafe, The Geisel School of Medicine at Dartmouth and Dartmouth Hitchcock Medical Center, Lebanon, NH*

Background: Genetic profiling of tumors is a powerful approach to predict drug sensitivity and resistance. However, oncologists are often unfamiliar with interpretation of genetic data. We established a Molecular Tumor Board (MTB) at our Cancer Center to interpret individual patients' tumor genetic profiles and provide treatment recommendations. **Methods:** DNA from tumor specimens was sequenced in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory to identify coding mutations in a 50-gene panel (*n*= 34), or a 255-gene panel (*n*= 1). Cases were evaluated by a MTB composed of molecular and anatomic pathologists, medical oncologists, basic research scientists, and genetic counselors. **Results:** Thirty-five cases were evaluated in one year by the MTB. The most common reason for MTB referral was a request for recommendations on targeted therapies (91.9%), and for potential germline mutations. Tumors exhibited a wide range of genetic heterogeneity: 71 different mutations were found across 30 genes, and 63 mutations were observed only once. In 56.3% of cases (18/32) of advanced/metastatic disease, MTB recommended non-standard therapy with a specific targeted agent (11 clinical trials; 7 off-label use) based on evaluation of tumor genetic profile, and disease and treatment histories. Four patients were subsequently treated with a MTB-recommended targeted therapy; 3 of these 4 patients remain on therapy, 2 of whom have experienced clinical benefit lasting > 10 months. The remaining 14 patients continued on current therapy because disease was stable (*n*= 4), were treated with non-MTB-recommended standard therapy (*n*= 4), declined conventional therapy (*n*= 5), or died prior to receiving further therapy (*n*= 1). **Conclusions:** Case evaluation by a multidisciplinary group of individuals in the context of a MTB frequently shapes treatment options and decisions. Importantly, anticipated obstacles to capitalizing on the benefits of a MTB such as access to drugs were rarely encountered. Instead, the most commonly encountered reasons that MTB-recommended therapy was not administered stemmed from patient preferences, and genetic profiling at a very late stage of disease.

1551 Poster Session (Board #375), Mon, 1:15 PM-4:45 PM

Polymorphisms in the estrogen pathway, estrogen receptor alpha gene (*ESR1*), daily cycling estrogen and mammographic density. *First Author: FrÃ¶ydis Nyborg Fjeldheim, Department of Oncology, Oslo University Hospital, Ullevål, Oslo, Norway*

Background: Single nucleotide polymorphisms (SNPs) involved in the estrogen pathway and SNPs in the estrogen receptor alpha gene (*ESR1, 6q25*), have been linked to breast cancer development. However, whether there is an association between daily estradiol levels, SNPs in *ESR1*and premenopausal mammographic density phenotypes has not yet been ascertained. **Methods:** Estradiol was assessed in daily saliva samples throughout an entire menstrual cycle, in 202 healthy premenopausal women (aged 25-35), participating in the Norwegian Energy Balance and Breast Cancer Aspects (EBBA) I study. DNA was genotyped using the Illumina Golden Gate platform. Mammograms were taken between days 7-12 of the menstrual cycle, and digitized mammographic density phenotypes were assessed using a computer-assisted method (Madena). Multivariable regression models were used to study the association between SNPs in *ESR1*, premenopausal mammographic density phenotypes and daily cycling estradiol. **Results:** We observed inverse linear associations between the minor alleles of 8 of 34 measured SNPs (*rs3020364, rs2474148, rs12154178, rs2347867, 6927072, rs2982712, 3020407, rs9322335)* and percent mammographic density (p values: 0.002 - 0.026), and these associations were strongest in lean women (BMI, $\leq$ 23.6 kg/m^{2}). The odds of above-median percent mammographic density (> 28.5%) among women with major homozygous genotypes were 3-6 times higher than those of women with minor homozygous genotypes in 7 SNPs. Women with *rs3020364*major homozygous genotype had an OR of 6.46 for above-median percent mammographic density (95% Confidence Interval 1.61, 25.94) when compared to women with the minor homozygous genotype. These associations were not observed in relation to absolute mammographic density. No linear associations between SNPs and daily cycling estradiol were observed. **Conclusions:** Our results support an association between eight selected SNPs in the *ESR1* gene and percent mammographic density. The results need to be replicated in larger studies.

1552 Poster Session (Board #376), Mon, 1:15 PM-4:45 PM

Genetic testing for hereditary breast cancer: The decision to decline. *First Author: Brook White, CMC, Charlotte, NC*

Background: Genetic testing is an important component of comprehensive cancer care. Testing for hereditary breast and ovarian cancer syndrome is well established, as commercial analysis of the BRCA1/2 genes has been available since 1996. The National Comprehensive Cancer Network (NCCN) guidelines identify those individuals appropriate for BRCA1/2 analysis, and define management recommendations for mutation carriers. Despite recommendations, not all who meet NCCN criteria undergo genetic testing. We assess the frequency that individuals meeting NCCN criteria decline BRCA1/2 analysis, as well as factors that affect the decision making process. **Methods:** A retrospective chart review was performed from September 2013 through August 2014 of individuals who had genetic counseling at the Levine Cancer Institute (LCI). **Results:** 1083 individuals identified through the retrospective chart review met NCCN criteria for BRCA1/2 analysis. 268 (24.5%) of the 1083 individuals did not pursue genetic testing. Of those who did not undergo testing, 21.3% (N = 57) did not desire testing and 40.3% (N = 108) were advised to gather additional genetic or medical information prior to genetic analysis. The remaining 38.4% (N = 103) had insurance and desired testing but did not pursue due to expense. The majority of the 103 individuals (N = 88) were responsible for the total cost of the test, although some (N = 15) had a prohibitive co-pay expense. **Conclusions:** Our analysis reveals that 38% of patients who meet NCCN guidelines for BRCA testing do not undergo testing based on financial barriers. This highlights the need to address public policy initiatives in this high-risk population.

1553 Poster Session (Board #377), Mon, 1:15 PM-4:45 PM

Identification of tropomyosin kinase receptor (TRK) mutations in cancer. *First Author: Nisha Nanda, Loxo Oncology, San Francisco, CA*

Background: TRK A, B and C, (encoded by NTRK1, NTRK2, and NTRK3 genes, respectively) and their neurotrophin ligands regulate growth, differentiation and survival of neurons. Chromosomal rearrangements resulting in kinase fusions have been described across the NTRK gene family, and may contribute to tumorigenesis in diverse clinical settings. We searched for potentially activating mutations in the NTRK gene family by applying biologically driven ranking criteria to an anonymized next-generation sequencing dataset, sourced from Foundation Medicine (FMI) and Compendia BioSciences (Compendia). **Methods:** Approximately 10,000 patient samples were analyzed for mutations in NTRK1, NTRK2 or NTRK3. Mutation data in other known cancer-related genes were also captured for these tumors. Data were reconciled across the disparate sources by mapping mutations to the canonical transcript for each gene where possible, or to a representative non-canonical transcript when the mutation occurred in a region not contained within the canonical transcript. Mutations were clustered together based on sequence proximity. Mutation groups were ranked by likelihood of oncogenic-activating potential using six biologically-driven component scores. **Results:** 732 distinct mutation clusters were identified across > 20 tumors. NTRK1, NTRK2 and NTRK3 represented 33%, 30% and 37%, respectively, of these mutation clusters. A disproportionate number of the most promising mutation clusters were in NTRK3: 59% of the top 5%, 58% of the top 10%, and 46% of the top 25%. In addition, the top 3 mutation clusters were in the NTRK3 kinase domain, and were observed in head and neck, lung, upper gastrointestinal, melanoma and colon cancers. **Conclusions:** This heuristic identified mutations in the NTRK family, especially in NTRK3, that hold promise as oncogenic activating mutations. The highest ranked mutations deserve further study, as they are clonally present in the kinase domain, exist in the absence of other known oncogenic drivers, and are infrequent in germline databases.

1554 Poster Session (Board #378), Mon, 1:15 PM-4:45 PM

Next-generation sequencing as an informing phenotype: A TP53 example. *First Author: Rosie O Shea, The Mater Hospital, Dublin, Ireland*

Background: Li-Fraumeni (LFS) and Li Fraumeni like (LFL) syndromes are characterised by early onset cancers such as breast cancer, leukaemia, sarcoma, brain tumours and adrenocortical carcinoma, and are defined traditionally by clinical criteria such as Chompret and Eeles. Genetic testing for *TP53* germline mutation is typically undertaken in families that satisfy these clinical criteria. Next generation sequencing and gene panel testing has resulted in more frequent *TP53* testing to include families that don't meet classic testing criteria. We investigated testing criteria and result outcome in a cohort of Irish probands undergoing *TP53*full sequencing. **Methods:** All *TP53 test* requests processed thought the national genetic testing laboratory between 2012 and 2014 were retrospectively reviewed. Family history data including diagnoses and age at diagnosis was ascertained through hospital charts or electronic pedigrees from two adult cancer genetic services in Ireland. Additional data including reason for testing, concordance with LFS/LFL criteria and test results were collected. **Results:** One hundred and thirty five *TP53* test requests were identified. Family history data and test results were available on 123 of the *TP53* test requests (118 female; 5 male). 74/123 (60%) didn't meet classic LFS or LFL criteria and were *TP53* mutation negative. Two individuals from this group harboured pathogenic *TP53* mutations. Both were female and had a personal history of early onset bilateral breast cancer with no reported LFS cancers in the family. 49/123 (40%) met LFS or LFL criteria and were all *TP53*negative, apart from one female with a variant of unknown significance. 22/49 (44%) met Chompret criteria, 19/49 (38%) met Eeles and 7/49 (14%) met Eeles and Chompret and 1/49 (2%)met Classic LFS criteria. **Conclusions:** Stringent testing criteria miss germline mutations in *TP53*. Broadening the criteria for *TP53* testing will redefine the clinical description of LFS and LFL, and improve our understanding of *TP53* mutation expression and penetrance in this syndrome

1555 Poster Session (Board #379), Mon, 1:15 PM-4:45 PM

The influence of BRCA variants of uncertain significance in cancer risk management decision-making. *First Author: Jing-Yi Chern, New York University Langone Medical Center, New York, NY*

Background: Among patients undergoing genetic testing for BRCA1/2 mutations, 7% will harbor a variant of uncertain significance (VUS), a finding with more emotional than clinical weight. The objective of this study was to compare cancer risk management decisions among women with BRCA VUS to those of women with negative results. **Methods:** Between 1/2006-12/2012, we identified patients whose genetic testing results yielded a VUS and those who had definitively negative results at a single institution. VUS patients were matched with negative patients of the same age and testing date. χ^2analyses were used to assess differences between the groups. **Results:** Three hundred and seventy-one patients underwent genetic testing during the study period. Eighty-two (22%) patients had a VUS and were matched with 82 control patients with negative genetic testing. The median age of study patients was 47 years for the 164 patients evaluated. Women with a VUS were more racially diverse than those with negative testing (38 of 82, 46% non-Caucasian vs. 16 of 82, 20%, p= 0.002). VUS patients were less likely to be of Ashkenazi descent (14 of 82, 17% vs. 32 of 82, 39%, p= 0.002). Patients with VUS were more likely to be referred to a gynecologic oncologist (42 of 82, 51% vs. 29 of 82, 35%, p= 0.058). Among VUS patients, 21% (17 of 82) were recommended to undergo ovarian cancer screening and 28% (23 of 82) risk-reducing bilateral salpingo-oophorectomy (RRBSO) vs. 15% (12 of 82) and 28% (23 of 82), respectively, for controls (p = 0.28). Ultimately, RRBSO was performed in 20% (32 of 164) of all patients, with no significant difference in rate of surgery based on the presence of a VUS. **Conclusions:** At our institution, patients with VUS are managed similarly to those with negative BRCA testing. In these groups of patients, screening and prevention strategies need to be individualized. The numbers of patients with VUS are likely to increase with the implementation of multi-gene testing. Our findings underscore the importance of genetic counseling in the management of genetic testing results.

1556 Poster Session (Board #380), Mon, 1:15 PM-4:45 PM

First one thousand families: Our multidisciplinary experience in the heredo-familial cancer unit from a Spanish University Hospital. *First Author: Ivan Marquez Rodas, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain*

Background: Patients with hereditary cancer syndromes (HCS) need a multidisciplinary approach: Different organs and systems may be involved and different risk reducing strategies (medical and surgical) should be provided. In 2010 we implemented a multidisciplinary heredo-familial cancer unit (HFCU) in Hospital General Universitario Gregorio Marañón (Madrid, Spain). **Methods:** A retrospective analysis of the first 1000 families attended in our HFCU (2010-2014). **Results:** 1167 patients, from 1000 different families were attended. 929 patients (79.6%) fulfilled international criteria for HCS; 84 are pending of gathering more information. Genetic test results were available for 426 patients, with 136 cases bearing pathological mutations. New mutation detection rate (first time diagnosis in a family) was 44/235 (18.7%). Two patients with no HCS criteria were diagnosed with BRCA1 and MSH2 mutations respectively. For the 136 patients with a pathological mutation, prophylactic surgery and /or follow up were offered according to international recommendations and patient's preferences (Table). In two BRCA1 mutation carriers, an early ovarian cancer was detected in prophylactic surgery. **Conclusions:** The first one thousand families attended in our HFCU demonstrate that a multidisciplinary assistance is the core of this clinical activity. The intervention resulted in risk reduction surgery in 31% of cases and intensive surveillance in all cases. A longer follow up is warranted in order to evaluate the long-term impact of these interventions and for improving the different steps of the cancer genetic counseling process.

MUTATION CARRIERS (%)	Prophylactic surgery (%)	Only follow-up (%)
BRCA1/2: 96 (70.6)	36 (38)	60 (62)
MLH1/MSH2/MSH6: 18 (13.2)	0	18 (100)
APC/MYH: 6 (4.4)	2 (33.3)	4 (66.7)
p53: 2 (1.5)	0	2 (100)
CDKN2A: 2 (1.5)	0	2 (100)
PTEN: 1 (0.8)	1 (100)	0
MEN1: 2 (1.5)	0	2 (100)
RET : 3 (2.2)	2 (66.7)	1 (33.3)
VHL : 1 (0.8)	0	1 (100)
CDH1 : 1 (0.8)	1 (100)	0
NF1: 1 (0.8)	0	1 (100)
PTCH: 1 (0.8)	0	1 (100)
FH: 1 (0.8)	0	1 (100)
Rb: 1 (0.8)	0	1 (100)
TOTAL: 136 (100)	42 (30.9)	94 (69.1)

1557 Poster Session (Board #381), Mon, 1:15 PM-4:45 PM

DNA repair landscape of discordant sibling pairs from hereditary breast cancer families. *First Author: Yongli Ji, University of Vermont, Burlington, VT*

Background: DNA repair plays a significant role in carcinogenesis. The aim of this study is to describe the landscape of germline DNA sequence variation among discordant sister pairs (one with and one without breast cancer) from breast cancer families with an emphasis on DNA repair pathways. **Methods:** Six sister-pairs were identified from a cohort of high-risk women at University of Vermont Cancer Center. To be eligible for inclusion families must have at least 3 cases of breast cancer, 1 diagnosed under age 50. The unaffected sister must be older than the affected sister's age at diagnosis. Germline DNA was isolated and full exome sequencing was performed for all 12 women. Computational genomics were utilized to identify putative single nucleotide polymorphisms in DNA repair pathway associated genes. Candidate variants were identified based on the quality of the variant call, distribution among sibling pairs, frequency in the general population, and predicted functional consequences. **Results:** We obtained high-quality exome sequences for each individual. We identified deleterious mutations in several known cancer-associated pathways, including DNA repair. The genetic variants and pathways include (see table): TSC1 (tuberous sclerosis complex) is a tumor suppressor gene; WRN is a member of the RECQ helicase family involved in DNA repair and maintaining genomic stability; PMS2 (postmeiotic segregation increased 2) is involved in mismatch repair;POLQ is a DNA polymerase; POLE is a DNA replicative polymerase. **Conclusions:** Using 6 discordant sister pairs from high-risk families we were able to obtain high-quality sequences and identify several interesting variants in DNA repair pathways. We have enrolled additional sister pairs and are funded to sequence and analyze 8 additional pairs. Future studies will focus on identification of rare familial variants and understanding the functional significance of identified variants.

Variant finding.

Gene	Variant	Findings	Rare?	Predicted Damaging?
TSC1	R37H	Het in one case	✓	✓
WRN	M1187V	Hets in 2 cases	✓	✓
WRN	C1367R	4/6 cases; p = 0.0625	≤ 0.3	✓
PMS2	N335S	Het in one case	✓	✓
POLQ	Q1546X	Het in one case	✓	Gained stop codon
POLE	A252V	Hets in 2 cases	≤ 0.1	Non- synonymous

1558 Poster Session (Board #382), Mon, 1:15 PM-4:45 PM

Intratumoral heterogeneity of cancer driver genomic alterations across several tumor types. *First Author: Kai Wang, Foundation Medicine, Inc., Cambridge, MA*

Background: Intratumoral heterogeneity (ITH) or variations in genomic alterations (GA) between different areas of primary tumors or in their metastases has been an area of intense investigation and is often cited as a reason for failure of targeted therapies. We used an NGS-based comprehensive genomic profiling assay (CGP) to examine 5 tumor types across 10 tissue sections in 5 patients each to determine the impact of ITH on GA relevant to cancer biology (cancer "drivers"). **Methods:** 250 FFPE 40u sections from 25 patients were obtained from 2 separate non-adjacent blocks at levels throughout the entire block thickness. CGP was performed at Foundation Medicine, as previously described (PMID: 24142049). 245/250 sections were processed successfully, obtaining coverage depth > 700x, with all classes of GA (substitutions, indels, copy number alterations - CNA) assessed. Heterogeneity in cancer driver GA was evaluated including raw data review, and associated with clonal architecture. **Results:** 837 total substitutions or indels (short variants – SV) were observed in 245 sections, with 217 assessed to be subclonal based on mutant frequency (MAF) and tumor content. Only 20 SV were not detected in paired sections from same PT, for a discordance rate of 2.3% (20/857). All discordances were in subclonal variants, with avg MAF < 6%. CNA concordance was 90.2%, with half of discordances associated with low tumor purity or coverage bias. Findings were similar across tumor types (Table), with key targetable GA including *EGFR* mutation in lung cancer and *ERBB2* amplification in breast cancer concordant across all sections. **Conclusions:** Our analysis reveals that intratumoral heterogeneity of cancer driver GA is limited. The data supports CGP of a single biopsy section as appropriate in most patients with advanced solid tumors, provided sufficient sensitivity is attained for sub-clonal events in impure clinical tissue.

Concordance	Breast Invasive Duct Carcinomas	Colorectal Adenocarcinomas	Head and Neck Squamous Cell Carcinomas	Renal (1 oncocytoma + 1 chromophobe, 1 urothelial and 2 unclassified carcinomas	Lung (3 adenocarcinomas + 2 squamous cell carcinomas)
Short Variant GA	95.0%	98.5%	99.4%	96.0%	98.1%
CNA	96.3%	86.4%	88.2%	80.0%	90.0%

1559 Poster Session (Board #383), Mon, 1:15 PM-4:45 PM

Feasibility of using memantine in smoking cessation among cancer survivors. *First Author: John Spangler, Wake Forest University, School of Medicine, Winston-Salem, NC*

Background: Memantine, an N-methyl-D-aspartate receptor noncompetitive antagonist, has been proposed for smoking cessation by virtue of opposing the effects of glutamate in the CNS "addiction center," the nucleus accumbens. This study evaluated Memantine's feasibility and preliminary efficacy for quitting smoking among cancer survivors. **Methods:** A prospective randomized feasibility trial was conducted by the Wake Forest CCOP Research Base. Feasibility outcomes included accrual, retention, adherence, and toxicity. Clinical outcomes included smoking cessation at 12 weeks (defined as no smoking in the past week). 130 patients were accrued between 9/12 and 11/13, 65 on Memantine (M) and 65 on Control (C). Ages ranged from 29 to 84 with a median of 57; 85% were female and 85% were Non-Hispanic White. 75% had breast cancer, 12% colorectal cancer, 11% lung cancer, and 2% prostate cancer. On average, patients started smoking at 16, had smoked for 40 years, and smoked a pack a day. Characteristics were similar in the two arms. **Results:** Over 20 CCOP sites participated; accrual was approximately 10 patients per month. Retention at 12 weeks was poor (54% M, 68% C). Self-reported adherence was good while patients were on study (86% M, 93% C). Four serious adverse events were noted (3 M, 1 C), none related to treatment. Toxicities were similar in the two arms. Only two patients reported being smoke-free at 12 weeks, both in the Control arm. The number of cigarettes smoked at 12 weeks was similar in the two arms. **Conclusions:** While accrual was robust and patients reported good adherence, 40% dropped out by 12 weeks and very few patients could remain smoke-free for one week prior to the 12 week evaluation following randomization. Other options for smoking cessation need to be assessed. (Funding for this study was provided by NCI to the Wake Forest CCOP Research Base, grant number U10CA081851). Clinical trial information: NCT01535040.

1560 Poster Session (Board #384), Mon, 1:15 PM-4:45 PM

Hormonal and lifestyle factors as modifiers of risk of breast cancer (BC) in *BRCA1* and *BRCA2* carriers (C). *First Author: Asunción Torres, Servicio de Oncología Médica, Hospital General de Almansa, Albacete, Spain*

Background: Mutations in the *BRCA1/2* genes confer a high lifetime risk of BC. Penetrance varies among populations and individuals suggesting that non-genetic factors may modify the inherited risk. Knowledge of modifiable factors will help to develop preventive strategies. **Methods:** The study was carried out in 874 women (W) with a *BRCA1/BRCA2* germ-line mutation (511 with BC, 51% *BRCA2*) from 414 families, followed at three Spanish Genetic Counseling Units. Participants gave their consent and the study was approved by the ethics committee. The association between BC, hormonal and lifestyle factors was studied using logistic regression. Huber-White robust estimators of variance were employed to take into account correlations between family members. Age, menopausal status and specific mutated gene were included as co-variables. **Results:** While late menarche ($\geq$ 14 years) was associated with a reduction in BC risk in *BRCA1* C (OR:0.48; 95%CI:0.42-0.88, p = 0.016), no similar effect was observed for *BRCA2* W (p = 0.252). Moreover, although pregnancy increased BC risk in both *BRCA1 and BRCA2* C (OR:2.38; 95%CI:1.26-4.49, p < 0.007; OR:1.89; 95%CI:0.91-3.95, p = 0.09 respectively), a deleterious effect of spontaneous abortion was found only in *BRCA1* C (OR:1.66; 95%CI:0.92-3.01, p = 0.09). Furthermore, oral contraceptive (OC) use was also associated with an increased BC risk in the *BRCA1* group (OR:1.65; 95%CI:0.98-2.78, p = 0.058). BMI also increased the risk of BC among *BRCA1* W (p-trend = 0.014). Finally, breastfeeding, smoking, alcohol intake and exercise did not significantly modify BC risk. **Conclusions:** Our preliminary data suggest that the hormonal changes associated with pregnancy increases BC risk in mutation C. Obesity and the use of OC also exert a deleterious effect in *BRCA1* germline mutation C and could be considered as potential modifiable factors for BC prevention in these group of W.

1561 Poster Session (Board #385), Mon, 1:15 PM-4:45 PM

Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. *First Author: Cécile Pizot, International Prevention Research Institute, Lyon, France*

Background: A lower risk of breast cancer among physically active women has been frequently reported, but the risk in women using hormone replacement therapy (HRT) appears to be higher. We quantified the association between physical activity and breast cancer, and we examined the influence that HRT use and other risk factors had on this association. **Methods:** After a systematic literature search, prospective studies were meta-analysed using random-effect models. As physical activity assessment and reporting of results were heterogeneous across studies, breast cancer risk associated with the highest level of physical activity was compared with the lowest level of physical activity. Dose-response analyses were also conducted with studies reporting physical activity either in hours/week or in hours of metabolic equivalent per week (MET-h/week). **Results:** The literature search identified 38 independent prospective studies published between 1987 and 2014 that included 4,183,888 women of which 116,304 breast cancer cases. Compared to the lowest level of physical activity, the highest level was associated with a summary relative risk (SRR) of 0.88 (95% CI (0.85, 0.90)) for all breast cancer, 0.89 (0.83, 0.95) for ER+/PR+ breast cancer and 0.80 (0.69, 0.92) for ER-/PR- breast cancer. Risk reductions were not influenced by the type of physical activity (occupational or non-occupational), the place of residence, adiposity, and menopausal status. Risk reductions increased with increasing amounts of physical activity, without threshold effect. In six studies that examined the influence of physical activity according to HRT use, the SRR was 0.78 (95% CI (0.70, 0.87)) in women who never used HRT and 0.97 (95% CI (0.88, 1.07)) in women who ever used HRT, without heterogeneity between studies. A sustained change from being physically inactive to engaging in 4 to 7 hours/week of mainly vigorous physical activity could lead to a 31% (95%CI (22, 40)) risk reduction in women who never used HRT. **Conclusions:** Increasing physical activity is associated with meaningful reductions in the risk of breast cancer. However in women who ever used HRT, the preventative effect of physical activity seems to be cancelled out.

1562 Poster Session (Board #386), Mon, 1:15 PM-4:45 PM

Impact of prior knowledge of mutation status on tumor stage in BRCA1/2 mutation carriers with newly diagnosed breast cancer. *First Author: Clinton Yam, Basser Research Center for BRCA at the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: BRCA1/2 mutation carriers have an elevated lifetime risk of developing breast cancer. Knowledge of one's BRCA1/2 mutation status may aid earlier detection of breast cancers due to increased awareness and screening with breast MRIs. **Methods:** Retrospective analysis of tumor characteristics of BRCA1/2 mutation carriers known to our institution who were diagnosed with breast cancer from 1/1/2009 - 12/31/2013. **Results:** 106 BRCA1/2 mutation carriers were diagnosed with their first breast cancer during the study period. 82 patients received care primarily at our clinical sites and were included in the study. 19.5% (16/82) were known BRCA1/2 mutation carriers prior to breast cancer diagnosis and the remaining 66 patients had genetic testing after cancer diagnosis. There were no differences in the median age at cancer diagnosis (p = 0.87) or distribution of BRCA1 vs BRCA2 mutation carriers between the 2 groups (p = 0.18). 62.5% (10/16) of known carriers were diagnosed with breast cancer following an abnormal MRI vs 0/66 of those identified as carriers only after breast cancer diagnosis (Table 1). Patients who knew their BRCA1/2 mutation status were more likely to have smaller tumors (p = 0.008) and node negative disease (p = 0.004). There were no differences in the ER, PR or Her2 statuses between the 2 groups. **Conclusions:** BRCA1/2 mutation carriers who have knowledge of their genetic status are more likely to have early stage disease at the time of breast cancer diagnosis, demonstrating the utility of identifying unaffected carriers who benefit from enhanced screening for early detection.

Summary of findings.

	Known at diagnosis (n = 16)		Unknown at diagnosis (n = 66)	p value
Median age	40 (25 - 70)	Years (range)	42.5 (28 - 74)	0.87
BRCA		Number (%)		
BRCA1	11 (68.8)		33 (50)	0.18
BRCA2	5 (31.3)		33 (50)	
Method of diagnosis				
MRI	10 (62.5)		0	<0.001
Mammogram	2 (12.5)		21 (31.8)	
Physical exam	2 (12.5)		45 (68.2)	
Prophylactic Mastectomy	2 (12.5)		0	
T stage				
Tis/T1	15 (93.8)		34 (51.5)	0.008
T2-4	1 (6.3)		31 (47.0)	
Tx	0		1 (1.5)	
Node negative	16 (100)		42 (63.6)	0.004
Stage				
0	4 (25)		3 (4.5)	0.011
I - II	12 (75)		52 (78.8)	
III - IV	0		11 (16.7)	
ER+	8 (50)		34 (51.5)	0.91
PR+	7 (43.8)		32 (48.5)	0.73
Her2+	1 (6.3)		6 (9.1)	0.73

1563 Poster Session (Board #387), Mon, 1:15 PM-4:45 PM

Development and external validation of a melanoma risk prediction model using self-assessed risk factors. *First Author: Kylie Vuong, University of Sydney, Camperdown, Australia*

Background: Melanoma incidence rates have been increasing in fair-skinned populations, with Australia having the world's highest melanoma incidence rates. By providing individuals with their overall risk instead of relying on individual risk factors, melanoma risk prediction models may lead to improved risk perception and sun protection behaviours. In addition to their clinical uses, these models may assist in planning intervention trials and population prevention strategies that target particular risk groups. We aimed to develop and validate a melanoma risk model predicting lifetime absolute risk of primary melanoma using self-assessed risk factors. **Methods:** We used unconditional logistic regression with backward selection to develop the melanoma risk model using the Australian Melanoma Family Study, a population-based case-control-family study with 629 population-based cases with first primary melanoma diagnosed before age 40 years and 535 controls from 2001 to 2005. Relative risk estimates from the model were combined with Australian melanoma incidence and mortality data using the Gail method to obtain lifetime absolute risk estimates. Subsequently we validated the model externally using the Western Australia Melanoma Study, a population-based study with 511 case-control pairs from 1980 to 1981. Multiple imputation was used to handle missing data. **Results:** Our model, which includes age, sex, state of residence, hair colour, naevus density, first degree family history of melanoma, previous non-melanoma skin cancer and lifetime sunbed use, demonstrated good discriminative performance on both internal [area under the receiver operating curve (AUC) = 0.71 (95% CI 0.68 - 0.73)] and external validation [AUC = 0.63 (0.60 – 0.65)]. **Conclusions:** The model, which is based on self-assessed risk factors, discriminates well between those with and without melanoma and may be useful in the design of melanoma prevention interventions.

1564 Poster Session (Board #388), Mon, 1:15 PM-4:45 PM

Aspirin and risks of non-colorectal second primary cancer in patients with prior colorectal cancer. *First Author: Yu-Ting Lee, Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

Background: Aspirin has been identified as reducing cancer incidence, especially colorectal cancer (CRC), distant metastasis and mortality. Secondary cancer prevention has not been investigated. To examine the potential effects of aspirin on non-colorectal SPMs prevention among patients with previous CRC **Methods:** We enrolled 92,392 patients with newly diagnosed CRC between January 1, 1997 and December 31, 2011 from the Taiwan's National Health Insurance database. Participants with more than 90 cumulative defined daily doses (cDDD) of aspirin exposure are defined as aspirin users (n = 7,488) compared with non-users (n = 84,904). Development of non-colorectal SPMs was obtained from the Taiwan's National Health Insurance database. The Cox proportional hazards model, and the Fine and Gray's proportional hazards model were used to estimate the cause-specific hazard ratios (HRs) and subdistribution HRs, respectively. Data analysis was conducted in April, 2014. **Results:** During the 15-year study period, 3,880 patients developed non-colorectal SPM among 92,392 recruited CRC participants. We compared 7,488 aspirin users with 84,904 non-users. Overall, the difference for risk of SPM was not significant. The cause-specific hazard ratios (HRs) and subdistribution HRs were 0.99 (95% CI 0.88–1.12) and 1.00 (95% CI 0.88–1.12), respectively. Propensity score analyses were done and matched 6,728 aspirin users with 26,912 non-users. The cumulative incidence of SPM showed no difference (p = 0.824). **Conclusions:** Among patients with prior CRC, aspirin use did not provide chemoprevention in non-colorectal SPMs.

1565 Poster Session (Board #389), Mon, 1:15 PM-4:45 PM

Cancer screening in France: Reaching a plateau? New edition of an iterative nationwide survey. *First Author: Jerome Viguier, Hôpital Bretonneau, Tours, France*

Background: The EDIFICE survey program began in 2005 and set out to ascertain participation rates of the French population in cancer screening and assess changes in these rates over time. After 2005, 2008 and 2011, the latest survey was conducted in 2014, and focused on colorectal, breast, prostate, cervical and lung cancers. **Methods:** EDIFICE 4 was conducted by phone interviews of a representative sample of 1602 subjects (age 40-75), using the quota method. Analysis focused on target populations as defined by guidelines when these exist. **Results:** For breast cancer, the rate of women declaring having had ≥ 1 mammography was 93%/94%/95%/97% in 2005/2008/2011/2014 respectively, with no impact of sociodemographic criteria. As recommended in the French program, a mammography had been done in the previous 2 years for 75%/83%/83%/81%, with a lower participation rate among the 65 to 74-year age group. For colorectal cancer, the rate of individuals declaring having attended ≥ 1 screening procedure, colonoscopy or fecal occult blood (FOB) test, was 25%/38%/59%/60%. The FOB test had been performed according to the recommended timing interval for NA/15%/32%/31%. Colorectal cancer screening has now reached a plateau for both genders, the only significant increase being seen in the 70 to 74-year age group. The rate of men having undergone at least one prostate cancer screening test (PSA and/or digital rectal exam) was 36%/49%/50%/49%, with a decrease in participation rates among the 50 to 59-year age group. For cervical cancer, 99% of women declared having already undergone conventional 'Pap' smears or liquid-based cytology during a gynecological exam. Average age for the 1st test was 26 years. With regard to lung cancer, 11% of participants declared having already undergone a lung cancer screening procedure; this figure was 6% in the first EDIFICE survey in 2005. **Conclusions:** Screening participation rates have stabilized and for most tumor locations, appear to be correlated with the history of implementation of national programs or recommendations. When organized screening programs exist, such as for breast and colorectal cancer, the difference between the plateau levels raises the question of the acceptability of the test.

1566 Poster Session (Board #390), Mon, 1:15 PM-4:45 PM

The influence of inflammation on mammographic breast density in women at increased risk of breast cancer. *First Author: Samir S. Ambrale, University of Vermont, Burlington, VT*

Background: Mammographic density is an important risk factor for breast cancer but the etiology of density is not well understood. Studies suggest that inflammation may play a role in density. We evaluated the association between serum inflammatory markers and breast density in women at increased risk for breast cancer. **Methods:** Women previously enrolled in the University of Vermont IRB-approved High-Risk database were eligible for inclusion if they had a baseline serum sample and a mammogram available within 120 days of each other (N = 174). A subset of eligible women also had a paired serum sample and mammogram at 4 years from study entry (N = 38). Blood samples were analyzed for C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1b (IL-1b) and tumor necrosis factor-α (TNF-α). Breast density was calculated using 2 methods; the semi-automated Cumulus method and fully automated University of Pennsylvania (UPenn) method. **Results:** Mean age of the cohort was 46.2 (range 24-71 years) and 63.8% were premenopausal. Mean baseline density was 35.8% and 31.8% using the Cumulus and UPenn method respectively. Mean baseline values were 20,005 ng/ml for CRP, 10.6 pg/ml for TNF-α, 0.78 pg/ml for IL-1b and 0.84 pg/ml for IL-6. Body mass index correlated with CRP (spearman correlation coefficient [r] = 0.58; $p< 0.0001$), IL-6 (r = 0.17; $p= 0.003$) and TNF-α (r = 0.19; $p= 0.02$). Linear regression adjusted by age and BMI found that baseline IL-6 had significant association with breast density calculated by either density methods (Cumulus: β coefficient 1.62, $p= 0.04$; UPenn: β coefficient 1.95, $p= 0.01$). No other biomarker had a statistically significant relationship with density. There was no significant correlation between change in inflammatory marker levels and change in density at 4 years. **Conclusions:** Mammographic breast density was found to be elevated among women with higher serum IL-6 levels, a finding that supports prior data suggesting a relationship between inflammation and density. This study strengthens the evidence for consideration of anti-inflammatory agents as chemoprevention for breast cancer. Further research is needed to elucidate the mechanism by which IL-6 is associated with breast density.

1567 Poster Session (Board #391), Mon, 1:15 PM-4:45 PM

Impact of a risk model based on routine lab results on colorectal cancer screening in average risk population. *First Author: Shimon Ben Boursi, University of Pennsylvania, Philadelphia, PA*

Background: Risk scores for colorectal cancer (CRC) screening use limited variables and have low predictive values. We sought to develop and validate a novel CRC risk prediction model based on routinely available data from electronic medical records including laboratory results. **Methods:** We conducted a nested case-control study using a population-based database. The cohort was randomly divided into test and validation datasets. Cases were defined as those with a diagnostic code of CRC, aged 50-85. Subjects with CRC syndromes or IBD were excluded. For every case, 4 controls matched on practice site and duration of follow-up were selected using incidence-density sampling. Lifestyle parameters, medical history, medications, and lab results were examined as CRC risk factors using univariate conditional logistic regression. Variables with p-value < 0.25 were evaluated for the multivariate model, after correcting for linearity, using backward elimination. Discrimination ability was calculated using receiver operator curve (ROC). Goodness of fit was evaluated using the McFadden's R2. For the final model we calculated the net reclassification index (NRI) compared to a model including lifestyle parameters only. **Results:** Our study cohort included 45,498 subjects in the test set (n = 9,299 [20.44%] cases) and 22,490 subjects in the validation set (n = 4,580 [20.36%] cases). A multivariate model based on lifestyle parameters only (age, sex, height, obesity, ever smoking, alcohol dependence and previous screening colonoscopy) had an AUC of 0.58 (95%CI 0.57-0.59) with low goodness of fit. A model based on lab results only (hematocrit, MCV, lymphocytes and neutrophil to lymphocyte ratio [NLR]) had an AUC of 0.76 (95%CI 0.76-0.77) and a McFadden's R2 of 0.21 with a NRI of 47.6%. A combined model including sex, hemoglobin, MCV, white blood cells, platelets, NLR and medication prescriptions for oral hypoglycemics reached an AUC of 0.80 (95%CI 0.79-0.81) with a McFadden's R2 of 0.27 and a NRI of 60.7%. Similar results were shown in the validation set. **Conclusions:** A risk score based on sex, CBC, and medication use has good discriminating power for CRC risk in the average risk population.

1568 Poster Session (Board #392), Mon, 1:15 PM-4:45 PM

Trends in CRC screening by average-risk Medicare enrollees over age 75: 2002-2010. *First Author: Charles L. Bennett, South Carolina Coll of Pharm, Columbia, SC*

Background: Since 2001, Medicare has covered colorectal cancer (CRC) screening for average-risk enrollees. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended against routine CRC screening of the average-risk over age 75. Although Medicare CRC screening policy has no age limit on screening eligibility, there are concerns about inappropriate use of CRC screening services. **Methods:** The data consist of a 1998-2010 5% non-cancer sample of Medicare enrollees residing in SEER registry areas. We constructed 9-year panel data from 2002 to 2010. Each panel was assembled in the similar fashion. For illustration purpose, average-risk Medicare beneficiaries were included in the 2010 panel if they were 76 years or older in 2010; enrolled in FFS plans and Part A&B benefits in every single month in 2010 and the previous 9 years; not diagnosed with any indications for higher risks in 2010 and the previous 4 years. The outcomes are the up-to-date overall adherence status, and the specific modality (conditional on adherence). Chi-squared tests were used for statistical analyses. **Results:** The sample size of 9-year panel data of average-risk Medicare enrollees over age 75 ranges from 23,536 in 2002, 19,847 in 2008, to 19,609 in 2010. The overall CRC screening adherence rates increased from 12.69%, 17.44% and 20.88%, respectively. For the adherence rates by modality, the rates of adherence to colonoscopy increased from 2.18%, 14.67%, and 19.03%, respectively, while the rates of adherence to other modalities decreased rapidly. There was variation in overall adherence rates. Blacks were less likely than whites to be adherent ($P < 0.01$); women were less likely than men to be adherent. For the subpopulation over age 85, the rates of adherence to colonoscopy were .74%, 7.14%, and 11.24%, respectively. The differences in colonoscopy adherence by race and gender among the subpopulation were consistent to these among the population over age 75 ($P < 0.01$). **Conclusions:** Overall adherence rates have risen rapidly since 2002, largely driven by 2001 Medicare coverage decision on colonoscopy. The high proportion of the average-risk over age 75 who received screening colonoscopy services, a practice against USPSTF recommendation, warrants more research.

1569 Poster Session (Board #393), Mon, 1:15 PM-4:45 PM

Prediction models for primary melanoma: an independent external validation study in an Australian population. *First Author: Kylie Vuong, University of Sydney, Camperdown, Australia*

Background: There are a growing number of melanoma risk prediction models; however few assessed model external validity. External validation refers to the process of establishing model performance in an external, independent population and provides an indication of generalizability. Model performance tends to be poorer when measured in an external, independent data set compared with the data set that was used to develop the model. To help clinicians decide which models are potentially most useful, we assessed the external validity of six published melanoma models on an independent population. **Methods:** The Australian Melanoma Family Study, a population-based, case-control-family study with 629 population-based cases with first primary melanoma diagnosed before age 40 years and 535 controls from 2001 to 2005 were used to validate the models. We compared performance using discrimination (separation of those with and without melanoma) by calculating the area under the receiver operating curve (AUC). **Results:** Model performance ranged from fair to good. The models of Mar [AUC = 0.79 (95% CI 0.73 – 0.79)] and Fears for men [AUC = 0.79 (0.71 -0.86)] showed comparable discrimination. Other models yielded lower discrimination: Guther [AUC = 0.70 (0.67-0.72)], Williams [AUC = 0.66 (0.64-0.69)], Cho [AUC = 0.63 (0.61-0.65)] and Fears for women [AUC = 0.63 (0.56-0.69)]. **Conclusions:** The six models discriminate well between those with and without melanoma in the Australian population suggesting potential for these models to be developed for use in targeted melanoma prevention interventions. However further external validation in different populations and prospective evaluation of efficacy is required before they can be routinely used in clinical settings.

1570 Poster Session (Board #394), Mon, 1:15 PM-4:45 PM

Beliefs and behavior regarding e-cigarettes in a large cross-sectional survey. *First Author: Sebastien Couraud, Acute Respiratory Medicine and Thoracic Oncology Department, Lyon Sud Hospital and Lyon University Cancer Institute, EMR 3738 "Therapeutic Targeting in Oncology", Lyon Sud, Pierre Benite, France*

Background: The use of e-cigarettes has developed dramatically in recent years. However, the role of e-cigarettes in helping cigarette cessation or in lowering social stigma of tobacco use remains controversial. It is therefore useful to assess beliefs and behavior about e-cigarettes. **Methods:** The 4th French nationwide observational survey, EDIFICE 4, was conducted among a representative sample of 1602 subjects aged 40 to 75 years, using the quota method, from June 12 to July 10, 2014. Profile, beliefs and behavior were assessed by phone interviews of the general population with no history of cancer (n = 1463), and compared with those of cigarette smokers and e-cigarette users (eC+). **Results:** Of the 1463 individuals analyzed, 93 (6%) were e-cigarette users (74 current and 19 former cigarette smokers), with a mean daily consumption of 9.9 (±11.0); 88% used nicotine-based e-liquid. Among cigarette users (C+), current C+/eC+ were more likely to be men, to have a lower socioeconomic status (56% vs 39%), and to be more dependent on nicotine according to the Fagerström test (58% vs 46%), in comparison with cigarette smokers alone (C+/eC-). In the general population, 58% believed that e-cigarettes are potentially useful in helping to reduce cigarette smoking, and for 31%, they can help to quit smoking. In contrast, these proportions were 24% and 69% respectively, among e-cigarette users (C+/eC+). In the general population, 42% and 54% believed that e-cigarette smoke is less toxic than cigarette smoke for the user and for passive smokers, respectively. These figures were both greater among e-cigarette users (C+/eC+), reaching 68% and 87% respectively. Of the total population, 12% felt that e-cigarettes are likely to be effective for controlling lung cancer mortality (18% among current smokers vs 9% and 12% in former- and never-smokers), compared to 33% of e-cigarette users (C+/eC+). Lastly, current C+/eC+ smokers believed they have a higher risk of lung cancer than that of current C+/eC- smokers. **Conclusions:** Current cigarette smokers and current e-cigarette smokers both tend to have a lower awareness of e-cigarette toxicity and to emphasize the potential benefit of e-cigarettes for quitting smoking.

1571 Poster Session (Board #395), Mon, 1:15 PM-4:45 PM

Omentin as a potential biomarker related to exercise and cancer risk. *First Author: Michaela Onstad, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Omentin is a protective adipokine whose circulating levels are inversely related to BMI, waist circumference, and insulin resistance. Serum levels are lower in women with endometrial and ovarian cancers compared to healthy controls. Our in vitro studies demonstrate that exogenous omentin suppresses ovarian cancer cell motility and invasion potential and inhibits tumor growth indirectly. Given its inverse relationship with obesity and insulin resistance, we hypothesized that serum omentin can be increased with exercise. **Methods:** We conducted a pilot study of healthy individuals participating in a 10 week community exercise program aimed at training beginning runners for a 5K race. At the start of the program, anthropometric measures were taken, serum collected, and a whole body dual-energy X-ray absorptiometry (DXA) was done to measure percent body fat (%BF) and percent lean body mass (%LBM). These were repeated at completion of the program. Spearman's rank correlation was used to analyze the association between omentin, anthropometric measures and body composition. Paired t-tests and Wilcoxon signed-rank test were used to analyze changes in omentin. **Results:** 40 participants were enrolled and 28 completed all follow-up studies. Baseline omentin was negatively associated with waist circumference ($p = 0.03$) and %BF ($p = 0.01$), and positively associated with %LBM ($p = 0.009$). 11 participants decreased their %BF at completion of the program, whereas 17 had no improvement or increased their %BF. Those who decreased %BF had in increase in serum omentin (median = + 89.23ng/mL), whereas those who had no improvement or increased their %BF showed a decrease in omentin (median = - 69.98ng/mL). The change in omentin was different between these groups, approaching statistical significance ($p = 0.06$). **Conclusions:** Omentin is negatively associated with waist circumference and %BF, and positively associated with %LBM. Changes in serum omentin due to exercise may be reflective of changes in body composition. As the correlation between omentin and cancer risk is further established, it may serve as a useful biomarker for patients to receive specific interventions. Omentin warrants inclusion in future research involving energy balance and cancer.

1572 Poster Session (Board #396), Mon, 1:15 PM-4:45 PM

Effect of green tea catechins in prostate cancer chemoprevention. *First Author: Nagi B. Kumar, H Lee Moffitt Cancer Ctr At Univ of S Florida Coll of Medcn, Tampa, FL*

Background: Preclinical, epidemiological and prior clinical trial data suggest that green tea catechins may reduce prostate cancer (PCa) risk. **Methods:** We, therefore, conducted a placebo-controlled, randomized clinical trial of one year of Polyphenon E (PolyE), a proprietary mixture of green tea catechins containing 400 mgs of epigallocatechin-3-gallate (EGCG) per day, in 97 men with high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferstion (ASAP) on prostate biopsy. The primary study endpoint was the total number of PCa diagnoses on the PolyE versus placebo arm at one year. **Results:** No differences in prostate cancer rates were observed in the two groups (4/49 PolyE vs 6/48 placebo, $P = 0.25$). A prespecified analysis comparing the combined rates of PCa + ASAP in the subgroup of men with HGPIN-only at baseline, showed a decrease in this composite endpoint (3/26 PolyE vs 10/25 placebo, $P < 0.024$). This was largely driven by a reduction in ASAP (0/26 PolyE vs 5/25 placebo). In another prespecified analysis, a decrease in serum PSA was observed the PolyE arm.(-0.90 ng/mL; 95% CI:-1.67, -0.12; $P < 0.05$). Adverse events related to the study agent did not significantly differ between the two study groups. **Conclusions:** Daily intake of a standardized, decaffeinated catechin mixture containing 400 mgs EGCG per day for 1 year accumulated in plasma and was well tolerated, but did not reduce the likelihood of a subsequent PCa diagnosis in men with baseline HGPIN or ASAP over this period of time. Clinical trial information: NCT00596011.

1573 Poster Session (Board #397), Mon, 1:15 PM-4:45 PM

Do patients with longstanding IBD have higher cancer risk compared to the general population? Results from the IBSEN study. *First Author: Milada Cvancarova, Department of Gastroenterology, Oslo University Hospital, Oslo, Norway*

Background: Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory bowel diseases (IBDs) that affect the gastrointestinal tract. The incidence and prevalence of IBD have increased worldwide. Involvement of extraintestinal organs is not uncommon; therefore many studies have focused on the risk of organ-specific cancers in IBD patients. In addition to longstanding disease, the presence of primary sclerosing cholangitis, a family history of colorectal cancer (CRC), the degree of inflammation of the bowel, and greater anatomic extension of colitis increase the risk of developing CRC. The aims of the present study were to determine the cancer prevalence in a well-defined population-based cohort of IBD pts 20 years after diagnosis and to compare the risk of cancer development in IBD pts to the general population. **Methods:** The IBSEN (Inflammatory Bowel South-Eastern Norway) study has prospectively followed all patients diagnosed with IBD from 1990 to 1994, in total 843 IBD pts followed regularly for 20 years. All IBD patients were age-and gender matched with 25 individuals from the general population (controls). Complete data on death and all cancers in the IBD cohort and in the controls were collected from the Norwegian Cancer Registry. Overall risk for cancer and CRC-specific risk was computed using Cox model. **Results:** In total we have analyzed 843 IBD pts and 20950 controls. There were 117 (14%) cancers in the IBD patients and 2095 (10%) in the controls. Overall, IBD pts had 1.5 times higher risk of cancer development compared to their matched controls (HR = 1.52 (95 % CI (1.26- 1.83) $p < 0.001$). There was no sex difference in all cancers risk. A total of 19 subjects in the IBD group developed CRC (17) or small bowel cancer (2). Males with IBD had a significantly increased risk of CRC-specific cancer compared to controls (HR = 2.54 (95% CI (1.40-4.63) $p = 0.002$), however this risk was not significant for women (HR = 1.31, 95%CI (0.58-2.98). **Conclusions:** Patients who have had IBD for 20 years have about 50 % higher cancer risk compared to the age- and gender matched controls from the general population. Most of this difference is caused by increased risk for bowel cancer in male IBD patients.

1574 Poster Session (Board #398), Mon, 1:15 PM-4:45 PM

Association between geriatric assessment findings and clinical depression in 1092 older patients with cancer: The ELCAPA Cohort study. *First Author: Christophe Tournigand, APHP, Henri-Mondor Hospital, Oncology department, Creteil, France*

Background: Few studies assessed jointlygeriatric and oncological factors associated with clinical depression in geriatric oncology setting. To assess the prevalence and associated factors of clinical depression in older patients with cancer. **Methods**: We studied a prospective cohort of cancer patients aged ≥ 70 years and referred to geriatric oncology clinics between 2007 and 2012. A multidimensional geriatric assessment (GA) was performed before treatment. Clinical depression was diagnosed by senior geriatricians by a semi-structured interview. It encompassed criteria of the Diagnostic and Statistical Manual of Mental Disorders (4^{th} edition, DSM-IV) and of the International Classification of Diseases (10^{th}edition, ICD-10). Multivariate analysis was based on multivariate logistic models. Systematic adjustement for gender was done. **Results**: Of 1121 consecutive patients, 1092 had available data (mean age, 80.4 years; women, 48.8%; metastases, 51.3%; cancer location: colorectal 21.1%, breast 16.8%, kidney bladder or urinary tract 14.0%, and prostate 11.4%). The overall prevalence of clinical depression was 28.4% (95% confidence interval, 25.7-31.2). Factors independently associated with clinical depression by multivariate analysis adjusting for all following factors and gender were impaired mobility (adjusted OR [aOR], 2.41; 1.64-3.54), impaired functional status defined as ECOG-PS ≥ 2 (aOR, 2.42; 1.83-3.76), inpatient status (aOR, 1.66; 1.18-2.32), metastatic status (aOR, 1.42; 1.01-2.01), inadequate social support (aOR, 1.58; 1.11-2.25), cognitive impairment (aOR, 1.73; 1.23-2.43), polypharmacy defined as five or more nonantidepressant drugs (aOR, 1.70; 1.18-2.44), and multimorbidity ($aOR_{\text{additional CIRS-G point}}$, 1.07; 1.04-1.11). **Conclusions:** In older patients with cancer at various sites and stages, clinical depression was highly prevalent. Clinical depression was independently associated with several GA findings (impaired mobility and function, inadequate social support, cognitive impairment, polypharmacy, and multimorbidity) independently from with gender, tumor site, and metastatic status.

1576 Poster Session (Board #400), Mon, 1:15 PM-4:45 PM

Comparison of breast cancer risk in women with and without systemic lupus erythematosus in a Medicare population. *First Author: Waseem Khaliq, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Studies have suggested a decreased breast cancer risk in patients with systemic lupus erythematosus (SLE). However, these studies enrolled primarily younger patients at lower risk of breast cancer identified from lupus clinics. Therefore, we examined a large population-based cohort assembled from a Medicare beneficiary population to compare the incidence of breast cancer among women with SLE with women without a diagnosis of SLE. **Methods:** We used 20% sample from 2006 Medicare claims data to assemble a cohort of women (N = 3,670,138), 84% of whom were ≥ 65 years. Women with a SLE diagnosis (ICD-9-CM 710.0) and population-based controls were identified and the incidence of breast cancer for women with and without SLE was determined during the following 5 years. **Results:** Of the 18,423 women with SLE who met inclusion criteria, 21% were African Americans and 53% were ≥ 65 years. Among women with SLE and without SLE the age adjusted risk for breast cancer was 2.23 (95% CI, 1.94-2.55) and 2.14 (95% CI, 1.96-2.34) per 100 women over five years respectively. The age and race adjusted incidence ratio for breast cancer was 1.04 (95% CI 0.90-1.21). Stratification by age and race showed no difference in the incidence ratio for breast cancer among women with SLE compared to their respective age-group controls. **Conclusions:** In contrast to clinic based cohorts, we found a similar risk of breast cancer in women with and without SLE in a population based cohort. Because the presence of SLE may affect breast cancer therapies, early detection is critical, so that optimal screening recommendations should be followed.

1577 Poster Session (Board #401), Mon, 1:15 PM-4:45 PM

Factors associated with early mortality in metastatic breast cancer (MBC) in a population based cohort. *First Author: Ines Maria Vaz Duarte Luis, Dana Farber Cancer Inst, Boston, MA*

Background: Significant improvements in survival time have been achieved for patients (pts) with MBC. Nevertheless, some still die soon after diagnosis. Data regarding features associated with early death are limited. **Methods:** Using Surveillance, Epidemiology, and End Results data, we studied 4,032 pts with *de novo* MBC diagnosed between 01/2010-06/2011(when Human Epidermal Growth Factor Receptor 2 [HER2] status started to be recorded) with follow up of at least 6 months. Multivariate logistic regression models assessed features associated with death within 1 and 6 months of diagnosis, adjusting for the variables in the table. **Results:** The median age was 61 (22-99), 75% were white, 93% were insured. Disease subgroups were the following: hormone receptor (HR)+HER2- (61%); HR+HER2+(15%); HR-HER2+ (9%) and triple negative (15%). Approximately 8% died by 1 month and 20% died by 6 months. Older age, lack of insurance, and triple negative subtype were associated with early death. SeeTable. **Conclusions:** Among a population based cohort, one fifth died within 6 months. This study highlights that both clinical factors and insurance type seem to impact early death. These data suggest the importance of studying how differences in insurance reform and other disease characteristics may modify risk for early death and may also inform interventions aimed at those at risk for early death.

	% Death within 1 month (row)	Adj OR (95%CI)	% Death within 6 months (row)	Adj OR(95%CI)
Age				
≤40	2	1	6	1
40-49	4	2.6 (1.1-6.4)	10	2.1 (1.3-3.4)
50-59	6	4.0 (1.9-8.4)	17	3.7 (2.4-5.5)
60-69	8	5.9 (2.7-12.8)	20	4.8 (3.2-7.1)
≥70	13	10.6 (5.7-19.7)	30	8.5 (5.5-13.1)
Marital status				
Married	6	1.0	15	1.0
Single	10	1.3 (0.9-1.8)	23	1.3 (1.0-1.5)
Insurance				
Insured	8	1	17	1
Medicaid	8	1.4 (1.1-1.8)	21	1.4 (1.1-1.9)
Uninsured	16	3.1 (2.3-4.2)	27	2.2. (1.6-3.1)
Unknown (UK)	6	0.7 (0.4-1.5)	24	1.6 (0.8-3.0)
Site				
Distant lymph node	2	1	7	1.0
Distant metastases	8	4.3 (1.9-9.7)	21	3.7 (2.3-5.9)
Local extension	4	1.6 (0.5-4.4)	12	1.4 (0.7-2.8)
UK	11	5.6 (2.0-15.5)	21	3.6 (1.8-7.0)
Subtype				
HR+HER2-	8	1	17	1
HR+HER2+	8	1.3 (0.9-1.9)	22	1.2 (1.1-1.4)
HR-HER2+	7	1.4 (0.9-2.2)	16	1.8 (1.2-2.7)
HR-HER2-	12	2.0 (1.7-2.4)	35	3.1 (2.5-3.8)
Total (N,%)	326 (8)		792 (20)	

by race, registry, grade, histology.

1578 Poster Session (Board #402), Mon, 1:15 PM-4:45 PM

Breast cancer in male AYA. *First Author: Rashmi Bawa, John Wayne Cancer Institute, Santa Monica, CA*

Background: Breast cancer is one of the most common cancers in female adolescent and young adults (AYA: ages 15-39 years), which may develop de novo or in patients previously treated for cancer. However, there is scant data about primary or secondary (SMN) male breast cancer in AYAs. This study investigates factors effecting the overall survival (OS) of male breast AYA and compares the demographic, tumor, treatment characteristics, and OS of primary versus SMN in this population. **Methods:** All 589 cases of invasive AYA male breast cancer in the 1998-2010 American College of Surgeons National Cancer Database were examined. Kaplan-Meier with log-rank test and Cox-proportional regression analyses analyzed OS in the entire cohort. Patients were divided into two groups according to primary or secondary occurrence and compared with appropriate statistical methods. **Results:** For the entire cohort, non-white race ($p = 0.004$), government/military/medicare or no insurance ($p < .001$), lower socioeconomic status (SES) ($p = .026$), larger tumor size ($p = 0.034$), distant metastases ($p < .001$), not having any surgery ($p < .001$) or no nodal surgery ($p < .001$) all led to worse OS. On multivariate regression, tumor size (HR 1.02, CI 1.01-1.03), distant metastases (HR 4.95, CI 2.23-10.99), and lower SES (HR 2.15, CI: 1.31-3.49) had worse OS. 35 patients (5.9%) had a SMN, with similar demographic, tumor and treatment characteristics (when stratified by stage) to primary male breast cancers. However, there was a trend for SMN patients to present with less nodal disease (0.063), receive less radiation ($p = 0.068$), and occur less commonly in Blacks ($p = 0.084$). 3-year OS was 86.3% for primary cancer and 76.2% for SMN patients ($p = 0.20$). SMN patients without insurance ($p = 0.035$), with distant metastases ($p = 0.048$), and not having nodal surgery ($p = 0.008$) had worse OS. **Conclusions:** Larger tumor size, distant metastasis and lower SES are associated with worse OS in male AYAs with breast cancer. Outcomes are similar regardless of primary or secondary tumor status.

1579 Poster Session (Board #403), Mon, 1:15 PM-4:45 PM

Treatment intensity differences in screen-detected and community-detected early stage breast cancer (ESBC). *First Author: Kenneth Jack Elder, Royal Melbourne Hospital, Melbourne, Australia*

Background: The value of population based mammographic screening has been questioned by those who believe that the reduction in mortality from earlier diagnosis is outweighed by harms including overdiagnosis and overtreatment as well as harms of false positive recall for assessment. Intensity of treatment received is rarely mentioned in the debate. We hypothesised that screen-detected (SD) cancers would receive less extensive surgical treatment and less intense adjuvant therapies than community-detected (CD) cancers. If demonstrated, the extent of these differences would form an important component of the debate over the role of mammographic screening. **Methods:** Retrospective analysis of a consecutive cohort of female patients aged 40-75 and managed for ESBC between 2009-2013 within a large metropolitan Breast Service in Melbourne, Australia, diagnosed either via a population screening program (SD) or clinically referred to the Service (CD). Data on patient characteristics, symptoms, tumor characteristics and treatment recommendations were derived from hospital records. **Results:** 718 cases were identified. 28 had previous breast cancer and 7 metastatic disease, leaving 682 for analysis. 54% (367/682) were SD. Mean tumor size was smaller in the SD group (1.55cm vs 2.61cm, $p < 0.0001$) and nodal involvement was less common (24% vs 46%, $p < 0.0001$). Compared to CD cases, SD cases received less extensive surgery (mastectomy 14% vs 36% ($p < 0.0001$), axillary dissection 17% vs 40% ($p < 0.0001$)), less intensive adjuvant radiotherapy (radiotherapy after wide excision 93% vs 97% ($p = 0.052$), radiotherapy after mastectomy 34% vs 58% ($p = 0.0039$)). Endocrine therapy was more common in SD cancers reflecting differences in receptor status (93% vs 80% ($p < 0.0001$)), but chemotherapy was much less frequently used (32% vs 65% ($p < 0.0001$)). **Conclusions:** Women diagnosed with ESBC through a population based screening program are less likely to receive mastectomy and/or axillary dissection, less likely to be recommended to receive radiotherapy, and less likely to receive adjuvant chemotherapy. This difference in treatment intensity should be considered in the current debate surrounding mammographic screening.

1580 Poster Session (Board #404), Mon, 1:15 PM-4:45 PM

Association of body mass index with survival outcome in three breast cancer subtypes. *First Author: Takeo Fujii, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: High body mass index (BMI) is a poor prognostic indicator in breast cancer patients. However, data are still limited about the association between baseline BMI and survival according to breast cancer subtype. We evaluated the relationship between BMI and survival among breast cancer receptor subtypes (hormone receptor positive (HR), HER 2 positive (HER), and triple-negative breast cancer (TNBC). **Methods:** This study included 4069 patients with stages I, II, or III breast cancer diagnosed between 1990 to April 30, 2013 who had received neoadjuvant systemic therapy and subsequent definitive surgery collected from Breast Medical Oncology database under IRB-approved protocol. Baseline clinical information including BMI (kg/m^2) was collected, and patient characteristics were tabulated. HR is defined as either estrogen or progesterone receptor positive (positive by immunohistochemistry (IHC) or $> 10\%$ staining) with negative HER2 receptor, and HER2 is defined as HER2 positive (IHC 3+ or HER2/CEP17 ratio ≥ 2.0) regardless of their hormone receptor status. Correlation between BMI as a continuous variable and survival was analyzed by using univariable and multivariable Cox proportional hazard models. **Results:** Median follow-up for survivors was 37 months. Baseline characteristics are shown in Table. A univariable analysis showed a trend towards unfavorable overall survival in TNBC patients whose BMIs were 27.2-40.4. In multivariable analysis, BMI was a significant predictor of poor overall survival only in the HR (hazard ratio 1.017; 95%CI 1-1.033, adjusted $p = 0.046$). **Conclusions:** Our large cohort analysis demonstrated that higher BMI was significantly associated with poor survival only in HR, suggesting that baseline BMI might be a prognostic indicator only for the least aggressive subtype, HR.

	HR (n = 2054)	HER2 (n = 1075)	TNBC (n = 940)
BMI, median (range)	27.6 (15.5-66)	27.5 (15.9-67.6)	28.5 (14.3-61.7)
Recurrence-free survival at 5 years (95%CI)	77.8 (75.5-79.9)	76.4 (73.1-79.3)	63.2 (59.5-66.8)
Overall survival at 5 years (95%CI)	83.4 (81.2-85.3)	82.8 (79.6-85.5)	67.2 (63.3-70.8)

1581 Poster Session (Board #405), Mon, 1:15 PM-4:45 PM

Incidence, prevalence, and risk factors of malignancy in lung transplant recipients. *First Author: Vikas Kumar Singh, UPMC Mckeesport, Mckeesport, PA*

Background: Solid organ transplant is associated with post-transplant malignancy (PTxM) due to chronic immunosuppression, but data is limited in lung transplant recipients (LTRs). Our goal was to analyze the Organ Procurement and Transplant Network (OPTN) database to determine the incidence, prevalence and risk factors for developing PTxM in LTRs. **Methods:** All LTRs in the OPTN database from May 4, 2005 to March 3, 2014 were included in this study. LTRs aged <18 years and those without malignancy follow up data were excluded. Prinary endpoint was the development of PTxM. Multivariate logistic regression was done for non-skin PTxM with variables age, sex, smoking history, previous history of malignancy and pre-transplant diagnosis. **Results:** A total of 10,894 subjects were included. Diagnoses among LTRs were COPD (27%), Idiopathic Pulmonary Fibrosis (IPF) (38%), Cystic Fibrosis (CF) (12%) and others (23%). 791 (7.3%) had history of pre-transplant malignancy. Recurrence rate of pre-transplant malignancy as PTxM was 2.3%. Median follow up time was 4.7 years (IQR 2.0-8.0). Incidence and prevalence are provided in table-1. Post-transplant lymphoproliferative (PTLD) disorder prevalence was 1.3%, of which 50% occurred within one year of transplant. Prevalence of any PTxM was highest in patients with IPF (16%) and lowest among patients with CF(6%). Significant risk factors ($p<0.001$) for non-skin PTxM included: history of previous cancer (Odds Ratio, OR 1.52), age (OR 1.03), smoking history (OR 1.2), male gender (OR 2), and pre-transplant diagnoses of COPD (OR 1.5) or IPF (OR 1.6). **Conclusions:** Prevalence of PTLD was comparable to published prevalence in renal transplant recipients. Prevalence of any type of cancer is significantly higher in LTRs as compared to 0.19% in the general adult population reported by CDC in 2014. Lower prevalence in CF group could be explained by younger median age of 29 in this diagnostic group.

Malignancy incidence and prevalence in adult lung transplant recipient.

	1-Year follow up		Entire follow up period	
Malignancy Type	**Prevalence N (%)**	**Incidence***	**Prevalence N (%)**	**Incidence***
All types combined	247 (2.3%)	2.03	1,471 (13.5%)	25.3
Other than Skin	174 (1.6%)	1.4	1,321 (12.1%)	22.7

* per 1,000 person-year.

1582 Poster Session (Board #406), Mon, 1:15 PM-4:45 PM

Novel algorithms to predict the occurrence of in-hospital venous thromboembolism in cancer patients: Machine learning classifiers developed from the 2012 national inpatient sample. *First Author: Spencer L. James, Geisel School of Medicine at Dartmouth, Hanover, NH*

Background: Cancer poses a significant risk for venous thromboembolism (VTE), but predicting VTE in patients is challenging. Oncology admissions accrue significant amounts of clinical data, but currently only a limited amount of this data is used to predict VTE. Machine learning is a discipline of computer science whereby computers study high dimensional data features to discover rules that can predict an outcome. The advent of the electronic medical record (EMR) offers a plethora of patient-specific data that could be used for more complex risk modeling, although it is unknown whether this can accurately be used to predict VTE occurrence in the oncology patients. We aimed to measure the accuracy of machine learning classifiers in predicting VTE in patients hospitalized with cancer using information that would be available to the EMR. **Methods:** Using the 2012 National Inpatient Sample (NIS), we applied multiple different machine learning classifiers to develop a predictive model of cancer associated in-hospital VTE and tested its ability to predict which cancer related admissions would be associated with VTE. Accuracy was measured as the percentage of admissions correctly associated with VTE. **Results:** Of the 7,296,968 admissions in the 2012 NIS, 996,506 were associated with a cancer diagnosis, and of those, 47,045 were associated with VTE. Of the patients with a cancer diagnosis, we sampled 1,089 with VTE and 1,089 without VTE. We then conducted 100 train-test simulations where classifiers were trained on a random sample of the data and then made VTE predictions on a separate sample. Of the 100 trials performed, the random forest classifier in the scikit-learn package was able to correctly classify VTE versus non-VTE 74% of the time (range: 69.0% - 79.0%). **Conclusions:** Machine learning classification is capable of harnessing complex signals in clinical datasets and is a promising approach to assess the in-hospital VTE risk of admitted cancer patients. With further validation, such classifiers could be included in EMR systems to provide risk assessment for patient admissions and suggest appropriate use of pharmacological prophylaxis.

1583 Poster Session (Board #407), Mon, 1:15 PM-4:45 PM

Male breast cancer as a second primary cancer (SPC): Increased risk following hematologic malignancies. *First Author: Deborah Elaine Farr, Northwestern University, Chicago, IL*

Background: Male breast cancer accounts for approximately 1% of all breast cancer. The association of male breast cancer with other malignancies has been described; however the risk of males developing breast cancer as an SPC, after specific types of index primary malignancies, relative to population risk, has not been reported. **Methods:** SEER 9 data was used to identify male breast cancer patients with a prior index malignancy. In the period 1973-2011, the five most common index primary sites included breast, prostate, colorectal, ureter and urinary bladder, and hematologic malignancies (leukemia, lymphoma and myeloma). Standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) of male breast cancer as an SPC were calculated (observed/expected rates) for each of these five most common index malignancies. Excess risk was expressed per 100,000. All analyses were conducted using SEER*Stat software, version 8.1.5. **Results:** Over a 38-year period, 512 male breast cancers were identified as second primary malignancies. The most common index malignancies were breast (SIR 28.44, 95% CI 20.32-38.73) hematologic (SIR 1.55, 95% CI 1.11-2.10), ureter/urinary bladder (SIR 1.10, 95% CI 0.80-1.46), prostate (SIR 0.97, 95% CI 0.84-1.11), and colorectal (SIR 0.94, 95% CI 0.72-1.21). Apart from the known association with prior breast cancer, the only significant association was with a prior hematologic malignancy (p-value 0.007). 42.6% of SPC breast malignancies occurred within 5 years of the index malignancy. When incidence rates were compared from 1973-1974 to 2010-2011, the rate of primary breast cancer remained stable at 1.15 and 1.11 respectively, while the incidence rate of breast cancer as SPC increased from 0.12 to 0.39, a 225% increase (p-value < 0.001). **Conclusions:** Compared with the general population, the risk of developing male breast cancer was significantly elevated after initial hematologic malignancies. The risk of developing breast cancer as SPC increased markedly from 1973 to 2011. These observations have implications for clinical surveillance in this population, and point to potential etiologic connections with prior therapy, or with genetics.

1584 Poster Session (Board #408), Mon, 1:15 PM-4:45 PM

Pre-diabetes and breast cancer outcomes: Abrogating the confounding effect of anti-diabetic therapy. *First Author: Varinder Kaur, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Multiple studies indicate that type II diabetes is associated with an increased mortality in breast cancer. However, in these studies the class of anti-diabetic therapy, remains an obvious confounding factor. Higher mortality has been reported in breast cancer patients treated with insulin than with metformin. Choosing a population of breast cancer patients with pre-diabetes, not receiving anti-diabetic therapy, could overcome such confounders. **Methods:** We conducted a retrospective cohort study to evaluate the relationship between elevated random blood sugar (RBS) levels and breast cancer outcomes. Only patients without a previous history of diabetes and who were not receiving any anti-diabetic therapy were included. The effect of elevated RBS on overall survival (OS), event-free survival (EFS) and time to tumor recurrence (TTR) were analyzed using Kaplan-Meier curves and log-rank test, and reanalyzed adjusting for age, race and obesity using multivariate Cox regression. Fisher's exact test was used to compare binary proportions and Spearman rank correlations were used for ordinal category data in conjunction with correlation chi-square tests. **Results:** 234 patients with stage I-III breast cancer (mostly stage II, 177) were analyzed, of which 159 patients had a documented RBS level. 72 patients had elevated RBS ($>$ 120 mg/dL) and 87 had RBS $<$ 120 mg/dL. We observed that patients with elevated RBS experienced significantly shorter OS (HR = 2.89; p = 0.0001), shorter EFS (HR = 2.44; p = 0.0006) and shorter TTR (HR = 2.16; p = 0.023). After adjusting for age ($<$ / $\geq$ 50), obesity and race via Cox regression, elevated RBS continued to display a high and statistically significant association with shorter OS (HR = 3.63; $p < 0.0001$), shorter EFS (HR = 3.20; p = 0.0002) and shorter TTR (HR = 3.52; p = 0.001). Additionally, among patients under 50 years of age, elevated RBS levels were associated with a significantly greater frequency of high grade tumors compared to RBS $<$ 120 mg/dL(80% vs 45%; p = 0.02), suggesting that elevated RBS may have more impact in younger patients. **Conclusions:** High random blood sugar levels, reflective of a pre-diabetic state, are associated with shorter overall survival in breast cancer patients.

1585 Poster Session (Board #409), Mon, 1:15 PM-4:45 PM

"Fight fat with fat": The impact of brown adipose tissue (BAT) on breast cancer prognosis–A retrospective analysis. *First Author: Orlando Esteban Silva, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Two types of adipose tissue exist: white adipose tissue (WAT) and BAT. WAT is the main energy store in humans and is associated with obesity and inflammation. BAT is thought to be protective against obesity and acts as an energy dissipating organ, which may fight obesity by reducing adipokines, inflammatory cytokines, and insulin resistance. The relationship of brown fat activation and cancer prognosis is unknown. We hypothesize that BAT may be protective to breast cancer patients by shifting glucose pool away from tumors and reducing tumor activity. **Methods:** Through a retrospective chart review of over 900 patients treated by the Breast Cancer Group at our institution, we identified 98 patients with BAT on PET CT scans. We collected information on patient demographics, lifestyle, staging and treatments received and response, progression of disease, overall survival, labs (lipids, hemoglobin A1C, Vitamin D, CRP), metabolic syndrome, metformin use, and antidepressants. **Results:** Of the 98 cases identified, 26 had Stage I disease at diagnosis, 32 had Stage II, 27 had Stage III, and 13 had Stage IV. The median age at diagnosis was 46. 62% of patients were Hispanic, 30% Caucasian, and 5% African-American. The majority of cases (86%) were of ductal histology. 77% were ER positive and 24% were HER2 positive. The median BMI of our cohort was 25.1. The 5 year PFS for our cohort was 74.6% (CI 64.2-82.4). The 5 year breast cancer specific OS was 94.2% (CI 86.6-97.6), with OS by stage showing I 100%, II 92.9% (CI 74.6- 98.2), III 91.7% (CI 70.5-97.9), and IV 92.3% (CI 56.6-99.0). While the total OS is within the range of 89.2% reported by SEER, our stage III and IV patients had a markedly improved OS compared to historical controls (41-67% and 15%, respectively, per ACS). **Conclusions:** To date, we have compiled the largest cohort of breast cancer patients with known BAT. While knowledge and clinical applicability of brown fat is still in its infancy, we hope that our study, with its remarkable OS for advanced stage disease, will shed light on the manner in which the presence of brown fat activation affects metabolism, treatment response, tumor microenvironment, and long-term prognosis.

1586 Poster Session (Board #410), Mon, 1:15 PM-4:45 PM

Development of CNS metastasis and subsequent survival in patients with inflammatory breast cancer. *First Author: John Thomas French, MD Anderson Cancer Center, Bellaire, TX*

Background: Inflammatory breast cancer (IBC) is associated with a poor prognosis and high risk of central nervous system (CNS) metastases. We determined the cumulative incidence rate of developing CNS metastasis and overall survival (OS) in stage III IBC patients (pts) compared to pts with non-inflammatory invasive ductal carcinoma (NI-IDC). The purpose of this study was to evaluate the incidence rate of CNS metastasis from 1 year after diagnosis and analyze OS after CNS metastasis occurrence. We also sought to identify prognostic factors using univariate and multivariate competing risk regression models. **Methods:** We performed a retrospective review using the MD Anderson Cancer Center breast cancer database looking at stage III IDC pts treated between 1/1/1984 and 12/31/2011. For inclusion, pts were required to have initiated primary treatment within one year of their diagnosis and have follow-up for at least 1 year before the development of CNS metastasis or death. **Results:** 2323 pts were identified (589 IBC and 1734 NI-IDC). 81 IBC pts developed CNS metastasis compared to 154 NI-IDC pts. The 2-, 5-, and 10-year cumulative incidence rates of CNS metastasis in IBC and NI-IDC were 9.8%, 15.8%, and 17.4% and 6.5%, 10.1%, and 12.7%, respectively. This occurrence was significantly different between IBC and NI-IDC pts ($p = 0.0037$). However, multicovariate competing risk regression models looking at 18 variables in IBC and NI-IDC pts including patient, tumor, and treatment characteristics showed no statistically significant associations with the risk of developing CNS metastasis. In terms of survival, with a median follow up of 7.2 years, median post CNS metastasis OS was not significantly different between IBC (7.6 months) and NI-IDC (5.6 months) pts. At last follow up, 190 pts with CNS metastasis have died. HER2 positive pts had better OS with a median 14.1 months vs 4.3 months ($p = < 0.0001$). In addition, age > 50 ($p = 0.012$) but not IBC status ($p = 0.49$) was a significant predictor of post CNS metastasis survival. **Conclusions:** IBC pts have a higher incidence rate in the development of brain metastasis but OS following brain metastases is similar to its NI-IDC counterpart. Only HER2 status and age appears to play a role in prognosis.

1587 Poster Session (Board #411), Mon, 1:15 PM-4:45 PM

Prevalence of malnutrition in PS 0-1 cancer patients: Results of the NutriCancer2 one-day national survey in 2,197 cancer patients. *First Author: Jean-Philippe Durand, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France*

Background: The performance status (PS) measured by the ECOG scale, and malnutrition are both prognostic and risk factors for treatment-related toxicities in cancer patients (pts). In the medical literature, pts characteristics are usually limited to PS without description of the nutritional status. There is a serious issue concerning the under-estimation of the risk prior to anticancer treatments initiation. The prevalence of malnutrition in "fit" PS 0-1 pts remains unknown. **Methods:** We conducted a prospective one-day prevalence survey, NUTRICANCER 2, in 283 wards of private or public hospitals in France in 2012**.** Height, present and usual body weight were systematically assessed in out-pts and in-pts. Malnutrition was defined as a BMI < 18.5 or < 21 in pts older than 75 years, or a loss of body weight $>$ 10% since the diagnosis of malignancy. **Results:** A total of2197 patients (1,132 men and 1,046 women, 19 not evaluable) were included. PS alteration was significantly more frequent in malnourished patients. Indeed, 58.9% of pts with malnutrition had a PS > 2 versus 31% of pts without malnutrition. Malnutrition was found in 48.1% (276/574), 66.7% (166/249), and 69.8% (44/63) of the pts with a PS ranging from 2 to 4, respectively ($chi2 = 223.95$; $p < 0.001$). In pts assumed as fit for chemotherapy, the prevalence of malnutrition was 17.3% (76/440) in PS0 and 33.2% (262/790) in PS1 pts. Almost one third of the patients with apparent good general status were already malnourished and therefore at high risk of severe acute toxicity. **Conclusions:** This national prevalence survey indicates that Performance Status is not sensitive enough for risk assessment in oncology, requiring a systematic nutritional status assessment prior to anticancer treatments initiation.

1588 Poster Session (Board #412), Mon, 1:15 PM-4:45 PM

The long-term use of calcium channel blockers and the risk of breast cancer. *First Author: Sara V. Soldera, Department of Oncology, McGill University Health Center, Montreal, QC, Canada*

Background: The association between calcium channel blockers (CCBs) and the risk of breast cancer is controversial. The objective of this study was to determine whether the use of CCBs is associated with an increased risk of breast cancer overall, and to assess whether this risk varies with cumulative duration of use. **Methods:** A cohort of 273,152 women newly treated with antihypertensive drugs between January 1, 1995 and December 31, 2009, followed until December 31, 2010, was identified using the UK Clinical Practice Research Datalink. CCB use was treated as a time-varying variable, with exposure lagged by one year for latency considerations and to minimize reverse causality. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident breast cancer associated with the use of CCBs. A secondary analysis was conducted to assess whether the risk varied with cumulative duration of use. All models were adjusted for a number of potential confounders, including age, smoking status, body mass index, alcohol consumption and use of hormone replacement therapy or other prescription drugs. **Results:** During 1,567,104 person-years of follow-up, 4520 women were newly diagnosed with breast cancer (incidence rate: 2.9 per 1000 per year). Compared with other antihypertensive drugs, the use of CCBs was not associated with an increased risk of breast cancer (2.8 vs. 3.1 per 1000 per year, respectively; HR: 0.98, 95% CI: 0.92-1.04). In a secondary analysis, the risk did not vary according to cumulative duration of use (< 5 years, HR: 0.97, 95%: 0.90-1.03; 5-10 years, HR: 1.08, 95% CI: 0.94-1.25; ≥ 10 years, HR: 0.69, 95% CI: 0.36-1.33). **Conclusions:** The results of this large population-based study indicate that the long-term use of CCBs is not associated with an increased risk of breast cancer.

1589 Poster Session (Board #413), Mon, 1:15 PM-4:45 PM

Overall survival in solid tumor patients with abnormal renal function or renal insufficiency. *First Author: Vincent Launay-Vacher, Pitie Salpetriere Hospital, Paris, France*

Background: Data still remain scanty on the potential impact of renal insufficiency (RI) on the mortality of cancer patients. The results of 3 clinical studies we conducted (IRMA-2, CANDY and MARS) were pooled. In all 3, methodology and investigators were the same regarding RI. Pooled analysis was thus allowed to study the potential association between RI and overall survival (OS), and to stratify the risk, if any, depending on the GFR **Methods:** The KDIGO definition and classification of CKD was used. GFR was estimated with the MDRD formula. RI was defined as GFR<60 ml/min/1.73 m^2. **Results:** Population included 5908 solid tumor patients (2181 breast, 854 colorectal, 556 lung, 366 ovarian, 293 prostate for the main tumors). Median age 59.2, mean BMI 24.4, 64.0% were women. 70.7% of these patients were alive at the end of the follow-up period of one year. Univariate analysis reported that RI was strongly linked to mortality ($p < 0.0001$), when analysing together all types of patients and tumors. Furthermore, Hazard-Ratio became statistically significant at a GFR of 85 ml/min/1.73m^2. For non-metastatic patients (n = 4671), RI was also significantly associated with mortality ($p = 0.008$), with a significant higher risk of death starting at a GFR of 86. Finally, multivariate Cox model adjusted for sex, age, metastasis and the 5 main types of tumor reported that GFR was significantly associated with OS with an increased risk of mortality at a GFR of 75. This risk gradually increased along with the decrease in GFR. **Conclusions:** The IRMA studies already reported the high prevalence of RI in cancer patients. But our pooled analysis reported that the reduced OS began at an early stage of CKD, for a GFR< 75. These results underline that assessing, monitoring and managing renal function in cancer patients is crucial in order to prevent or at least minimise renal dysfunction because of its potential impact on survival.

Multivariate Cox model regression.

GFR cut-off	HR [95% CI]; p-value
GFR < 90	HR = 1.03 [0.93-1.14]; p > 0.05
GFR < 85	HR = 1.06 [0.96-1.17]; p > 0.05
GFR < 75	HR = 1.13 [1.02-1.26]; p = 0.01
GFR < 60	HR = 1.15 [1.03-1.27]; p = 0.01
GFR < 30	HR = 1.53 [1.23-1.86]; p = 0.0001

GFR = Glomerular Filtration Rate (mL/min/1.73m^2); HR=Hazard-Ratio

1590 Poster Session (Board #414), Mon, 1:15 PM-4:45 PM

Determinants for no definitive therapy for early-stage non-small cell lung cancer in U.S. population. *First Author: Yu-Wei Chen, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA*

Background: Surgery or radiation therapy (RT) remains the definitive treatment for early-stage (Stage I/II) non-small cell lung cancer (NSCLC). Early-stage NSCLC should be treated appropriately since survival decreases progressively with advanced stages. Our study aims to identify the factors associated with receiving no definitive therapy among US patients. **Methods:** Patients ≥ 18 years and diagnosed with stage I/II NSCLC from 2004-2011 in Surveillance, Epidemiology and End Results Program (SEER) were identified. Definitive therapy was defined as receiving surgery and/or RT. Socio-economic characteristics (income, educational status and residence type) were collected at county-level. Predictors for no definitive therapy were estimated with a multivariable logistic regression model. **Results:** A total of 32,401 patients were identified. 4,997 patients (15%) had no definitive therapy and among them only 456 (9%) did not receive surgery due to contraindications/patient refusal. Independent predictors for no definitive therapy include individual characteristics, such as older age, male, African Americans, not-married status, histology types other than adenocarcinoma, as well as county-level characteristics include living in a county with lower median household income, higher percentage of population with education level < high school, and a non-metropolitan setting. **Conclusions:** A significant proportion of patients diagnosed with early-stage NSCLC in the US did not receive definitive therapy. Socio-economic characteristics should be explored further to explain this phenomenon.

Independent Predictors

	Adjusted OR 95% CI
Age (every 10 years increase)	1.86 (1.80-1.92)
Median house Income (every 10,000 USD increase)	0.86 (0.81-0.91)
%Education < high school level (every 20% increase)	1.39 (1.23-1.56)
Sex	
Male vs Female	1.32 (1.02-2.10)
Race	
Black vs White	1.67 (1.51-1.85)
Other vs White	1.14 (0.99-1.31)
Marital status	
Married/Domestic partners	Ref
Single/Divorced/Separated/Widowed	1.96 (1.83-2.10)
Residence	
Non-Metropolitan vs Metropolitan	1.12 (1.02-1.24)
Histology type	
Squamous cell carcinoma vs Adenocarcinoma	1.13 (1.04-1.23)
Others vs Adenocarcinoma	2.37 (2.20-2.56)

1592 Poster Session (Board #416), Mon, 1:15 PM-4:45 PM

Effect of current smoking on risk of triple negative breast cancer. *First Author: Dhivya Prabhakar, University Hospital/Case Western Reserve University, Cleveland, OH*

Background: A number of lifestyle factors have been associated with risk of breast cancer. Studies have suggested that risk factors for triple negative breast cancer (TNBC) are different from other forms of breast cancer, and have suggested that parity, family history and body mass index (BMI) are associated with risk of TNBC. Here we sought to explore these associations and investigate the association of previously underexplored variables with risk of TNBC. **Methods:** Newly diagnosed breast cancer patients (N = 1236) were recruited from University Hospitals Case Medical Center (UHCMC) from 2007 to 2014. Patients were ineligible if they had a prior cancer or were known to be a BRCA1/2 carrier. Controls (N = 936) were recruited from the mammography center at UHCMC and were eligible if they were not diagnosed with cancer and were not known to be BRCA1/2 positive. All participants completed a lifestyle risk factor survey. Medical records were abstracted to obtain ER, PR and HER2 status. Patients were classified as TNBC if ER, PR and HER2 were negative, or non-TNBC if at least one was positive. Statistical significance of differences in physical activity, family history, parity, smoking, hours of sleep per night and BMI for both TNBC patients and non-TNBC patients compared to controls was assessed using a t-test or chi-square test. A multivariate logistic regression was used to assess significance after adjusting for age, race and BMI. **Results:** Of the patients, 121 were classified at TNBC and 932 were classified as non-TNBC. We noted a statistically significant association of current smoking with risk of TNBC (OR = 2.67, 95% CI = 1.05-6.76, p = 0.038 in multivariate regression). There was no association between former smoking at risk of TNBC ($p = 0.28$). There was no association between current smoking at risk of non-TNBC ($p = 0.34$). We did not note a statistically significant association between any other of the risk factors and TNBC ($p > 0.05$). **Conclusions:** There have been mixed results regarding the association of smoking with breast cancer, and, in particular, TNBC. Our data suggests that current smoking is a risk factor for TNBC, but not other subtypes of breast cancer. The lack of association between former smoking and TNBC suggests that quitting smoking may reduce risk.

2000 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Tumor treating fields (TTFields): A novel treatment modality added to standard chemo- and radiotherapy in newly diagnosed glioblastoma—First report of the full dataset of the EF14 randomized phase III trial. *First Author: Roger Stupp, University Hospital Zurich & University of Zurich, Zurich, Switzerland*

Background: TTFields is an established antimitotic treatment modality delivered to patients by a portable, home use, medical device. Here we evaluate whether this antimitotic effect can be translated into improved survival in a clinical setting. Based on a pre-specified interim analysis on 315 patients, the IDMC recommended early trial closure; we here report the first analysis of the full dataset of 700 randomized patients. **Methods:** This prospective phase 3 trial randomized patients with newly diagnosed glioblastoma, after completion of concomitant chemoradiotherapy, to receive either adjuvant temozolomide (TMZ) chemotherapy alone, or TMZ with TTFields (TTF/TMZ). The primary endpoint was progression-free survival, with overall survival, safety, cognitive function and quality of life as secondary endpoints. **Results:** (ITT) From 2009 to 2014, 700 Grade IV astrocytoma (glioblastoma) patients (68% male) were randomized 2:1. Patient characteristics were well balanced: median age was 56 and 57 years in the TMZ and TTF/TMZ arms, respectively. Tumor was resected in 87% of patients. MGMT was centrally assessed in 77% of patients, 35% and 39% of the tumors had a methylated promoter; 10% and 8% of the results were invalid. Median time from diagnosis to randomization was 3.8 and 3.7 months. Progression-free survival was 7.1 for TTF/TMZ vs 4.2 months for TMZ alone, hazard ratio (HR) 0.694 (95% CI 0.558-0.863) log rank p = 0.0010; overall survival 19.4 vs 16.6 months, HR 0.754 (0.595-0.955), p = 0.0222. This translates into 2-year survival rates of 43% (CI 36-50%) vs. 29% (CI 21-38%). No significant added toxicity was seen in the TMZ/TTF arm. Quality of life and gross cognitive function were comparable in the 2 arms. **Conclusions:** This is the first randomized trial demonstrating improved progression-free and overall survival of patients treated with Tumor Treating Fields. It sets a new standard of care for patients with glioblastoma, and warrants further investigation in other clinical indications. Clinical trial information: NCT00916409.

2001 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. *First Author: Wolfgang Wick, Neurology Clinic, Heidelberg, Germany*

Background: NOA-04 compared the efficacy and safety of radiotherapy *versus* (*vs)*chemotherapy in patients with newly-diagnosed, centrally assessed, supratentorial gliomas of WHO grade III and had not demonstrated a difference in efficacy parameters between arms. Here, long-term clinical follow-up for the intention-to-treat population (n = 274) and the biomarker group (n = 207) are presented. **Methods:** Patients with anaplastic astrocytoma (52.6%) and anaplastic oligodendroglial tumors (47.4%) were randomized 2:1:1 (A:B1:B2) to receive radiotherapy to 54-60 Gy or four 6-week cycles of procarbazine, CCNU and vincristine (PCV) or eight 4-week cycles of temozolomide. The primary endpoint was time-to-treatment-failure (TTF) defined as progression after radiotherapy and one chemotherapy in either sequence, or any time before if no further therapy could be administered. Exploratory analyses of the correlation between molecular status and TTF, progression-free (PFS) and overall survival (OS) were part of the study. **Results:** With a median observation period of 11.8 years (ys) median TTF [4.6 (3.4-5.1) ys *vs* 4.4 (3.3-5.3) ys], PFS [2.5 (1.3-3.5) ys *vs* 2.7 (1.9-3.2) ys], and OS [8 (5.5-10.3) ys *vs* 6.5 (5.4-8.3) ys] were not different between arms (A vs B1/B2). Oligodendroglial *vs* astrocytic histology, but more so subgroups according to CpG island methylator phenotype (CIMP) and 1p/19q co-deletion status revealed a strong prognostic value of $CIMP^{pos}$ with (CIMP-codel) *versus* without 1p/19 co-deletion (CIMP-non-codel) *vs* $CIMP^{neg.}$, but no differential efficacy of radio- and chemotherapy for any of the observed endpoints (PFS CIMP-codel: 8.8 (4-11.2) ys for A versus 7.6 (4.1-9.5) ys for B). In $CIMP^{neg.}$ mainly astrocytic tumors hypermethylation of the O6-*methyl-guanyl-DNA methyltransferase*promoter (MGMT) provided a large risk reduction for PFS in arms B1/B2, but not arm A. **Conclusions:** NOA-04 long-term data do not support a differential efficacy of primary temozolomide monotherapy or PCV polychemotherapy *vs* radiotherapy in any of the histological or molecular subgroups of anaplastic glioma. Molecular diagnosis is superior to histology. MGMT is predictive in $CIMP^{neg.}$ gliomas. Clinical trial information: NCT00717210.

2002 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Results of NRG oncology/RTOG 9813: A phase III randomized study of radiation therapy (RT) and temozolomide (TMZ) versus RT and nitrosourea (NU) therapy for anaplastic astrocytoma (AA). *First Author: Susan Marina Chang, UC San Francisco, San Francisco, CA*

Background: TMZ is efficacious in recurrent anaplastic glioma and newly diagnosed glioblastoma. The primary objective was to compare the overall survival (OS) of patients with AA treated with RT and either TMZ or NU. Secondary endpoints were to compare the time to tumor progression (TTP), relative toxicities of the 2 arms and correlate molecular analyses with clinical outcome. **Methods:** Eligibility: age ≥ 18 years, central histological confirmation of AA and KPS ≥ 60. Patients were randomized 1:1 to RT 59.4 Gy with TMZ 200 mg/m^2daily on days 1-5 of the first week of RT with adjuvant TMZ every 28 days for 12 cycles versus NU (BCNU or CCNU). Median survival time (MST) for the NU arm was assumed to be 3 years with an estimated increase in the TMZ arm to 4.5 years- hazard ratio (HR) 0.67. A sample size of 216 patients per arm would provide an overall statistical power of 90% with a one-sided significance level of 0.05. The distribution of the OS of the 2 arms was compared using the Cox proportional hazard model and the log-rank test. **Results:** Because accrual goals were not met, the trial was closed in 2007.From 2002-2007, 196 eligible patients were randomized, 97 (RT+TMZ) and 99 (RT+NU). Stratification factors (age, KPS, surgery) were balanced between the 2 arms. 65% of patients have died at the time of this report and the median follow-up time for patients still alive was 9.1 years (1.9-11.6 years). There was no difference in OS between the RT+TMZ and the RT+NU arm (p-value 0.37). The MST for the RT+TMZ arm is 3.9 years (95% CI 3.0-7.0) and the MST for the RT+NU arm is 3.8 years (95% CI 2.2- 7.0). The associated HR is 0.94 (95% CI 0.67-1.33). The differences in PFS and TTP between the 2 arms were not statistically significant. The RT+NU arm had a significantly higher rate of worse overall grade ≥ 3 toxicity (75.8% versus 47.9% p < .001), mainly related to bone marrow toxicity. **Conclusions:** RT+TMZ did not appear to significantly improve OS or TTP for AA compared with RT+ NU. RT+TMZ was better tolerated. Correlative molecular, genetic and epigenetic analyses with clinical outcome are pending. NCT00004259 Support**:** U10CA21661, U10CA180868, U10CA180822 (NCI) and Schering Plough. Clinical trial information: NCT00004259.

2003 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Continuing or ceasing bevacizumab at disease progression: Results from the CABARET study, a prospective randomized phase II trial in patients with recurrent glioblastoma. *First Author: Elizabeth J. Hovey, Prince of Wales Hospital, Sydney, Australia*

Background: In patients (pts) with recurrent glioblastoma (rGBM), the benefit of bevacizumab beyond progression (BBP) remains uncertain. Retrospective studies of pts with rGBM receiving BBP have been inconclusive. This study prospectively evaluated BBP in patients with rGBM who experienced initial progression while on bevacizumab (Bev). **Methods:** CABARET is a prospective randomized Phase 2 study of pts at first recurrence of GBM (rGBM) who had previously been treated with surgery, radiotherapy and temozolomide. Pts were randomized to carboplatin plus Bev or Bev monotherapy (Part 1). On progression, eligible pts were stratified according to planned additional chemotherapy and then randomized again to continue or cease Bev (Part 2). Those pts on the Bev monotherapy arm in Part 1 could receive carboplatin or supportive care and those who had received Bev + carboplatin in Part 1, ceased carboplatin and could receive temozolomide, etoposide or supportive care; according to clinician choice. Part 2 endpoints included response rate (RR), progression-free survival (PFS) and overall survival (OS). **Results:** Of 120 pts who received treatment in Part 1, 48 (40%) continued to Part 2, with 23 pts continuing Bev and 25 pts ceasing Bev. The median time on treatment was 1.2 months. There were no radiological responses in either arm. Median PFS (Bev vs no Bev) was 1.8 versus 2.0 months (HR 1.08, 95% CI 0.59–1.96, p = 0.81). Median OS was 3.4 versus 3.0 months (HR 0.84, 95% CI 0.47–1.50, p = 0.56). There were no treatment-related deaths or unexpected serious drug-related adverse events. Preliminary assessment of quality of life scores shows no difference between arms. **Conclusions:** Continuing Bev after progression of rGBM did not improve PFS or OS in this prospective study. Clinical trial information: ACTRN12610000915055.

2004 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

NCCTG N0872 (Alliance): A randomized placebo-controlled phase II trial of bevacizumab plus dasatinib in patients with recurrent glioblastoma (GBM). *First Author: Evanthia Galanis, Mayo Clinic, Rochester, MN*

Background: Preclinical data indicate that Src kinase signaling is markedly upregulated at the invasive GBM front following administration of the anti-VEGF antibody bevacizumab (Bev). The broad spectrum Src kinase inhibitor dasatinib can effectively block Bev-induced glioma invasion (Huveldt et al, 2013). We therefore hypothesized that combining dasatinib with Bev could increase Bev efficacy in the recurrent GBM setting. **Methods:** Eligible patients (pts) had progressive GBM; up to 1 chemotherapy regimen was allowed for recurrent disease. Following a 16 pt phase I dose escalation trial that established Bev 10 mg/kg every 2 weeks in combination with dasatinib 100 mg PO bid as the phase II dose of the combination, the randomized placebo-controlled phase II portion of the trial was initiated. The study followed a 2:1 randomization procedure with 85% power to detect a 20% difference in progression-free survival at 6 months (mo) (primary endpoint) between the two arms, and a type I error rate of 0.15 **Results:** This analysis includes 121 evaluable patients. Median follow-up was 6.8 mo for Arm A (Bev/Dasatinib, N = 83 pts), and 7.8 mo for Arm B (Bev/placebo, N = 38 pts). Although a higher percentage of Arm A patients were progression free at 6 mo, (27.16% vs 18.42%), this difference did not reach statistical significance (p = 0.30). There was no significant difference in OS (7.2 mo vs 7.9 mo; HR 0.86, 95% CI 0.56-1.31, p = 0.48). Response rate was 18.3% in Arm A and 26.5% in Arm B (p = 0.48). The overall incidence of grade 3+ hematologic and non-hematologic toxicity was comparable in Arms A and B (19.3% vs 16.7% for hematologic toxicity and 45% vs 43.4% for non-hematologic toxicity). Grade 2+ treatment-related hypophosphatemia and diarrhea were more common in the dasatinib arm than in the placebo arm (21.7 vs 5.3% and 19.3 vs 2.6%, respectively). **Conclusions:** The combination of the Src kinase inhibitor dasatinib with Bev did not improve the outcome of recurrent GBM pts as compared to single agent Bev. Ongoing correlative analysis in baseline tumor samples is exploring associations between sarc family kinase expression (c-Sarc, Lyn, c-Yes) and activation of downstream signaling pathways and outcome. Clinical trial information: NCT00892177.

2005 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

A randomized phase II trial of standard dose bevacizumab versus low dose bevacizumab plus lomustine (CCNU) in adults with recurrent glioblastoma. *First Author: Shiao-Pei S. Weathers, The University of Texas MD Anderson Cancer Center, Brain and Spine Center, Houston, TX*

Background: Antiangiogenic therapy can rapidly reduce vascular permeability, but high doses of bevacizumab (BEV) may induce selective pressure to promote resistance. This trial evaluated the efficacy of low dose BEV in combination with lomustine (CCNU) compared to standard dose BEV in patients with recurrent glioblastoma. **Methods:** Eligibility criteria included age > 18 yrs with recurrent glioblastoma after temozolomide chemoradiotherapy. Patients were stratified by age, KPS, $1^{st}/2^{nd}/3^{rd}$ recurrence, and scheduled surgery and randomized to BEV 5 mg/kg every 3 weeks plus CCNU 90 mg/m^2 every 6 weeks or BEV 10 mg/kg every 2 weeks. The primary objective was progression free survival (PFS) with secondary objectives of radiographic response (RR), 6 month progression-free survival (PFS-6), overall survival (OS), time to progression (TTP), and safety. **Results:** 70 of 82 patients accrued were randomized and 68 were treated from 2010-2014. Median follow-up was 30.5 months. At the time of this analysis, 62 patients had progressed or died. For 68 evaluable patients, median PFS was not significantly longer in the BEV + CCNU arm (4.34 months, CI: 2.96-8.34) compared to the BEV alone arm (4.11 months, CI: 2.69-5.55, p = 0.19). In patients with one recurrence (n = 24 and 23, respectively), there was a trend towards statistical significance in longer median PFS time in the BEV + CCNU arm (4.96 months, CI: 4.17-13.44) compared to the BEV alone arm (3.22 months CI: 2.5-6.01, p = 0.08). Median OS in patients with 1 recurrence on BEV + CCNU was longer (13.05 months, CI: 8-19.17) than those treated with BEV alone (8.79 months, CI: 6.42-20.22, p = 0.77) but this did not reach statistical significance. No unexpected grade 3 or 4 toxicities were observed. The trial was closed early due to futility. **Conclusions:** The combination of low dose BEV + CCNU is a safe and effective regimen. The study was not designed to test only at first recurrence, but in that subgroup there was a strong trend towards the combination supporting the findings of the recently published BELOB trial.With a larger sample size, a statistically significant difference in median PFS between treatments arms would likely have been observed. Clinical trial information: NCT01067469.

2006 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Radiotherapy in relation to temozolomide: Subgroup analysis of molecular markers of the randomized phase III study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033) in patients with a high risk low-grade glioma. *First Author: Brigitta G. Baumert, University of Bonn Medical Centre, Bonn, Germany*

Background: A subgroup analysis based on molecular markers of patients randomized between standard radiotherapy (RT) and temozolomide (TMZ) alone in the randomized EORTC22033 trial. **Methods:** A posthoc analysis of molecular markers was done for 407 patients (of 477 randomized). The IDH status was determined by immunohistochemistry for the most common IDH mutant, complemented by sequencing of *IDH1* and *2* for all negative cases. The status of 1p/19q codeletion was evaluated by LOH or FISH, the *MGMT*promoter methylation status on the HM450k beadchip (Illumina) and classified by MGMTSTP27. **Results:** IDH1 and IDH2 mutations were detected in 83% (327/392) and 2.8% (n = 9). Co-deletions of 1p/19q were identified in 33% (n = 117/357). MGMT was methylated in 90% (135/150), of which 86% were IDH mutant (128/140). For 318 patients the status for both IDH1/2 and 1p/19q codel was available: 269 (85%) were IDHmt, 104 (39%) IDHmt/codel and 49 (15%) IDHwt. Mutation of the IDH 1 or 2 (IDHmt) regardless of 1p/19q co-deletion was a positive prognostic factor. Exploratory analysis of these 318 patients showed that patients with IDHmt/non-codel tumors had a shorter PFS after treatment with TMZ than after RT (HR 1.86; 95% CI, 1.21-2.87; logrank p = 0.0043), while no difference was observed between these treatments for patients with IDHwt, and IDHmt/codel tumors. **Conclusions:** Subgroup analysis suggests that PFS is longer in patients with IDHmut/non-codel tumors when treated in first-line with RT compared to treatment with TMZ. With still only a few events no such difference is visible in 1p/19q co-deleted tumors. However, maturation of survival data is needed to derive more firm conclusions. Clinical trial information: NCT00182819.

	Progression-free survival				
Treatment	Patients	Observed Events	HR (95% CI)	P-Value	Median (95% CI) (Mths)
RT-IDHmt/codel	45	17	1.00	0.0000	61.6 (42.3, N)
RT-IDHwt	29	25	5.4 (2.9, 10.1)	0.0000	19.1 (11.3, 25.7)
RT- IDHmt/non-codel	89	37	1.1 (0.6, 2.0)	0.6655	55.4 (47.9, 65.9)
TMZ-IDHmt/codel	59	24	1.1 (0.6, 1.9)	0.8509	55.0 (37.9, N)
TMZ-IDHwt	20	15	3.1 (1.6, 6.3)	0.0013	23.7 (5.6, 42.3)
TMZ-IDHmt/non-codel	76	47	2.1 (1.2, 3.6)	0.0103	36.0 (28.4, 46.9)

2007 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Molecular classification of diffuse cerebral gliomas using genome- and transcriptome-wide profiling. *First Author: Michael Weller, Department of Neurology, University Hospital Zurich, Zurich, Switzerland*

Background: WHO grade II and III cerebral gliomas represent a major challenge for histological classification and clinical management. Here, we aimed to improve prognostically relevant patient stratification by characterizing genomic and transcriptional profiles in a prospective patient cohort of the German Glioma Network. **Methods:** We performed microarray-based genome- and transcriptome-wide molecular profiling of primary tumor samples from 137 patients with cerebral gliomas. Integrative bioinformatic analyses were employed to define molecular subgroups, which were then related to histology, molecular biomarkers, including isocitrate dehydrogenase 1 or 2 *(IDH1/2)* mutation, 1p/19q co-deletion and telomerase reverse transcriptase (*TERT)*promoter mutations, and patient outcome. **Results:** Genomic profiling identified five distinct glioma groups, including three *IDH1/2* mutant and two *IDH1/2* wild-type groups. Expression profiling revealed eight transcriptionally different tumor groups (five *IDH1/2* mutant, three *IDH1/2* wild-type), which were only partially linked to the genomic groups. Correlation of DNA-based molecular stratification without-come allowed for the definition of three major prognostic groups with characteristic genomic aberrations. The best prognosis was found in patients with *IDH1/2* mutant and 1p/19q co-deleted tumors. Patients with *IDH1/2* wild-type gliomas and glioblastoma-like genomic alterations, including gain of chromosome arm 7q (+7q), loss of chromosome arm 10q (-10q), *TERT* promoter mutation and oncogene amplification, displayed the worst outcome. Intermediate survival was seen in patients with *IDH1/2* mutant but 1p/19q intact, mostly astrocytic gliomas, and in patients with *IDH1/2* wild-type gliomas lacking the +7/-10q genotype and *TERT* promoter mutation. **Conclusions:** DNA-based molecular subgrouping stratified patients into prognostically distinct groups better than histological classification, whereas addition of gene expression data did not further improve prognostic stratification.

2008 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

The landscape and clonal architecture in lower grade glioma. *First Author: Hiromichi Suzuki, Department of Neurosurgery, Nagoya University School of Medicine, Nagoya Ctity, Japan*

Background: Lower grade gliomas (LGGs, WHO grade II/III gliomas) account for approximately one third of all gliomas. Although LGGs are typically slowly progressive, their clinical course is invariably indolent and most patients ultimately succumb to death. In contrast to glioblastoma, our knowledge about the genetic lesions and clonal evolution in LGG is still incomplete. **Methods:** To obtain a complete registry of gene mutations involved in LGG pathogenesis and their role in clonal evolution, we analyzed whole exome sequencing and/or targeted sequencing of 757 LGG cases from Japan and the Cancer Genome Atlas consortium. Clonal evolution in LGG was investigated using multi-time point/regional sampling in 14 cases with LGGs. **Results:** Massive parallel sequencing revealed LGGs were clearly grouped into three subgroups with or without IDH1/2 mutation and 1p/19q loss of heterozygous (LOH). Type I tumor with IDH1/2 mutation and 1p/19q LOH had a most favorable survival and harbored mutations in TERT promoter, CIC, FUBP1 and NOTCH1. Type II tumor with IDH1/2 mutant/1p19q intact subtype represented TP53 bialleleic inactivation and/or ATRX mutations. Type III tumor with IDH1/2 intact showed GBM-like mutation profile and poor prognosis. Multi regional/time-points sampling analysis supported mutational order and revealed a close correlation of regional heterogeneity with the history of clonal evolution, illustrating the way by which a tumor expands from its origin to surrounding regions, while increasing intratumor heterogeneity and spatially intermingling different evolutional branches in periphery. **Conclusions:** Our findings delineated the landscape of gene mutations in LGG. LGG had mutually exclusive mutational patterns with hierarchical order in discrete subtypes. LGG contiguously developed and generated heterogeneity through acquiring new mutations in a complex but ordered fashion.

2009 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

ReACT: Overall survival from a randomized phase II study of rindopepimut (CDX-110) plus bevacizumab in relapsed glioblastoma. *First Author: David A. Reardon, Dana-Farber Cancer Institute, Boston, MA*

Background: EGFRvIII, a constitutively active EGFR deletion driver mutation, is associated with poor long-term survival in glioblastoma (GB). The investigational vaccine rindopepimut consists of a peptide sequence unique to EGFRvIII conjugated to keyhole limpet hemocyanin (KLH), delivered intradermally with GM-CSF. Three phase II studies of rindopepimut in newly diagnosed, resected, EGFRvIII+ GB demonstrated encouraging progression-free survival (PFS), overall survival (OS) and safety profile. Compassionate use experience suggests that rindopepimut may also provide benefit in relapsed GB, particularly with agents such as bevacizumab (BV). **Methods:** In the Phase II "ReACT" study, BV-naïve pts in 1st or 2nd relapse with EGFRvIII+ GB were randomized 1:1 to BV plus double-blinded injection of rindopepimut or control (KLH). Endpoints: 6-month PFS (PFS6; primary), objective response rate (ORR), PFS, OS and safety. **Results:** Accrual is complete (n = 72); study follow-up continues (n = 30). Primary rindopepimut toxicity is Grade 1-2 injection site reaction. For rindopepimut+BV vs. KLH+BV (per investigator; RANO criteria): PFS6 = 27% (9/33) vs. 11% (4/35) (p = 0.048, 1-side chi-square test); ORR = 24% (7/29) vs. 17% (5/30). Central PFS/ORR assessment is underway. Median (95% CI) OS = 12.0 (9.7, -) vs. 8.8 (6.8, 11.4) months (HR = 0.47 [0.25, 0.91]; p = 0.0208), with 8 vs 4 pts progression-free on study. OS analyses favor rindopepimut including when adjusted for various prognostic factors. Rindopepimut induced robust anti-EGFRvIII titers (1:12,800 to 1:6,553,600) in 80% of pts. Rapid anti-EGFRvIII titer generation was associated with prolonged OS (HR = 0.47 [0.18, 1.27]; p = 0.128) within the rindopepimut arm, and was most frequent in pts with KPS ≥ 90 (odds ratio = 9.75; p = 0.007). Additional evaluation of humoral response quality and HLA typing vs. outcome are underway. In an additional cohort of BV-exposed pts (n = 53), four pts experienced objective tumor response. **Conclusions:** These near-final data show that rindopepimut induces potent EGFRvIII-specific immune response and tumor regression, and appears to significantly prolong survival when administered with BV, in pts with relapsed GB. Clinical trial information: NCT01498328.

2010 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Phase II multicenter study of gene mediated cytotoxic immunotherapy as adjuvant to surgical resection for newly diagnosed malignant glioma. *First Author: Laura K. Aguilar, Advantagene Inc, Auburndale, MA*

Background: New therapies are desperately needed for malignant gliomas since aggressive standard of care (SOC) treatment with surgery, radiation, and temozolomide leads to median survival of less than 15 months. Gene Mediated Cytotoxic Immunotherapy (GMCI) generates a polyvalent anti-tumor immune response through local delivery of aglatimagene besadenovec (AdV-tk) plus prodrug, synergizing with SOC to improve patient outcomes. **Methods:** A Phase II open-label multicenter trial was designed to assess safety and overall survival (OS) after GMCI+SOC compared to a concurrent matched control group meeting protocol criteria and SOC at an institution not active in the treatment trial. AdV-tk was injected into the resection bed followed by oral valacyclovir for 14 days. Primary efficacy analysis was planned on the null hypothesis of no improvement in the 2-year survival over the SOC group with planned subset analysis of significant disease prognostic factors. **Results:** From 2006 to 2010, 48 patients completed SOC+GMCI and 134 SOC in the matched cohort. There were no dose-limiting toxicities. Fever, fatigue, and headache were the most common GMCI-related symptoms. Median OS increased by 3.6 months, from 13.5 for SOC to 17.1 months for GMCI+SOC (p = 0.0417). Survival at 1- 2- and 3-years increased from 57%, 22%, and 8% to 67%, 35%, and 19%, respectively. The improvement was mostly in patients that underwent gross total resection: median OS increased from 16.9 to 25 months (p = 0.0492); 1- 2- and 3-year survival rates from 64%, 28% and 6% to 90%, 53% and 32%. **Conclusions:** GMCI can be safely combined with SOC in newly diagnosed malignant gliomas. Survival rates compared favorably to historical reports and a matched control group. Survival outcomes were significantly improved in patients with minimal residual disease after total resection. The 2-year survival rate met the planned statistical threshold for significance. No significant differences were observed for subtotal resections. This is the first study to demonstrate a correlation between maximum debulking and a survival advantage using immunotherapy. These data strongly support further evaluation of GMCI for malignant gliomas. Clinical trial information: NCT00589875.

2011 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Newly diagnosed glioblastoma patients treated with an autologous heat shock protein peptide vaccine: PD-L1 expression and response to therapy. *First Author: Orin Bloch, Northwestern University, Chicago, IL*

Background: Standard therapy for glioblastoma (GBM) consists of surgical resection followed by concurrent chemo and radiotherapy with a median overall survival of 16 months. In this phase II, single arm study, addition of an autologous heat shock protein peptide vaccine was evaluated for newly diagnosed GBM. Expression of PD-L1 on peripheral monocytes has been shown to be elevated in GBM patients and was evaluated as a predictor of survival. **Methods:** Adult patients with GBM underwent surgical resection followed by chemoradiotherapy. Vaccine was generated from tissue obtained at surgery. Key eligibility criteria included ≥ 90% tumor resection and collection of sufficient tumor tissue to generate at least four 25 μg doses of vaccine. Within 5 weeks of completing radiotherapy, patients received weekly vaccinations, followed by adjuvant temozolomide with monthly vaccinations until depletion of vaccine or tumor progression. The primary endpoint was overall survival. Relative PD-L1 expression on circulating monocytes was measured from peripheral blood obtained at surgery. **Results:** A total of 46 patients from eight centers received the vaccine in addition to standard therapy. Median progression-free survival was 17.8 months (95% Confidence Interval [CI], 11.3-21.6) and median overall survival was 23.8 months (95% CI, 19.8-30.2). The vaccine was well-tolerated with no severe (grade 3 or 4) events attributed to vaccination. The median overall survival for patients with high PD-L1 expression (above the median, 54.5% of monocytes) was 18.0 months (95% CI, 10.0 – 23.3) as compared to 44.7 months (95% CI not calcuable) for low PD-L1 expressors (hazard ratio for death 3.35; 95% CI, 1.36 – 8.23; p = 0.003). A multivariate proportional hazards model revealed MGMT methylation status and PD-L1 expression as the greatest independent predictors of survival. **Conclusions:** Vaccination with autologous tumor-derived heat shock proteins improves survival compared to standard therapy for newly diagnosed GBM. Systemic immunosuppression driven by peripheral monocyte expression of PD-L1 is a previously unidentified factor that may mitigate vaccine efficacy. Clinical trial information: NCT00905060.

2012 Poster Discussion Session; Displayed in Poster Session (Board #1), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Brain Tumor Trials Collaborative Bayesian Adaptive Randomized Phase II trial of bevacizumab plus vorinostat versus bevacizumab alone in adults with recurrent glioblastoma (BTTC-1102). *First Author: Vinay K. Puduvalli, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Bevacizumab (Bev) is approved in the US for patients (pts) with recurrent glioblastoma based on response rate. However, adaptive resistance to antiangiogenic agents can result in tumor recurrence. Deacetylase inhibitors such as vorinostat (Vor) have pleotropic effects against several pathways potentially relevant to adaptive resistance to Bev. **Methods:** We conducted a phase II multicenter trial with Bayesian adaptive randomization of patients to Bev alone or Bev+Vor with a primary endpoint of progression-free survival (PFS) and secondary end points of overall survival (OS) and patient-reported symptoms using the M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT). Eligible patients were adults ($\geq$ 18y) with histologically confirmed GB who had recurrent disease after prior radiation and temozolomide therapy, KPS $\geq$ 60, and no prior Bev or HDAC inhibitors. **Results:** Of the 90 pts (Bev+V: 49, Bev: 41) enrolled between Oct 2012 and Oct 2014, 83 were evaluable for the primary endpoint (Bev+V: 46, Bev: 37). MDASI-BT scores were available for 81 pts. There was no significant difference between the two arms in median PFS (4.2 vs.3.6 months, p = 0.53) or median OS (8.3 vs. 7.0 months, p = 0.93). Analysis of the MDASI-BT scores showed no significant differences between the two arms in overall symptom burden or interference (p = 0.48, 0.71 respectively). Overall, 61 pts had died by the time of analysis (Bev+V: 35, Bev: 26) with one treatment related death due to pulmonary embolism. Toxicity $\geq$ grade 3 included hypertension (n = 17), neurological changes (n = 2), infections (n = 2), wound dehiscence (n = 2), DVT/PE (n = 2), and colonic perforation (n = 1). **Conclusions:** In this trial, Bev+Vor did not yield an improved PFS or OS or clinical benefit in terms of reduced symptom burden compared with Bev alone in patients with recurrent GB and does not warrant further investigation. To our knowledge, this trial represents the first prospective Bayesian adaptive randomized therapeutic study against gliomas and demonstrates the feasibility of conducting studies with adaptive trial designs in a multicenter setting. Clinical trial information: NCT01266031.

2013 Poster Discussion Session; Displayed in Poster Session (Board #2), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Randomized, placebo-controlled, phase II study of dasatinib with standard chemo-radiotherapy for newly diagnosed glioblastoma (GBM), NCCTG N0877 (Alliance). *First Author: Nadia N. Laack, Mayo Clinic, Rochester, MN*

Background: Dasatinib is a potent oral ATP competitive multi-targeted kinase inhibitor of multiple members of the Src kinase family known to be involved in gliomagenesis, tumor invasion, and radiosensitivity. N0877 is a phase I/randomized phase II trial evaluating the combination of dasatinib, radiation (RT) and temozolomide (TMZ) in newly diagnosed GBM. **Methods:** Following a 13 patient phase I dose escalation trial which established the MTD and phase II dose of dasatinib to be 150 mg PO daily when given with RT and TMZ, the randomized placebo-controlled phase II portion of the trial was initiated. The study followed a 2:1 randomization procedure with 85% power to detect a hazard ratio of 1.6 or higher in overall survival (OS) between the two arms and a type I error rate of 0.10. Dasatinib or placebo was given orally for 42 days, beginning with the first day of RT (total dose 60 Gy) and first dose of TMZ (75 mg/m2/d). Following a 24 - 42 day rest, patients then received 6 cycles (28 day cycles) of dasatinib or placebo (days 1-28) and TMZ (days 1-5). At the completion of 6 cycles of TMZ + dasatinib/placebo, patients continued on dasatinib/placebo only (28 day cycles) until progressive disease. **Results:** Data from 187 of 196 patients enrolled were available for analysis. Median follow-up was 12.6m for dasatinib (N = 133 pts), and 14m for placebo (N = 63 pts). There was no significant difference in PFS between dasatinib and placebo (6.7m vs 7.8m, respectively; HR 0.80 favoring placebo, 95% CI 0.57-1.1, p = 0.18) or OS (15.5m vs 20.6m; HR 0.71 favoring placebo, 95% CI 0.46-1.1, p = 0.12). Response rate (CR+PR) was 10.5% for dasatinib and 8.3% in placebo arm (p = 0.77). The overall incidence of grade 3 or higher hematologic toxicity was lower in the dasatinib arm (43.9% vs 68.8%, p = 0.0012) primarily due to lower rates of lymphopenia. Grade 3 or higher non-hematologic toxicities were similar between arms (53.8% vs 41.3%, p = 0.1384). Analysis by MGMT status will be forthcoming. **Conclusions:** The combination of the Src kinase inhibitor dasatinib with standard RT/TMZ did not improve the outcome of newly diagnosed GBM patients as compared to standard therapy alone. Clinical trial information: NCT00869401.

2014 Poster Discussion Session; Displayed in Poster Session (Board #3), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A phase II study of galunisertib monotherapy or galunisertib plus lomustine compared to lomustine monotherapy in recurrent glioblastoma. *First Author: Alba Ariela Brandes, Department of Medical Oncology, Azienda USL, Bologna, Italy*

Background: Based on preclinical data suggesting an additive antitumor effect of galunisertib (G), a TGF-β RI kinase inhibitor, and lomustine (L), this study evaluated the activity of G+L in patients (pts) with recurrent glioblastoma (GB). We report safety, population pharmacokinetics (PK), and efficacy final results. **Methods:** G (300 mg/day) was given as intermittent dosing (each cycle = 14 days on/14 days off). L was given on day 7 of cycle 1 every 6 weeks as approved. Pts received L with either G or placebo (P) thereby blinding for G; pts who received G alone were unblinded (randomization 2:1:1). Primary objective was overall survival (OS) assessed by Bayesian analysis incorporating prior clinical data for L. Secondary objectives were safety, progression-free survival (PFS), tumor response assessed by Response Assessment in Neurooncology (RANO) criteria, and population PK analysis. **Results:** 158 pts were randomized to treatment: G+L (N = 79), G alone (N = 39), P+L (N = 40). Study included, male (64.6%), Caucasian (75.3%); mean age 57 years, 63% had ECOG PS 1, 93.7% had primary GB. The median number of cycles for G was 2 in all 3 arms. G PK was not altered by co-administration with L. G was rapidly absorbed and had median half-life of ~8h with moderate between-patient variability on exposure (CV 41%). The median OS (95% CI) for G+L was 6.7 months (5.3-8.5), [HR (G+L):(L+P) 1.13 (0.8-1.7)], 8.0 months (5.7-11.7) for G alone, [HR (G):(L+P) 0.93 (0.6-1.5)], 7.5 months (5.6-10.3) for L+P control arm. Success criteria for superiority of G+L to L+P was not met [P (HR < 1) < 85%]. The median PFS in months (95% CI) were 1.8 (1.7-1.8) for G+L, 1.8 (1.6-3.0) for G, and 1.9 (1.7-1.9) for P+L. Best overall response according to RANO included 1 CR in G+L and 2 PR in G. 34 pts had Grade 3/4 adverse events (AEs) related to study drug, 24% G+L, 13% G, 26% L+P. The most common drug-related Grade 3/4 AEs (G+L, G, L+P) were: thrombocytopenia (8%, 0%, 13%); lymphopenia (9%, 3%, 0%); neutropenia (8%, 0%, 5%). **Conclusions:** The observed efficacy outcomes including OS and PFS were similar in all 3 treatment arms suggesting no efficacy improvement when adding G to L. The treatment was safe and well tolerated in all arms. Clinical trial information: NCT01582269.

2015 Poster Discussion Session; Displayed in Poster Session (Board #4), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Onartuzumab plus bevacizumab versus placebo plus bevacizumab in recurrent glioblastoma (GBM): HGF and MGMT biomarker data. *First Author: Timothy Francis Cloughesy, UCLA, Los Angeles, CA*

Background: The phase II GO27819 study assessed the monovalent MET inhibitor, onartuzumab, plus the anti-VEGF antibody, bevacizumab (O+B) versus placebo plus bevacizumab (P+B) in recurrent GBM. Exploratory univariate biomarker analyses correlated efficacy with levels of the MET ligand HGF and MGMT methylation. **Methods:** GBM patients (pts) at first recurrence after chemoradiation were randomized 1:1 to receive O (15 mg/kg, q3w) + B (15 mg/kg, q3w) or P+B until progression. Primary endpoint: progression-free survival (PFS); secondary endpoints: overall survival (OS), objective response rate (ORR), safety; exploratory endpoint: biomarker analysis. Baseline tumor HGF levels were quantitatively assessed by cobas PCR; MGMT methylation was assessed by Quantitative Methylation Specific PCR. **Results:** In the ITT group (64 O+B, 65 P+B) no difference in PFS, OS or ORR was seen between the arms. A total of 119 pts (58 O+B, 61 P+B) had HGF-PCR results and 110 (56 O+B, 54 P+B) had MGMT data. Assessing the P+B arm only showed that GBM pts may have a worse prognosis if they have high expression of HGF-PCR (PFS HR 1.67; OS HR 1.65) or unmethylated MGMT (PFS HR 3.19; OS HR 3.39). In pts with HGF-PCR expression in the upper 25%, longer PFS (HR 0.37, 95% CI 0.16–0.86; p = 0.0201) and OS (HR 0.29, 95% CI 0.08–1.06; p = 0.0458) were seen with O+B (n = 14) v P+B (n = 16). These pts also had higher ORR with O+B (35.7% v 0%, p = 0.014). Shorter PFS (HR 1.39, 95% CI 0.87–2.20; p = 0.1589) and OS (HR 1.86, 95% CI 1.03–3.36; p = 0.0381) were seen with O+B (n = 44) v P+B (n = 45) in the lower 75% HGF-PCR group. Of the pts analyzed for MGMT methylation, 57.3% had unmethylated MGMT. These pts had higher ORR (15.6% v 8%) and extended PFS (HR 0.46, 95% CI 0.25–0.84; p = 0.0108) and OS (HR 0.53, 95% CI 0.26–1.10; p = 0.0836) with O+B v P+B. Pts with methylated MGMT had shorter PFS (HR 1.52, 95% CI 0.75–3.08; p = 0.2440) and OS (HR 3.18, 95% CI 1.19–9.51; p = 0.0150) with O+B v P+B. **Conclusions:** While the GO27819 ITT results showed no efficacy benefit for O+B, these exploratory data suggest that high HGF levels and unmethylated MGMT are prognostic in GBM and may be predictive of response to onartuzumab. Further research on onartuzumab in these subgroups may be warranted. NCT01632228. Clinical trial information: NCT01632228.

2016 Poster Discussion Session; Displayed in Poster Session (Board #5), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase I study of ABT-414 mono- or combination therapy with temozolomide (TMZ) in recurrent glioblastoma (GBM). *First Author: Hui K. Gan, Austin Health and Ludwig Institute for Cancer Research, Melbourne, Australia*

Background: GBM remains almost universally fatal and new therapies are needed. The epidermal growth factor receptor (EGFR) is a key oncogenic target. ABT-414, an antibody-drug conjugate with a toxic payload (monomethylauristatin F) targeted to activated EGFR, showed efficacy in preclinical models. We report the data of patients (pts) with recurrent GBM (Arms B + C) from an ongoing phase 1, open-label, 3-arm study (NCT01800695). **Methods:** Eligible pts (≥ 18 years) had recurrent supratentorial GBM and KPS ≥ 70. ABT-414 was given i.v. every 2 weeks combined with TMZ re-challenge (150–200 mg/m^2 days 1–5 q28; Arm B) or as monotherapy (Arm C). ABT-414 doses were escalated using a modified continual reassessment method. Primary objectives were safety, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of ABT-414; secondary objectives included antitumor activity. **Results:** As of Jan 2015, accrual included 18 pts in Arm B treated in 4 dose groups (0.5, 1.0, 1.25, 1.5 mg/kg) and 28 pts in Arm C treated at 1.25 mg/kg. Median age was 51/57 years (Arms B/C), 50%/50% were male, 56%/75% had KPS ≥ 80, and 11/7 pts had amplified EGFR. Treatment-emergent adverse events (AEs) occurring in ≥ 25% of pts either in Arm B or C were blurred vision (n = 11/15), fatigue (n = 6/10), foreign body sensation in the eyes (n = 8/5), photophobia (n = 5/7), nausea (n = 9/2), constipation (n = 5/1), and GGT increase (n = 5/1). Grade 3/4 AEs in ≥ 10% of Arm B or C pts were keratitis (n = 1/3), GGT increase (n = 3/0), fatigue (n = 2/0), and thrombocytopenia (n = 2/0). Dose-limiting toxicities in Arm B were corneal deposits and GGT increase (n = 1 each); none occurred in Arm C during dose escalation. ABT-414 MTD was 1.5 mg/kg in Arm B and 1.25 mg/kg in Arm C; RP2D is 1.25 mg/kg for both arms. Best objective responses were complete response (CR) in 1 pt and partial responses (PR) in 4 pts in Arm B, and 1 CR and 1 PR in Arm C. EGFR amplification was found in all pts with confirmed responses. Confirmed responses were durable, ranging from 5–16 months. **Conclusions:** The ABT-414 RP2D is 1.25 mg/kg for monotherapy or combined with TMZ. The unique ABT-414 safety profile included ocular AEs. ABT-414 appears to have antitumor activity in recurrent GBM pts, particularly those with amplified EGFR. Clinical trial information: NCT01800695.

2017 Poster Discussion Session; Displayed in Poster Session (Board #6), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Defining the cutoff value of MGMT gene promoter methylation and its predictive capacity. *First Author: Andrea Rocca, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*

Background: Adult glioblastoma (GBM) is the most common type of malignant primary brain tumor. Despite advances in treatment, median survival is between 12 and 15 months. Standard care is concomitant radiotherapy (RT)/chemotherapy (CT) and adjuvant temozolomide (TMZ) for 6 cycles. At progression, subsequent treatments are at the discretion of the patient's physician. MGMT gene promoter methylation status is acknowledged worldwide as a predictive marker. When MGMT promoter values fall into a "methylated" range, a better response to TMZ treatment is expected. **Methods:** We retrospectively analyzed data from 105 patients with GBM treated from 2011 to 2014 within the oncology network of the wide catchment area of Romagna, Italy. MGMT promoter methylation status was determined by analyzing 10 CpG islands by pyrosequencing. We evaluated whether variability in the methylation profile of each patient can influence the predictive capacity of MGMT promoter methylation and also aimed to identify the best cutoff value. **Results:** All patients were treated by RT followed by TMZ. MGMT promoter methylation status was classified into three types: unmethylated 0 – 9%, methylated 10 – 29% and methylated 30 - 100%. Statistical analysis showed that an assumed methylation cut-off of 9% led to an overestimation of responders. All of the patients in the 10–29% methylation group relapsed before the 18-month evaluation. Patients with a methylation status > 30% showed a median overall survival (OS) of 25.2 months compared to 15.2 months in all other patients, indicating that this is the best methylation cut-off. We also analyzed the methylation status of each CpG island in patients' profiles but, despite observing a great variability among individual profiles, did not find any correlation between single CpG island values and relapse or death (Wilcoxon test and ROC curves). **Conclusions:** Our results did not highlight an impact of specific CpG island methylation status on the predictive value of MGMT. The predictive role of MGMT promoter methylation was maintained only when 30% was used as cut-off value.

2018 Poster Discussion Session; Displayed in Poster Session (Board #7), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Impact of bevacizumab added to temozolomide-chemoradiation on time to health-related quality of life deterioration in unresectable glioblastoma: Results of a phase II randomized clinical trial. *First Author: Franck Bonnetain, Methodology and Quality of Life Unit, Department of Oncology, EA 3181, University Hospital of Besançon; French National Platform Quality of Life and Cancer, Besançon, France*

Background: Two clinical trials investigating the addition of bevacizumab (BEV) to TMZ treatment (Chinot et al., NEJM 2014; Gilbert et al., NEJM 2014) for unresectable glioblastoma (GB) highlighted an improvement of progression-free survival (PFS) but no effect on overall survival. Health-related quality of life (HRQoL) results were divergent and compromised the conclusion about clinical benefit of bevacizumab. A phase II clinical trial evaluated BEV and irinotecan (IRI) in addition to TMZ-based chemoradiation for unresectable GB (Chauffert et al., Annals of Oncology 2014) was conducted. The primary objective 6-month PFS rate from 50% to 66% was not reached. This present study focuses on the HRQoL analysis (secondary endpoint). **Methods:** EORTC QLQ-C30 and its BN20 brain cancer module were used at baseline, during treatment and every 4 weeks until progression. Time until definitive HRQoL score deterioration (TUDD) was used as a modality of longitudinal HRQoL analyses (Bonnetain et al., EJC 2010), with a 10-point Minimal Clinically Important Difference including or not death as an event. TUDD was estimated with the Kaplan-Meier method. Cox model was used to estimate Hazard Ratios (HR) and its 95% confidence interval (CI). Multivariate Cox model investigated factors associated with TUDD. **Results:** Among the 134 patients included from 2009 to 2011, 101 patients (75%) filled the baseline HRQoL questionnaires (51 in BEV/IRI arm, 50 in TMZ arm). For TUDD or death, patients in BEV/IRI arm presented a longer TUDD than those of TMZ arm for 10/15 dimensions of the QLQ-C30 and 10/11 dimensions of the BN20. As an example, patients in BEV/IRI arm presented a longer TUDD of motor dysfunction than those of TMZ arm (Median 4.6 months (95%CI 3.2-9.4) for BEV/IRI vs. 3.3 (95%CI 2.8-6.7) for TMZ, HR = 0.70 (95%CI 0.45-1.08)). A sensorial deficit is associated with shorter TUDD of Weakness of legs dimension or death (HR = 2.74 (95%CI 1.41-5.30). **Conclusions:** Patients in BEV/IRI arm presented a longer TUDD than those of the TMZ arm. These HRQoL results are consistent to those obtained with AVAGLIO trial suggesting HRQoL benefit for patients with BEV. Clinical trial information: 2008-002775-28.

2019 Poster Discussion Session; Displayed in Poster Session (Board #8), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Outcome of neurofibromatosis type 1 patients treated with first line vinblastine for optic pathway gliomas: A Canadian multicenter study. *First Author: Alvaro Lassaletta, The Hospital for Sick Children, Toronto, ON, Canada*

Background: To date, the first line chemotherapy treatment in the majority of countries for children with NF-1 and OPG is vincristine + carboplatin. Toxicity of this regimen consists mostly in neuropathy, allergic reactions, and hearing loss. Vinblastine has shown promising activity in a phase II study in children with recurrent/refractory low grade glioma (LGG). The aim of this study was to assess the activity of vinblastine in chemotherapy naïve children, and to assess the toxicity profile. **Methods:** Patients < 18 years old with unresectable or progressive LGG were eligible if they had not received any previous treatment with chemotherapy or radiation. Vinblastine was administered weekly at a dose of 6 mg/m2 over a period of 70 weeks. Patients who showed progression on 2 consecutive imaging studies or evidence of clinical progression were removed from treatment. **Results:** Overall, the study enrolled 54 patients with LGG. A total of 13 patients (24.1%) had NF-1. Patients with NF-1were younger at diagnosis: median age 3.84 y (range, 1.74-16.36 y) vs. 7 years in non-NF-1. Tumor location in all NF-1 patients was the optic pathway. Treatment was very well tolerated, however, 5 patients (38%) needed dose reductions. Most common toxicity was hematological: only 1 patient who experienced grade 3+ neutropenia (vs. 10 patients non-NF1). There were only 2 episodes of febrile neutropenia, no RBC transfusions and no toxic death. Best response to chemotherapy was assessed centrally by an independent radiologist: 2 PR, 1 MR, 8 SD, and 2 PD, for a response rate of 23.1%. At a median follow-up of 5.37 years (3.45 – 6.57 years): Only two NF-1patients had progression. Five year progression free survival (PFS) was 85.1± 9.7% (vs. 42±7,9% for all non-NF1, p = 0.01; and 41.7±14% for non-NF1 with OPG, p = 0.01). None of the NF1 patients received radiation (0 vs. 6 patients non-NF1). No patients died of progression (0 vs. 3 patients non-NF1). **Conclusions:** Weekly vinblastine is well tolerated and can be used in NF-1 children with OPG as first line chemotherapy with good results. The toxicity profile is lower than with other chemotherapies, offering a better quality of life to these patients. Clinical trial information: NCT00575796.

2020 Poster Discussion Session; Displayed in Poster Session (Board #9), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A multi-institutional prospective observational study of stereotactic radiosurgery (SRS) for patients with multiple brain metastases (BMs): Updated results of the JLGK0901 Study—Long-term results of irradiation-related complications and neurocognitive function (NCF). *First Author: Masaaki Yamamoto, Katsuta Hospital Mito GammaHouse, Hitachi-Naka, Japan*

Background: The JLGK0901 study (UMIN ID; 000001812) showed the non-inferiority of SRS alone as initial treatment for patients with 5-10 BMs as compared to those with 2-4 in terms of overall survival as well as most secondary endpoints (Lancet Oncol 2014;15:387-95). However, a study weakness was that observation periods were not long enough to allow confirmation of the long-term safety of SRS alone in patients with 5-10 BMs. **Methods:** This was a prospective observational study of SRS-treated patients with 1-10 newly-diagnosed BMs enrolled at 23 facilities between 3-1-2009, and 2-15-2012. **Results:** The 1194 eligible patients (471 females, 723 males, mean age; 66 [range; 30-91] years), enrolled from March 2009 to February 2012, were categorized into three tumor number groups, i.e., A; 1 (455), B; 2-4 (531) and C; 5-10 (208). During observation periods ranging from 0.3 to 67.5 (median; 12.0, IQR; 5.8-26.5) months as of the end of 2014, SRS-induced complications occurred in 145 patients (12.1%) with the median post-SRS period being 9.3 (IQR; 4.1-17.4) months; 46, 54, 29, 11, and 5 for CTCAE grades 1, 2, 3, 4, and 5, respectively. Cumulative incidences of complications determined with a competing risk analysis (group B vs C) were 8.3% vs 5.8%, 10.9% vs 10.6%, 11.3% vs 12.1% and 12.2% vs 12.9% at the 12th, 24th, 36th and 48th post-SRS months, respectively (HR; 1.052, 95% CI; 0.666-1.662, p = 0.829). NCF maintenance (MMSE decrease < 3 from baseline) rates of groups A/B/C were 92%/91%/89% (p = 0.69), 90%/96%/88% (p = 0.25), 94%/92%/100% (p = 0.75) and 94%/92%/100% (p = 0.51) at the 12th, 24th, 36th and 48th post-SRS months, respectively. These statistical results were confirmed to be similar even with missing data analyses. **Conclusions:** There were no significant differences in the incidences of post-SRS complications and NCF maintenance between groups B and C. We conclude that the already-reported non-inferiority hypothesis of SRS alone for patients with 5-10 versus 2-4 BMs gains further support, in terms of treatment safety, from this longer-term follow-up study. Clinical trial information: 000001812.

2021 Poster Discussion Session; Displayed in Poster Session (Board #10), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Results of a randomized, global, multi-center study of whole-brain radiation therapy (WBRT) plus veliparib or placebo in patients (pts) with brain metastases (BM) from non-small cell lung cancer (NSCLC). *First Author: Pierre Chabot, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada*

Background: Veliparib (V) is a potent, orally bioavailable PARP inhibitor that crosses the blood brain barrier. Phase 2 trials in BRCA pts as monotherapy or in unselected pts in combination with platinum-based chemotherapy have demonstrated evidence of efficacy. V plus radiation has shown promising efficacy in preclinical models and clinically in combination with WBRT. **Methods:** Pts were randomized 1:1:1 to WBRT plus V 50 mg BID (V50), V 200 mg BID (V200), or P BID. Treatment began within 28 days (d) of diagnosis. Pts received 30 Gray WBRT in 10 fractions. V50, V200, or P BID was self-administered starting on d 1 of WBRT and continuing until 1 d after completion. The primary endpoint was overall survival (OS). Survival was assessed at 2 month (m) intervals for 6 m then every 3 m ($\geq$36 m). Pts who received $\geq$1 dose were included in the safety analyses; AEs were compared across arms using Fisher's exact test. **Results:** 307 pts were randomized. OS, intracranial response rate, and time to clinical or radiographic progression were not statistically significantly different between any of the V arms and the P arm. There were no differences in all grade adverse drug reactions (ADRs) across arms and a modest improvement in grade 3/4 AEs in the V arms. **Conclusions:** Although preclinical and early clinical data suggested that V might synergize with radiotherapy, there was no difference in multiple study endpoints between V50 or V200 and P in this setting. Safety parameters observed in the V arms were generally similar to the P arm; no new safety signals of V were identified. Clinical trial information: NCT01657799.

	P N=102[a]	V50 N=103	V200 N=102
Median age, years	60	60	62
Sex, n Male	56	61	66
Graded Prognostic Assessment (GPA), n ≤2.5	91	91	92
Median OS, d (95% CI)	185 (137–251)	209 (169–264)	209 (138–255)
Objective Response Rate, %	41.2	36.9	42.2
Median time to clinical BM progression per event review board, d (95%CI)	348 (216–NR)	286 (192–NR)	255 (204–342)
Median time to radiographic BM progression per central imaging center, d (95%CI)	259 (184–NR)	226 (147–360)	224 (137–358)
All ADRs, %	37	37	40
Gr 3/4 AEs, %	43	28 (p=.040)	26 (p=.012)

[a]1 not dosed or included in the safety analysis; NR, not reached.

2022 Poster Session (Board #11), Mon, 1:15 PM-4:45 PM

A phase II study of temozolomide in the treatment of adult patients with supratentorial low-grade glioma. *First Author: Michael Traut Wahl, UC San Francisco, San Francisco, CA*

Background: Optimal adjuvant management of low-grade gliomas (LGGs) remains controversial. Radiotherapy has been shown to improve progression-free survival compared to observation, but carries the potential for substantial late toxicity. In an effort to delay or obviate the need for radiation, there has been increasing interest in the use of adjuvant chemotherapy in LGGs. However, there is a dearth of prospective studies with long-term follow-up evaluating the efficacy of adjuvant chemotherapy without radiation in patients with newly diagnosed LGGs. **Methods:** Patients over the age of 18 with histologically proven supratentorial LGG (WHO grade II) who underwent subtotal resection or biopsy were eligible for enrollment. Daily temozolomide (TMZ) was administered at 200 mg/m^2 for 5 days, and repeated every 28 days for up to 12 cycles or until disease progression. Patients were assessed for radiographic response and progression with MRIs every two months during and after treatment. The primary outcome was objective radiographic response rate; secondary outcomes included progression-free and overall survival. **Results:** 120 patients were enrolled in the trial (57 oligodendrogliomas, 20 oligoastrocytomas, 43 astrocytomas), with a median follow-up of 6.9 years. Objective responses were seen in 7 patients (6%), and 86% demonstrated stable or improved disease during treatment with TMZ. Median progression-free survival was 4.2 years, and median overall survival was 9.7 years. Univariate analysis demonstrated oligodendroglioma histology (p = 0.02), subtotal resection (p = 0.009) and lack of tumor crossing midline ($p < 0.001$) were associated with improved overall survival. Treatment was well tolerated with minimal toxicity. **Conclusions:** In this high-risk cohort of newly diagnosed LGGs undergoing subtotal resection or biopsy, adjuvant TMZ alone achieved progression-free survival comparable to that seen in similar cohorts treated with adjuvant radiation. TMZ was very well tolerated, and could be considered as adjuvant therapy in appropriately selected patients. Work is ongoing to determine the demographic, pathologic and molecular characteristics of patients who are optimal candidates for adjuvant TMZ. Clinical trial information: NCT00313729.

2023 Poster Session (Board #12), Mon, 1:15 PM-4:45 PM

Phase I/II study of dianhydrogalactitol in patients with recurrent malignant glioma. *First Author: Kent C. Shih, Tennessee Oncology, Nashville, TN*

Background: Glioblastoma multiforme (GBM) is the most common brain cancer. Front-line systemic therapy with temozolomide is often ineffective due to O^6-methylguanine-DNA-methyltransferase (MGMT)-mediated resistance. Dianhydrogalactitol (VAL-083) is a bi-functional DNA alkylating agent that crosses the blood-brain barrier and overcomes resistance to MGMT in vitro. The goal of this clinical trial is to determine an appropriate dose for phase III trials in refractory GBM. **Methods:** Open-label, single-arm phase I/II dose-escalation study in patients with histologically-confirmed GBM, previously treated with radiation and must have failed both bevacizumab and temozolomide, unless contraindicated. The study utilizes a 3+3 dose-escalation design. Patients receive VAL-083 IV on days 1, 2, and 3 of a 21-day cycle. Tumor response is assessed according to RANO criteria prior to every other 21-day treatment cycle. **Results:** 25 patients have been enrolled across 8 dose cohorts ranging from 1.5 to 50mg/m^2/d. A dose limiting toxicity consisting of grade 4 thrombocytopenia was observed at dose level 8 (50mg/m^2/d). The DLT-related symptoms resolved rapidly and spontaneously without concomitant treatment. Prior to this, other treatment related toxicities have been mild to moderate and included two grade 1 lymphopenias and one grade 1 thrombocytopenia. Maximum tolerated dose (MTD) will be determined based on 3+3 design. Three patients had a response (stable disease or partial response) reporting improved clinical signs (maximum response of 84 wks). Pharmacokinetic analyses show dose-dependent linear systemic exposure with a short plasma 1-2h terminal half-life; Cmax ranged from 1130–739 ng/mL (7.7–5.1μM) at 40mg/m^2/d. Compared to historical trials, the present regimen delivers substantively more drug by Cmax and dose intensity. A dose intensity of 25 mg/m^2/wk in combination with radiation was previously shown superior to radiation alone against GBM; a dose intensity of 50 mg/m^2/wk is achieved in the current trial. **Conclusions:** VAL-083 dosing may be limited by myelosuppression. The MTD will be studied in a Phase II expansion and possible phase III registration trial. Clinical trial information: NCT01478178.

2024 Poster Session (Board #13), Mon, 1:15 PM-4:45 PM

ACRIN 6684: Assessment of tumor hypoxia in newly diagnosed GBM using FMISO PET and MRI. *First Author: Elizabeth Robins Gerstner, Massachusetts General Hospital, Boston, MA*

Background: Tumor hypoxia is a potent mediator of treatment resistance because of the negative impact on the efficacy of radiation and associated poor tumor delivery of cytotoxic chemotherapy. We designed a multicenter study to evaluate if pre-treatment tumor hypoxia as measured by FMISO PET and abnormal tumor vascularity as assessed by MRI are associated with worse survival. **Methods**: Patients with newly diagnosed GBM who had residual enhancing or nonenhancing tumor by local MRI read after surgery were eligible. Patients were treated with standard RT and temozolomide alone or with an additional investigational agent. Prior to start of chemoRT, a PET scan was acquired 110min after FMISO injection and 3 blood draws were acquired to allow for calculation of tumor to blood ratios. MRIs were also performed and included standard anatomic sequences as well as perfusion (DSC) and permeability (DCE) imaging. Cox models tested the association of PET and MRI parameters with OS (primary endpoint) and PFS (secondary endpoint). ROC curve analyses examined whether these parameters could predict survival at 1 year. **Results**: Fifty patients from 11 centers were enrolled. Thirty-eight, 37 and 31 patients had evaluable FMISO PET scans, DSC imaging and DCE imaging, respectively. Median age was 57 (range 27-77). In the univariate model, higher peak SUV was associated with worse survival (HR 1.54, 95%CI 1.00-2.36, p = 0.048) as was mean K^{trans} (HR 1.17, 95%CI 1.02-1.34, p = 0.024) and median K^{trans} (HR 1.32, 95%CI 1.01-1.72, p = 0.045). After adjusting for age and enhancing tumor volume, only mean K^{trans} remained statistically significant. Higher median K^{trans}as well as normalized rCBV and rCBF were associated with shorter PFS. Max SUV, peak SUV, standardized rCBV and normalized rCBF were predictive of survival at 1 year. **Conclusions**: Higher baseline tumor hypoxia was associated with shorter survival, re-iterating the poor prognostic implications of tumor hypoxia. Increased vascular permeability and perfusion measurements at baseline were also associated with worse survival. These results raise the possibility that hypoxia may mediate treatment resistance in areas of tumor expected to have adequate delivery of intravascular therapies across the BBB. Clinical trial information: NCT00902577.

2025 Poster Session (Board #14), Mon, 1:15 PM-4:45 PM

Phase II study of tivozanib, an oral VEGFR inhibitor, in patients with recurrent glioblastoma. *First Author: Xuezhu Cai, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA*

Background: Tivozanib, an oral, pure VEGFR tyrosine kinase inhibitor is an anti-angiogenesis drug which aims to modulate the tumor blood supply. This phase II study was designed to test the effectiveness of tivozanib on tumor vasculature in patients with recurrent GBM. **Methods:** Ten adult patients with recurrent GBM, median age of 62 (range 51-73), were enrolled on a Simon 2-stage design study and treated with tivozanib 1.5mg daily, 3 weeks on/1 week off in 28 day cycles. Brain MRI was done at baseline and after each cycle. The enhancing tumor and surrounding area of abnormal FLAIR hyperintensity were outlined and median tumor cerebral blood flow (CBF) and cerebral blood volume (CBV) values were derived from dynamic susceptibility contrast MRI to assess the performance of tivozanib. Vessel architectural imaging (VAI) was used to measure tumor vessel calibers and relative oxygen saturation. A t-test was used to compare baseline MRI parameters to the pre-cycle 3 visit. A univariate Cox model was used to test the association of each MRI parameter with time to progression. **Results:** Best MacDonald criteria responses were: CR (1), PR (1), SD (4), PD (4) and the median duration of response was only 3.6 mo (1.7-3.8mo) so the study was stopped per planned stopping rule. One patient was taken off study for unacceptable skin toxicity and nine patients for progressive disease. Given the dropout rate, only data up to cycle 3 was included in this analysis. There was no statistically significant change in enhancing tumor volume (p = 0.70), FLAIR volume (p = 0.31), or median CBV (p = 0.13) or median CBF (p = 0.54) within the enhancing tumor. Within the FLAIR hyperintensity, median CBV (p = 0.12) and median CBF (p = 0.41) also did not change significantly. No parameter was associated with time to tumor progression. VAI showed no change in vessel calibers or tissue oxygenation. **Conclusions:** Tivozanib was well tolerated but most patients progressed rapidly. The majority of patients had no significant change in tumor enhancement and perfusion imaging demonstrated insignificant changes in tumor and peritumoral blood volume, flow, vessel caliber, and oxygenation, suggesting that this anti-angiogenic agent had limited impact on brain tumor vasculature. Clinical trial information: NCT01846871.

2026 Poster Session (Board #15), Mon, 1:15 PM-4:45 PM

Characteristics and outcomes of breast cancer patients with leptomeningeal metastasis at Memorial Sloan Kettering Cancer Center (MSKCC). *First Author: Aki Morikawa, University of Michigan, Ann Arbor, MI*

Background: Breast cancer (BC) is one of the most common solid tumors with metastases to the leptomeninges. Disease presentation, prognostic factors, and treatment patterns for BC patients (pts) with leptomeningeal metastasis (LM) are not well-characterized. In this study, we examined pt characteristics and outcomes of BC pts with LM. **Methods:** 318 consecutive BC pts diagnosed with LM from January 1998 to December 2013 were identified. Clinical, pathologic, and treatment information were obtained by retrospective review. Pt characteristics at the time of LM diagnosis (dx) and their associations with time from LM dx to death or last follow up were evaluated by Kaplan-Meier curves, log-rank tests, and Cox proportional hazard models. **Results:** The median age at LM dx was 54 years (range 23-85). Of the 318 pts, 44% were HR+HER2-,18% HR+HER2+, 8.5% HR-HER2+, and 25.5% triple negative;4% had missing information. 43% had cranial LM only, 26% had only spinal LM, and 26% had both; 5% were unspecified due to missing imaging information in either the spinal or cranial compartment. At the time of LM dx, 53% of pts had concurrent progression of non-CNS metastases. LM specific treatment included intrathecal/intraventricular therapy (14.5%), radiotherapy (64%), and IV high-dose methotrexate (20%). There were 292 deaths. The median follow-up for survivors was 10.1 mos (range 0.8 - 93.6). The median survival (OS) from LM dx was 3.5 mos (95% CI: 3.0, 4.0) with 63 pts (20%) surviving > 1 year. Recent diagnosis (after 2006), HER2+ subtype, higher KPS (> 70), cranial site of LM, and control of extra-CNS disease were independently associated with improved OS in multivariate analysis. **Conclusions:** Unexpectedly, the site of LM was an independent prognostic factor. This may be related to biologic, diagnostic, or treatment factors and needs further confirmation. Control of extra-CNS disease, KPS and receptor subtypes should be stratification variables for future clinical trials for LM. Although OS is poor, we have identified a subset of pts who had extended survival (> 1 year). A closer examination to identify factors that contribute to longer-term survival may provide insight to improve management of these pts.

2027 Poster Session (Board #16), Mon, 1:15 PM-4:45 PM

Histopathological markers at craniotomy and outcome in breast cancer brain metastases. *First Author: Megan Jean McKee, UNC Chapel Hill, Chapel Hill, NC*

Background: Brain metastases (BM) are a devastating consequence of advanced breast cancer (BC). Little is known about the clinical significance of histopathological features associated with BM tumor and stroma. Lymphocytic infiltrate (LymInf) has been shown to be predictive of response to therapy in primary BC and prognostic in patients (pts) with triple negative (TN) BC. Increased LymInf has been associated with better prognosis in melanoma BM. In a 3-institution cohort, we report on the association of LymInf and other histopathological markers in BCBM with prognosis. **Methods:** Under IRB approval, a clinically-annotated tumor bank of 83 BCBM was established from craniotomy tissues. LymInf, hemorrhage, and necrosis (Nec) were assessed on H&E stain (score 0-3); gliosis was scored as present/absent. Primary endpoint was survival from craniotomy. The Kaplan Meier method and Log-rank tests were used to evaluate survival. **Results:** Median age was 52 yrs. Median follow-up was 2.74 yrs. Hormone receptor (HR) status was 47% HR+ and 53% HR-. Subtype was: 36% (22/61) HR+/Her2-, 23% (14/61) Her2+, and 41% (25/61) TN. Higher Nec (2-3+) was observed more frequently in TN BCBM (76%) compared to HR+/Her2- (32%) or Her2+ (36%) BCBM, p = 0.004. Across all subtypes, higher Nec was associated with inferior survival post-craniotomy compared to low Nec (median 1.0 v 1.8 yrs, p = 0.02); this trend was notable in the HR+ BCBM (1.3 v 2.5 yrs, p = 0.19). LymInf was observed in 60% (48/81) of BCBM. Across all pts, higher LymInf was not associated with post-craniotomy survival (p = 0.3). In the HR- cohort, any LymInf (1-3+ v 0) was associated with longer survival post-craniotomy (0.9 v 0.3 yrs, p = 0.03); this held true for the TN pts (0.9 v 0.5 yrs, p = 0.14). Any LymInf was also associated with longer survival from diagnosis of primary BC in the TN group (4.3 v 3.1 yrs, p = 0.02). **Conclusions:** Higher necrosis as observed on H&E stain from BCBM at craniotomy is associated with TN subtype and with a negative prognosis. LymInf may be prognostic of an improved outcome, especially in the HR- population. Given that immunotherapy is being used successfully in metastatic melanoma and is being investigated in metastatic BC, evaluation of this approach in patients with BCBM is warranted.

2028 Poster Session (Board #17), Mon, 1:15 PM-4:45 PM

Determining viability of using APNG status as a prognostic marker in patients with glioblastoma multiforme. *First Author: Rikke Hedegaard Dahlrot, Department of Oncology, Odense University Hospital, Odense, Denmark*

Background: Expression of the enzyme alkylpurine-DNA-N-glycosylase (APNG) has been associated with poor outcome in patients with glioblastoma multiforme (GBM). APNG is part of the base excision repair system, and expression of APNG is related to resistance towards temozolomide (TMZ). This study evaluates the prognostic value of APNG in a population-based cohort of 185 Danish GBM patients diagnosed between 2005 and 2009. Due to GBM's cellular heterogeneity, APNG contribution from non-tumor cells was excluded. **Methods:** APNG expression was evaluated using image analysis and a novel quantitative immunohistochemical (IHC) assay (qIHC, Dako), where APNG protein levels were represented through dots. Non-tumor cells, which were found to express APNG, were excluded using an IHC/qIHC double-staining. To verify the qIHC results, APNG was measured in 177 of the patients using a quantitative in-house developed APNG immunofluorescence (IF) assay. MGMT methylation status was obtained in 152 patients by pyrosequencing. **Results:** Using qIHC, median expression of APNG was 0.31 dots/cell (range 0.099-0.96). An optimal cut-point was identified dichotomizing the patients at an APNG value of 0.24 (25% vs. 75% of the patients). In Cox regression high expression of APNG was associated with better overall survival (OS) (HR 0.53, p = 0.001) adjusting for the effect of age, performance status, tumor crossing midline, treatment and gender. APNG was associated with better OS (HR 0.57, p = 0.012) when adjusting for MGMT status. Retesting the cohort using IF, demonstrated similar results (HR 0.81, p = 0.2). Patients with methylated MGMT promoters and high APNG expression demonstrated a better OS, than with non-methylated MGMT promoters and low APNG expression (HR 0.55, p = 0.04). **Conclusions:** APNG measured by qIHC was found to be an independent significant prognostic factor for OS in GBMs, This was supported by IF measurements. Removing bias associated with APNG expression in non-tumor cells in both assays has, in this study contributed substantially to analyze the prognostic value of APNG in GBM patients. We expect that APNG qIHC can potentially identify patients who will not benefit from treatment with TMZ.

2029 Poster Session (Board #18), Mon, 1:15 PM-4:45 PM

A phase I trial of intravenous liposomal irinotecan in patients with recurrent high-grade gliomas. *First Author: Jennifer Leigh Clarke, UC San Francisco, San Francisco, CA*

Background: Treatment options for recurrent malignant glioma are limited. Preclinical activity of irinotecan has been seen in glioma models but only modest efficacy has been noted in clinical studies, perhaps related to drug distribution and/or pharmacokinetic limitations. In preclinical testing, liposomal irinotecan (nal-IRI, also MM-398, PEP02) demonstrates prolongation of drug exposure and higher tissue levels of drug due to slower metabolism. A Phase I study was undertaken in advanced solid tumor patients in Taiwan, and the MTD was 120 mg/m^2; UGT1A1 genotyping was not prospectively undertaken in that solid tumor study. Objectives: To assess the safety and pharmacokinetics (PK) of nal-IRI and to determine the maximum tolerated dose (MTD) in patients with recurrent malignant glioma stratified based on UGT1A1 genotyping. **Methods:** This Phase I study in recurrent malignant glioma stratified patients by UGT1A1 status, to homozygous WT ("WT") vs heterozygous WT/*28 ("HT"). Patients who were homozygous *28 were ineligible. Eligibility criteria included age $>=$ 18, KPS $>=$ 60, not on enzyme-inducing drugs (including enzyme-inducing seizure medications), and no prior treatment with irinotecan. The design was a standard 3+3 Phase I design. Patients who were WT were started at 120 mg/m^2 (the MTD from the Taiwanese study) with dose increases in 60 mg/m^2 increments. Patients who were HT were started at 60 mg/m^2, with dose increases in 30 mg/m^{2}increments. Dosing was given IV every 3 weeks. The DLT assessment period was 1 cycle (21 days). **Results:** In the WT cohort, the MTD was 120 mg/m^2. In the HT cohort, the MTD was 150 mg/m^2. DLTs in both cohorts included diarrhea, some with associated dehydration and/or fatigue. Analysis of PK data is in process, and will be presented at the meeting. **Conclusions:** Nal-IRI had no unexpected toxicities when given via IV. The toxicity profile of the drug was felt acceptable to move forward with additional testing using convection-enhanced delivery into intracranial tumors, and such a Phase I study is currently enrolling at our institution. Clinical trial information: NCT00734682.

2030 Poster Session (Board #19), Mon, 1:15 PM-4:45 PM

Differential molecular expression profile according to glioblastoma (GB) location. *First Author: Emilie Denicolai, AMU, Marseille, France*

Background: Initial GB topography occurred throughout the brain without established specific molecular profile. Our previous study suggested that cortical and subventricular GB exhibit distinct transcriptome profile. Based on these preliminary results, our objective was to evaluated the expression of ten selected genes (*VEGFC*, *FLT4*, *MET*; *HGF*, *CHI3L1*, *PROM1*, *NOTCH1*, *DLL3*, *PDGFRA*, and *BCAN*) according to GB locations. **Methods:** Fifty nine patients with newly GB were retrospectively included according to the availability of pre-surgery MRI and frozen tumors. Tumor locations were classified into cortical and periventricular (PV) locations, which were next segregated according to cerebral lobes: cortical fronto-parietal (N = 19), cortical temporal (N = 5), PV fronto-parietal (N = 12), PV temporal (N = 12), and PV occipital (N = 12). Expression levels of the selected genes were determined using real-time quantitative PCR, and were correlated with tumor locations. **Results:** Cortical GB were characterized by a lower expression of two mesenchymal genes, *VEGFC* (p = 0.001) and *HGF* (p = 0.001), than periventricular GB. Among cortical GB sub-groups, genes expressions were homogenous. In contrast, PV locations exhibit distinct expression profiles. PV temporal tumors were associated with higher expression of two proneural and cancer stem cell genes, *NOTCH1* (p= 0.028) and *PROM1* (p = 0.033) while PV fronto-parietal tumors were characterized by a higher expression of *FLT4* (p= 0.037) and *CHI3L1* (p= 0.006). PV occipital GB were associated with a lower expression of *VEGFC* (p = 0.032) than other PV GB and an over-expression of *MET*, correlated to *MET* amplification. Finally, *VEGFC* and *HGF* expressions were correlated (p < 0.001) as well as *NOTCH1* and *PROM1* expressions (p < 0.001). **Conclusions:** Our results suggest a differential expression profile of the selected genes according to initial GB location. These results should be validated in a prospective study.

2031 Poster Session (Board #20), Mon, 1:15 PM-4:45 PM

Use of a novel radio-sensitizer for treatment of GBM. *First Author: John Lloyd Gainer, Diffusion Pharmaceuticals LLC, Charlottesville, VA*

Background: Trans sodium crocetinate (TSC) was developed to increase tissue oxygenation. Since hypoxia may enhance radiation resistance, we tested TSC along with radiation therapy (RT) in GBM in a Phase I/II trial. 59 patients received TSC in an open GBM clinical trial together with TMZ and RT (www.clinicaltrials.gov , NCT01465347). Although final data for the first 2 years will not be available until late summer 2015, this abstract discusses results from 18 clinical sites which are available at 21 months. **Methods:** 59 patients with newly diagnosed GBM were enrolled between Jan. 2012 and March 2013 into a Phase I/II trial. All patients received standard of care RT and TMZ. In the Phase I portion of the trial TSC was initially administered 3x/week at half-dose to 3 patients prior to RT. Subsequently, 6 additional patients received full dose TSC for 6 weeks in combination with RT. No dose-limiting toxicities were identified in the 9 patients on the Phase I portion of the trial. Fifty additional patients were enrolled in the Phase II trial at full dose TSC in combination with TMZ and RT. Four weeks after completion of RT, all patients resumed TMZ for 5 days every 4 weeks, but no further TSC was administered. All patients were followed with bi-monthly neurologic exams, MRI's, KPS scores and Quality of Life questionnaires. **Results:** At a minimum of 21 months follow-up since the diagnosis of GBM: Radiologic Response: Pseudo progression occurred in numerous patients. Complete responses were observed in 10% of patients. *Survival*: Overall Survival: 38.2%. Survival did not correlate with initial tumor resection: 6/15 patients with original complete resection alive at 21 months and 8/15 biopsy-only patients. *Quality Of Life*: Both KPS scores and questionnaires indicate continued high QOL. *Safety*: Excellent patient toleration of dosing TSC with TMZ. **Conclusions:** TSC was well tolerated in combination with RT and TMZ. Our data at a minimum follow-up of 21 months suggest that TSC may promote radio-sensitization since there was a large incidence of pseudo-progression, with complete tumor regression in about 10% of patients and Overall Survival of 38.2%, This is one of the first demonstrations that a type of oxygen radio-sensitizer can be of benefit, being possible through the novel mechanism of TSC. Clinical trial information: NCT01465347.

2032 Poster Session (Board #21), Mon, 1:15 PM-4:45 PM

Long-term survival in patients with primary CNS lymphoma: Results from the G-PCNSL-SG1 trial. *First Author: Patrick Roth, Department of Neurology, University Hospital Zurich, Zurich, Switzerland*

Background: Although potentially curable, primary CNS lymphoma (CNS) is still a therapeutic challenge and only a minority of patients survive longer than 5 years. The factors which define the prognosis of PCNSL patients have only been partially elucidated. A more detailed insight into the parameters which promote long-term survival in PCNSL may allow for more patient-tailored therapies. **Methods:** We analysed the dataset of patients enrolled into G-PCNSL-SG1, the largest phase 3 study performed in PCNSL evaluating the role of whole-brain radiotherapy after high-dose methotrexate-based chemotherapy. Out of 459 patients with sufficient data quality, we identified 89 patients who had survived for five years or more after surgery and diagnosis of PCNSL. This long-term survival (LTS) cohort was compared with two different reference groups: first, patients who had died within one year of diagnosis for any reason (control 1 = C1 patients) and second, all patients who had survived for more than 1 year, but who did not reach a survival of 5 years from diagnosis (control 2 = C2 patients). Patients censored (i.e. alive but without further follow-up) before 5 years of follow-up were excluded. Within the LTS group, survival after 5 years was analysed using the Kaplan Meier method. **Results:** We compared baseline characteristics and treatment of the 89 patients surviving for 5 years or more with the C1 and C2 control populations. Patients within the LTS cohort were younger and had a higher performance score at diagnosis. Furthermore, they had less frequently multiple tumor manifestations, a better renal function and were less often affected by cardiovascular disease. High-dose methotrexate-based treatment resulted in a higher complete response rate and was associated with less toxicity, particularly a reduced frequency of myelosuppression. Within the group of LTS patients, age at diagnosis was the only prognostic factor for conditional survival from 5 years on. **Conclusions:** Within this large patient population, survival of 5 years or more was reached by approximately a fifth of the patients. Young and fit patients with single lesions are most likely to survive for 5 years or more following diagnosis of PCNSL.

2033 Poster Session (Board #22), Mon, 1:15 PM-4:45 PM

Timed-sequential therapy with mibefradil and temozolomide in patients with recurrent high-grade gliomas: A phase I Adult Brain Tumor Consortium study. *First Author: Matthias Holdhoff, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Mibefradil (MIB) is a selective T-type calcium channel blocker that had previously been approved for treatment of hypertension. MIB has shown significant preclinical activity in many cancers, including high-grade gliomas (HGG). MIB was found to impact cell cycle activity with arrest at G1/S in tumor cells, suggesting a possible chemo-sensitizing effect of the drug if given prior to cytotoxic therapy. This was a multi-center open label phase I study to determine the maximum tolerated dose (MTD) of MIB followed by temozolomide (TMZ) in recurrent HGG and to assess the safety and tolerability of MIB, particularly its myelosuppressive effects, in a timed-sequential combination with TMZ. **Methods:** Adult patients with recurrent HGG (WHO grade III and IV) who were selected to likely have a benefit from repeat treatment with TMZ (no progression $\geq$ 3 months from their last dose of TMZ) were eligible. MIB was given in 4 daily doses (QID) for 7 days followed 24 hours later by standard TMZ at 150-200 mg/m^2 for 5 days per 28-day cycle. Dose escalation of MIB was done using a modified 3+3 design, followed by an extension cohort of 10 patients at the MTD. **Results:** 27 eligible patients with recurrent HGG participated (at time of enrollment, 21 with WHO grade IV, 6 with grade III; median age 50y; median KPS 90). The MTD of MIB was determined as 87.5 mg po QID. Most common side effects (grade 1 and 2) were fatigue, nausea, constipation and anorexia. Grade 3 elevation of ALT/AST was observed in one patient. Dose limiting toxicities were elevation of ALT/AST and sinus bradycardia. 5 partial and 1 complete responses were observed based on review by the sites (response rate 22%; 95% CI:9-42%). Plasma concentrations of MIB achieved a steady-state after 4 days of dosing with a mean peak concentration of approximately 1,700 ng/mL and a peak-to-trough ratio of 1.1 at the MTD. **Conclusions:** MIB followed by TMZ was well tolerated in patients with recurrent HGG. The MTD for MIB in this setting was determined as 87.5 mg po QID. The lack of toxicity, including extensive myelosuppression, and the presence of responses in this selected patient population suggests that this regimen deserves further investigation. Clinical trial information: NCT01480050.

2034 Poster Session (Board #23), Mon, 1:15 PM-4:45 PM

Phase II study of bevacizumab and vorinostat for recurrent glioblastoma. *First Author: Ashley Ghiaseddin, Duke University Medical Center, Durham, NC*

Background: Prognosis for recurrent glioblastoma (GBM) remains dismal with a 9-15% 6-month progression-free survival (PFS). However, the addition of bevacizumab (BEV), a humanized monoclonal IgG1 antibody with effects at human vascular endothelial growth factor, has improved 6-month PFS to 40-50% and median overall survival (OS) to 9.2 months. Vorinostat (VOR) is a small molecule derivative of hydroxamic acid that crosses the blood-brain barrier and has anti-tumor effects directly by inhibition of histone deacetylase and indirectly by anti-angiogenic promotion. In light of VOR's mechanism of action and favorable toxicity/safety profile, we sought to evaluate the efficacy of VOR combined with BEV in recurrent GBM. **Methods:** A phase II single-center open-label, single arm study was performed to evaluate VOR and BEV in recurrent GBM. Primary endpoint was 6-month PFS. Secondary endpoints were safety/tolerability, radiographic response, PFS, and OS. Major eligibility criteria included age $\geq$ 18 yrs, KPS $\geq$ 70 and $\leq$ 2 prior progressions. Dosing regimen was BEV 10mg/kg IV q2weeks combined with VOR 400mg PO daily for 7 days, then 7 days off in a 28 day cycle. **Results:** Forty recurrent GBM patients were enrolled. To date, median follow-up time is 13.2 months with 6-month PFS of 30% (95% CI: 16.8%, 44.4%). Median OS is 10.4 months (95% CI: 9.3-13.1 months). Objective radiographic responses included 9 partial responses, 29 stable responses, and 1 radiographic progression with 1 patient not assessed due to early death (sudden death of vascular origin). Most common treatment related grade 2-3 toxicities were lymphopenia (55%), leukopenia (43%), neutropenia (33%) and hypertension (33%). Grade 4 toxicities were leukopenia (3%), neutropenia (3%), sinus bradycardia (3%), and thromboembolic event (3%). Two deaths occurred on study; one due to disease progression and the other was a sudden death of vascular origin. **Conclusions:** VOR and BEV combination therapy was well-tolerated in recurrent GBM, although it did not improve 6-month PFS when compared to BEV monotherapy. There was a trend towards improved OS in VOR and BEV in comparison to BEV monotherapy. Continued follow-up and research is needed to delineate better the role of chemotherapy in combination with BEV. Clinical trial information: NCT01738646.

2035 Poster Session (Board #24), Mon, 1:15 PM-4:45 PM

Patterns of response and relapse of primary central nervous system lymphomas (PCNSL) following first line of high-dose methotrexate-based chemotherapy (hdMTX): Analysis of a prospective ANOCEF randomized phase II trial. *First Author: Emeline Tabouret, Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France*

Background: Detailed neuro-imaging analyses of PCNSL are limited. Our objective was to evaluate MRI findings in PCNSL patients treated with hdMTX without radiotherapy, with a particular emphasis on T2-FLAIR MRI abnormalities. **Methods:** We reviewed MRI (T1, T1 post-gadolinium and T2/FLAIR) findings of 85 patients with PCNSL enrolled in a randomized multicenter phase II trial (NCT00503594) evaluating two hdMTX regimens (MPV-A and MTX-temozolomide), conducted in patients aged 60 and older. Response rate (IPCG criteria), number and volume of enhancing lesions, anatomical site, site of relapse and patterns of relapse were analyzed and correlated with outcome. Landmark analyses were performed at 2 and 4 months. **Results:** Objective responses (OR) were: complete response (CR): 56%, uncertain CR: 4%, partial response: 18%, stable disease: 7%, progressive disease: 15%. On multivariate analysis, location in the posterior fossa ($p = 0.008$) and tumor volume ($p = 0.006$), but not lesion number, were significantly associated with survival. OR at the first MRI (2months) and at the end of treatment (4 months) were significantly associated with overall survival in multivariate analysis ($p < 0.001$ and $p = 0.004$ respectively). Early versus delayed CR did not impact survival. Relapse in the brain involved the initial enhancing site, a site at distance, or both in 46%, 40% and 14% respectively. At baseline, non-enhancing T2-FLAIR hypersignal lesions at distance from the enhancing tumor site were detected in 18 patients (23%), among whom 16 (88%) displayed a marked decrease ($>$ 50%) after chemotherapy, confirming their neoplastic nature. Among these 18 patients, ten relapsed, and the initially non-enhancing T2-FLAIR lesions corresponded to the site of an enhancing relapse in half of them (N = 5). **Conclusions:** Relapse after hdMTX at distance from the initial enhancing tumor is frequent and may occur in the area of non-enhancing T2-FLAIR hyper-intensity identified at distance from the enhancing tumor at baseline. Future response criteria should take into consideration non-enhancing T2-Flair lesions.

2036 Poster Session (Board #25), Mon, 1:15 PM-4:45 PM

Comparative impact of treatment on clinical benefit in patients with glioblastoma (GBM) enrolled in the phase II trial of ICT-107. *First Author: Terri S. Armstrong, The University of Texas Health Science Center School of Nursing, Houston, TX*

Background: This study was a randomized double blind placebo-controlled phase 2 trial of dendritic cell(DC) Vaccine ICT-107 following standard treatment in newly diagnosed patients with GBM. Although OS was not different, PFS was longer in those receiving the vaccine. To evaluate the clinical benefit of this prolonged PFS, Karnofsky Performance Status (KPS) and steroid dosing, as well as patient reported QOL using the Functional Assessment of Cancer Therapy –Brain (FACT-BR) were evaluated during the progression free period. **Methods:** The FACT-BR was completed by patients at baseline, and longitudinally during the maintenance phase after four induction vaccinations and at the end of study visit. Corticosteroid dosing and KPS were evaluated throughout the progression free period at monthly timepoints for 12 months and every 6 months thereafter. Between arm differences were evaluated using Fisher test or ANOVA statistics. A p-value of 0.05 was considered significant when comparing the two treatment groups for all analyses. **Results:** Participants (81 patients in the ICT-107 arm and 43 patients in the control arm) completed baseline FACT-BR assessment (97% compliance), with 84% and 68% completing end of cycle 1 and end of study assessments respectively. Quality of life, as measured by the FACT-BR, was maintained equally until progression for ICT-107 and control patients. Performance level, as measured by KPS, was significantly higher during the treatment period in those receiving ICT-107 (p,0.05, Cycles 1-4 or maintenance phase). There was a trend for less steroid usage over time in the ICT-107 arm (30%) versus the control (44%) ($p = 0.1$, log rank). **Conclusions:** Based on these initial analyses of clinical benefit, increased PFS time with ICT-107 is not associated with a detrimental impact on self-report of QOL, and is associated with retention of performance capacity as measured by KPS, and may be associated with a longer corticosteroid free period than those receiving standard treatment. Clinical trial information: NCT01280552.

2037 Poster Session (Board #26), Mon, 1:15 PM-4:45 PM

Correlation of dynamic ^{18}FET-PET with IDH 1 mutation for prediction of outcome in anaplastic astrocytoma WHO° III independently from tumor vascularisation. *First Author: Bogdana Suchorska, Department of Neurosurgery LMU, Munich, Germany*

Background: Patients with an anaplastic glioma (WHO III°) without IDH1 mutation have a comparable disease course to glioblastoma. Dynamic ^{18}FET-PET has been shown to provide prognostic information in malignant glioma independent of other clinical parameters. Here, we analyzed whether dynamic parameters acquired from ^{18}FET-PET imaging correlate with IDH1 mutation status or tumor vessel density regarding the clinical course in anaplastic astrocytoma. **Methods:** 96 patients with a glioma WHO III ° who received a ^{18}FET-PET at primary diagnosis were analyzed with respect to IDH1/2 mutation, *MGMT* promoter methylation, LOH 1p/19q status and vascularity (vessel density quantified by CD34-positive tumor area). The maximum "tumor-to-brain ratio" (TBR_{max}) and the minimum "time-to-peak" (TTP_{min}) were analyzed as ^{18}FET-PET parameters. Clinical outcome measures were progression free survival (PFS) and overall survival (OS). **Results:** Vessel density varied from 1 to 25% and did not have an impact on OS or PFS ($p = 0.09/0.6$); furthermore, it was not intercorrelated with IDH1 mutation status or with TTP_{min}. 54 % of all patients showed no IDH1 mutation. The IDH 1 status did not correlate with TBR_{max} (2.9 vs. 3.2 without vs. with IDH 1 mutation; $p = 0.24$), but with TTP_{min} ($p < 0.001$): 37/41 (90%) patients with a $TTP_{min} \leq$ 12,5 min showed no IDH 1 mutation, while a $TTP_{min} >$ 12.5 min was often associated with IDH1 mutation (31/43 patients (72%), 4 patients could not be evaluated).; In an interim analysis of 53 cases, patients without IDH 1 mutation or with a $TTP_{min} \leq$ 12,5 min had a significantly shorter PFS (10.0 vs. 37.4 months vs. 37.4 months and 9.8; $p < 0.001$) and OS (20.5 and 22.0 months versus median not reached, respectively; $p < 0.001$). In the multivariate analysis, both $TTP_{min}$and IDH 1 status were independent predictors of OS . **Conclusions:** In anaplastic gliomas, early TTPmin ≤ 12.5 min is associated with a lack of IDH 1 mutation, but not with vessel density, MGMT mutation status or LOH 1p/19q. TTP_{min} and IDH1 mutation are both independently associated with clinical outcome.

2038 Poster Session (Board #27), Mon, 1:15 PM-4:45 PM

Prognostic model of lower grade gliomas. *First Author: Kosuke Aoki, Department of Neurosurgery, Nagoya University School of Medicine, Nagoya City, Japan*

Background: Lower grade gliomas (LGGs, WHO grade II/III gliomas) account for one third of all gliomas. Most LGGs generally show a slow progression, but some show a more aggressive clinical course. Large-scale and comprehensiveness in genetical and clinical studies enables establishment of a reliable prognostication system. **Methods:** Status of somatic mutations and copy number variations (CNVs) generated by whole exome/targeted sequencing and SNP array were investigated for 653 patients combined 269 Japanese patients with publically available 384 patients from the Cancer Genome Atlas, who were randomly divided into training (327 patients) and validation sets (326 patients). LGGs were genetically classified into 3 types according to *IDH* mutation and 1p/19q loss of heterozygosity (LOH): Type 1 (mutated *IDH* with 1p/19q LOH), Type 2 (mutated *IDH* without 1p19q LOH), and Type 3 (*IDH* wild type) which also were well correlated with overall survival (OS) (Nature Genetics, in press). In the current study, we sought significant risk factors in each LGG type contributing OS using Cox regression analysis and Akaike information criterion. We validated the accuracy of this classifier in the validation set. **Results:** In the training set, significant risk factors were extracted in Types 1 and 3, but not in Type 2. These types were sub-grouped into low- and high-risk groups (HR = 3.13, 2.81 and 95% CI = 1.36-7.19, 1.25-6.32 respectively). Eventually, all LGGs were divided into low- and intermediate- and high-risk group, showing significantly different OS. The performance of the new model was evaluated by receiver operator characteristic analysis, which showed significantly higher accuracy than previously reported clinical/histological parameters, in particular for long-term prognosis. **Conclusions:** We established a new classifier based on genetic parameters, which provides a reliable tool for predicting OS in LGG patients and should be useful to guide an individual molecular-targeted therapy.

2039 Poster Session (Board #28), Mon, 1:15 PM-4:45 PM

Phase I study of vorinostat combined with isotretinoin and temozolomide in adults with recurrent malignant gliomas. *First Author: Marta Penas-Prado, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Vorinostat (Vor), a histone deacetylase inhibitor, has shown preliminary activity in recurrent GBM. Preclinical studies demonstrated that Vor can overcome resistance to isotretinoin (cRA) and temozolomide (TMZ). We hypothesized that Vor could overcome resistance to cRA and cytotoxic chemotherapy in the treatment of recurrent gliomas. Carboplatin (CBP) was originally selected as the cytotoxic drug since eligible patients would have failed prior standard TMZ therapy. **Methods:** We conducted a Phase I study of combinations of these agents preceding a proposed adaptive randomized 3-arm Phase II study. Adults with recurrent malignant glioma were enrolled into one of 3 arms. Arm 1: Vor + cRA, Arm 2: CBP + cRA, or Arm 3: Vor + cRA + CBP. Dose escalation was by a 3 + 3 design to define the maximum tolerated dose (MTD). Due to excessive toxicity in arms containing CBP, this drug was replaced by dose-dense TMZ due to preliminary evidence of activity in recurrent gliomas. **Results:** A total of 55 patients (8 anaplastic gliomas, 47 GBM) were enrolled from 11/2007 to 03/2012. Among 52 evaluable patients, a total of 11 DLTs were seen, but none after introduction of TMZ to Arm 3. MTDs are summarized in Table. Toxicities included: Arm 1 – neutropenia, thrombocytopenia, pulmonary embolism, elevated AST (DLT), and hypertriglyceridemia (DLT); Arm 2/CBP – neutropenia, thrombocytopenia (DLT), and hypertriglyceridemia; Arm 3A/CBP - thrombocytopenia (DLT) and hypokalemia (DLT); Arm 3B/TMZ – thrombocytopenia, hypertriglyceridemia, fatigue. Best response was stable disease in 26 patients, for ≥ 4 months in 15 patients; 10 patients achieved 6-month progression-free survival; 7 of whom had GBM. **Conclusions:** Two and 3 drug combinations of Vor, cRA, and dose-dense TMZ were well tolerated with MTD that will be used in a multicenter adaptive randomized Phase II study in the near future. Clinical trial information: NCT00555399.

	MTD
Arm 1 (n=14)	Vor 400 mg/day, D 1-14 cRA 100 mg/m^2/day, D 1-21
Arm 2/CBP (n=12)*	CBP AUC 5, D 1 cRA 100 mg/m^2/day, D 1-21
Arm 3A/CBP (n=19)*	De-escalation to dose level -3 (Vor 300 mg/day x 14 days; cRA 100 mg/m^2/day x 21 days; CBP AUC 4)
Arm 3B/TMZ (n =10)	Vor 500 mg/day, D 1-7 & 15-21 cRA 100 mg/m^2/day, D 1-21 TMZ 150 mg/m^2/day, D 1-7 &15-21

*Not going to Phase II

2040 **Poster Session (Board #29), Mon, 1:15 PM-4:45 PM**

The impact of the time to start radiotherapy (TRT) on overall survival in newly diagnosed glioblastoma. *First Author: Vanessa Montes Santos, Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, Brazil*

Background: Glioblastoma (GB) is the most common malignant primary brain tumor in adults. The standard therapy for newly diagnosed glioblastoma is surgical resection followed by radiotherapy (RT) and temozolomide (TMZ). In some institutions it is difficult to start radiotherapy within 2 to 4 weeks following surgery, mostly due to logistic limitations. On the other hand it is unclear how TRT impacts OS in GB. This study aims to evaluate the impact of the time to start radiotherapy (TRT) on overall survival of GB treated with TMZ and RT. **Methods:** In this retrospective study we included all consecutive patients with GB treated at the Instituto do Cancer do Estado de São Paulo (ICESP) with TMZ and RT from 2008 to 2014. Patients with recurrent or secondary GB were excluded. TRT was defined as the time between surgery and the first day of RT, measured in days. The primary end point was overall survival (OS) with regard to TRT. Categorical data was showed as frequencies and percentiles. Survival analysis was performed using Kaplan-Meier curves and log-rank test for comparison between survival curves. Univariate and multiple Cox regression model were performed for overall survival, and stepwise forward method was used for selection variables. We considered 5% of level of significance for all hypotheses tests. All statistical analysis was performed using SPSS for Windows v.18. **Results:** A total of 89 patients were included in this study. The median OS was 27 months for the whole group. Median TRT was 70 days. In the multivariate analysis we identified age was the only significant independent predictor for OS. TRT analyzed as a continuous variable did not impact negatively on OS. When considering TRT at cutoff points of 45 and 60 days, again no negative impact on OS was observed, although a trend was observed for a TRT $>$ 60 days. (HR = 1.93 (95% CI 0.99 – 3.75); p = 0.053). The same adverse trend is observed when considering only younger patients (age $<$ 65 y.o.), for a TRT $>$ 60 days (HR = 2.14 (95% CI 0.99-4.67); p = 0.055). **Conclusions:** Within the limitations of this retrospective analysis, we could not show a clear statistical significant adverse impact of TRT on OS in glioblastoma up to 60 days. However it is a possible that a TRT $>$ 60 days adversely affects OS.

2041 **Poster Session (Board #30), Mon, 1:15 PM-4:45 PM**

Does extent of resection matter in recurrent glioblastoma? Lessons from the DIRECTOR trial. *First Author: Bogdana Suchorska, Department of Neurosurgery LMU, Munich, Germany*

Background: The role of surgery for recurrent glioblastoma is under debate. Tumor volume at recurrence was prognostic in single-institution retrospective studies, but no data from prospective multicenter trials for recurrent glioblastoma have been published to date. Here, we report the association with outcome of surgery for recurrent glioblastoma in a well characterized patient cohort treated in the DIRECTOR trial, which evaluated the effect of two different dose-intensified temozolomide regimens at first recurrence of glioblastoma. **Methods:** We analyzed prospectively collected clinical, molecular and imaging data from the DIRECTOR cohort (N = 105). Imaging data was available from 87 patients. Volumetric analysis was performed based on gadolinium (Gd) enhancement on MRI and correlated with progression-free survival (PFS) and overall survival (OS). Proportional hazard models were applied to obtain prognostic factors. **Results:** 71 of 105 patients received surgery at recurrence. Prognostic factors were balanced between patients who had undergone surgery and those who had not, including age (P = 0.358), O^6-methylguanine DNA methyltransferase (*MGMT)* gene promoter methylation (P = 0.965), isocitrate dehydrogenase (*IDH)-1* mutation (P = 0.724), Karnofsky performance score (P = 0.880), or steroid intake before randomization (P = 0.950). Mean tumor volumes in patients who had received surgery were smaller at study entry than in patients who had not undergone surgery (3.0 cm^3 [range 0-37] versus 6.8 cm^3[range 1-23], P $<$ 0.001). The outcomes in patients who did or did not receive surgery at recurrence were similar for PFS (2.0 months [95% CI 3.5-7.1] vs. 1.9 months [95% CI 1.9-6.4], P = 0.1974) and OS (9.2 months [95% CI 8.7-12.6] vs 9.4 months [95% CI 8.3-13.5], P = 0.9538). Among patients who underwent surgery for recurrence, post-surgery imaging was available in 59 cases. In these patients, complete resection of Gd-enhancing tumor (N = 39) versus residual detection of Gd enhancement (N = 20) was associated with improved OS (11.5 months [95% CI 9.3-15.1] vs. 6.7 months [95% CI 5.2-9.5], P = 0.006). **Conclusions:** Surgery at first recurrence of glioblastoma may improve outcome if complete resection of Gd-enhancing tumor is feasible.

2042 **Poster Session (Board #31), Mon, 1:15 PM-4:45 PM**

Effectiveness of transcranial magnetic stimulation in neurooncological patients. *First Author: Dmitriy P. Atmachidi, Rostov Scientific Research Institute of Oncology, Rostov-on-Don, Russia*

Background: Development of technologies of neurooncological treatment has not solved the problem of treatment for malignant brain tumors. Neurological and somatic complications reduce the length and quality of life of patients. Development of systemic therapeutic approach showed the effectiveness of multisystem influence factors. They include low-intensity extremely low frequency variable and static magnetic fields (ELFMF and SMF). The purpose of this study was to improve the results of complex treatment for malignant brain gliomas using transcranial magnetic stimulation (TMS). **Methods:** 30 patients received TMS during adjuvant chemoradiotherapy (CRT) on days 1-20 of the treatment: ELFMF to hypothalamus projection with frequency 0.03; 3; 9 Hz, induction from 5 to 0.8 mT, exposure 7 min.; and in 20 min. – SMF to the area of operation with induction 20 mT, exposure 15 min. X-ray computed tomography was performed using Toshiba-AsteionVR 2002. Toxicity was evaluated according to CTC-NCIC criteria, cerebral symptoms and somatic status (ECOG-WHO performance status) – according to the scale, Karnofsky Performance Score and identification of integral reactions of the body. **Results:** Remission maintained in CRT+TMS in 93.3±4.6 patients vs. 40+9.1% in the control, 2-year survival increased by 2.4 times. Rate and severity of toxic complications, especially neurological ones (cerebral symptoms, disturbances of speech and motor functions) reduced significantly. Dynamics of somatic status improved (0.32 vs. 0.18), as well as Karnofsky index (9.3 vs. 2.6% in the control, p$<$0.05). Rate of stress development decreased by 10.8 times after TMS, antistress responses prevailed. **Conclusions:** TMS in complex treatment for malignant brain gliomas provides protective effect on homeostatic regulation systems, increases body resistance, optimizes rehabilitation and improves quality of life of patients.

2043 **Poster Session (Board #32), Mon, 1:15 PM-4:45 PM**

Mutational analysis of matched initial and recurrent TP53 WT primary GBM. *First Author: David M. Ashley, Andrew Love Cancer Centre, Geelong, Australia*

Background: Glioblastoma (GBM) present as a heterogeneous disease with poor prognosis despite the use of multimodal therapy. Tumours at diagnosis are distinct from their recurrences, the latter being more therapy resistant. Pinpointing the associated molecular alterations may better inform new therapeutic options to tackle resistance of recurrent disease. **Methods:** A study cohort of 29 patients with primary, TP53 wild-type GBM, with associated annotated clinical data were examined. Of these, 409 cancer associated genes, were examined in 21 paired primary/relapse FFPE extracted DNA specimens using the Comprehensive Cancer Panel (Life Technologies) with sequencing to a mean depth of 1200x. Whole exome sequencing (WES; Illumina HiSeq 2000) was conducted on an additional eight patients (paired primary/relapse) to an average of 70-fold coverage. **Results:** An average of 67±3 (range 49-101) non-synonymous variants or frameshift insertion/deletions were detected in tumour specimens at diagnosis and 53±4 (range 32-127) at relapse. Of these, an average of 27±2 and 13±3 variants were unique to tumours at diagnosis and relapse respectively and 50% of variants that were detected in the initial tumour were also present at relapse. WES revealed an average of 9112 somatic mutations across the genome per sample (range 603-47701). As distinct from recent reports of recurrent lower grade glioma very few patients showed a "hypermutable" signature that is characterized by numerous temozolamide (TMZ) associated specific mutations after treatment. In total, only 2/29 samples (7%) appeared to be hypermutated at relapse, with 55.6% of these mutations being attributable to TMZ-associated mutagenesis in the first patient and 44.3% in the second. **Conclusions:** Overallwe observed few consistent differences between paired diagnosis and relapse specimens. In contrast to previous studies we found evidence of hypermutation associated with TMZ treatment in the minority of patients. We propose that this may be related to the wild-type TP53 status in these patient's tumours.

2044 Poster Session (Board #33), Mon, 1:15 PM-4:45 PM

A phase 2 study on efficacy, safety and intratumoral pharmacokinetics of oral selinexor (KPT-330) in patients with recurrent glioblastoma (GBM). *First Author: Ulrik Niels Lassen, Rigshospitalet, Copenhagen, Denmark*

Background: Patients (pts) with recurrent GBM have few treatment options and a poor prognosis. Selinexor is an oral inhibitor of XPO1 mediated nuclear export resulting in nuclear retention of multiple tumor suppressor proteins (TSPs) including p53, pRB, CDKN2A, p21 and FOXO. Mean IC_{50} of selinexor in pt derived GBM neurosphere cultures was 133 nM. In a pt derived orthotopic murine xenograft model, selinexor demonstrated marked inhibition of tumor growth *in vivo* and prolonged survival (P= .001). **Methods**: This study (NCT01986348) is an open label, multicenter, two-arm phase II trial enrolling pts with recurrent GBM after radiation therapy with concurrent and adjuvant temozolomide. Pts in Arm A received 3 doses (50 mg/m^2) of selinexor prior to surgery, and resumed selinexor after surgery. Pts in Arm B received selinexor alone (50 mg/m^2 BIW) until disease progression. **Results**: (Jan 22, 2015) 7 pts (6/1 M/F, median age 57, 1–2 prior treatment regimens) were treated on Arm A and 15 pts (11/4, M/F, median age 62; 1–3 prior treatment regimens) were treated on Arm B. Mean plasma PK concentration was 999 nM (311-2071 nM) and mean tumor concentration was 136 nM (40-291 nM) in 6 pts. Grade 1/2 AE's (Arm B) included thrombocytopenia (27%/27%), anorexia (13%/33%), fatigue (7%/40%), and hyponatremia (47%/0%). One Grade 3 AE was reported in ≥ 2 pts (fatigue) and no Grade 4 AEs were reported. Investigator reported best responses for 12 evaluable pts (Arm B) were: 2 partial responses (17%), 4 stable disease (33%) and 6 progressive disease (50%). Analysis of XPO1 and TSP expression in tumor tissue is ongoing. **Conclusions**: Oral selinexor at 50 mg/m^2 BIW achieves concentrations in GBM tissue exceeding the IC_{50} in pre-clinical models. Main toxicities are fatigue and anorexia. Partial responses and stable disease were observed. Clinical trial information: NCT01986348.

2046 Poster Session (Board #35), Mon, 1:15 PM-4:45 PM

IDH 1 /2 status and low grade gliomas (LGG): Correlation with outcome upfront Pignatti criteria and molecular profile in a retrospective analysis of a single-centre cohort from Spain. *First Author: Olatz Etxaniz, Medical Oncology Department, Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain*

Background: Current therapy of LGG is based on clinical, radiologic and histologic (Pignatti prognostic classification) features .In the last years genomic profile of LGG has been investigated showing a new tool to guide therapy . **Methods:** IDH analysis was performed by IDH1 and IDH2 genes sequencing in a series of 58 LGGs diagnosed from 1991 to 2012 and correlated with histology , Pignatti classification , molecular profile (p53 expression , 1p19q deletion status and MGMT promoter methylation) and outcome. **Results:** 56.9% of the pts were male and mean age was 45 years . Histological distribution was 39.7% , 22.4% and 37.9% for Astrocytoma (A), Oligodendroglioma (OD) and Oligoastrocytoma (OA) , respectively . Surgical resection was total in 41.4% , subtotal in 19% and only biopsy in 39.7% of the cases . Pts were classified by Pignatti criteria. Inmediate postsurgery therapy was administered performed in 41.4% of pts. IDH alterations were found in 61.9% (26/42) , 1p19q codeletion in 46.3% (25/54), overexpression of p53 in 17.3% (9/52) and MGMT methylation in 40.4% (19/47) of the cases .Median TTP was 61.6 months (95% CI 25.3-97.9) and median OS was 109.7 months (95%CI 73.0- 146.5). In univariate analysis ,1p19q codeletion ($p = 0.045$) and IDH mutation ($p < 0.001$) were associated with better TTP . Median OS was correlated with Pignatti classification ($p = 0.024$) and IDH mutation ($p < 0.001$) . A trend to a better OS was observed with 1p19q codeletion ($p = 0.052$) and MGMT methylation($p = 0.068$). In multivariate analysis, IDH mutation was the only independent prognostic factor after adjustment for histology, molecular profile and Pignatti criteria in terms of OS (HR = 0.120, 95%CI 0.031-0.459, $p = 0.002$) and TTP (HR 0.237,95%CI 0.072-0.779, $p = 0.018$). **Conclusions:** Our findings confirmed the favorable prognostic independent value of IDH mutation in LGG over other criteria.

2047 Poster Session (Board #36), Mon, 1:15 PM-4:45 PM

Time to response (TTR) and early tumor shrinkage (ETS) in recurrent glioblastoma patients treated with bevacizumab: an exploratory analysis of the prospective randomized AVAREG (ML25739) phase II study. *First Author: Enrico Franceschi, Bellaria Hospital, Bologna, Italy*

Background: The treatment of recurrent glioblastoma (GBM) remains an open issue, and the role of bevacizumab (BEV) has been widely debated since a few studies compared this agent with the standard treatments. **Methods:** a multicenter, randomized (2:1), phase II study (EudraCT: 2011-001363-46) with BEV 10 mg/kg iv every 2 weeks or fotemustine (FTM) 75 mg/m^2 iv day 1-8-15 followed, after a 35 days interval, by fotemustine 100 mg/m^2 every 3 weeks, was conducted. The primary endpoint was overall survival at 6 months (OS-6). ETS was assessed with central review exploratory analysis. T1contrast enhancing area and T2/FLAIR were evaluated as predictors for OS rates with ROC analysis and the test for AUC. The best cut-off values were found with the maximization of Youden's Index. The groups obtained were analyzed with Kaplan-Meier procedure and compared with univariate and multivariate Cox proportional hazards model. **Results:** 91 patients with recurrent GBM were enrolled in 10 Italian centers between 11/2011 and 9/2012. The median age was 57 years (range: 28-78). Fifty-nine patients were enrolled in the BEV arm and 32 patients in the FTM arm. OS-6 was 62.1% (95%CI: 48.4-74.5) and 73.3% (95%CI: 54.1-87.7), OS-9 was 37.9% (95%CI: 25.5–51.6) and 46.7% (95%CI: 28.3–65.7) in the BEV and FTM arms, respectively. Median OS was 7.3 months (95%CI: 5.8-9.2) in the BEV arm and 8.7 months (95%CI: 6.3-15.4) in the FTM arm. The response rate was 29% (95%CI: 18-42) and 9% (95%CI: 2-25) for patients treated with BEV and FTM, respectively. TTR ($p = 0.05$, HR = 0.46, 95%CI:0.21-1.00) and ETS > 15% in T1 contrast enhancing area at first disease assessment ($p = 0.040$, HR = 0.511, 95%CI:0.269-0.971) could predict OS in patients treated with BEV but not with FTM (TTR and ETS with FTM: $p = 0.19$ and $p = 0.4$, respectively). Patients achieving an ETS ≥ 15% had significantly longer OS than those achieving an ETS < 15% (8.4 vs 5.2 months). **Conclusions:** BEV and FTM are both active drugs in recurrent GBM. TTR and ETS might be helpful predictors of GBM outcome in patients treated with BEV. Clinical trial information: NCT01474239.

2048 Poster Session (Board #37), Mon, 1:15 PM-4:45 PM

The role of salvage radiation in recurrent glioblastoma after bevacizumab failure. *First Author: Nehaw Sarmey, Cleveland Clinic, Cleveland Heights, OH*

Background: Bevacizumab is FDA-approved for patients with recurrent glioblastoma (GBM). Despite bevacizumab treatment most patients progress, and there are limited therapeutic options for them. We evaluated the role of radiation therapy (RT) after bevacizumab failure in recurrent GBM. **Methods:** With IRB approval, the Cleveland Clinic's database was used to identify all recurrent GBM patients who received salvage treatment after initial bevacizumab failure. Patients were stratified by whether or not they received a RT-containing regimen. Kaplan-Meier analysis and log-rank method were used to compare overall survival (OS) and progression-free survival (PFS) from time of initial bevacizumab failure. Univariable and multivariable Cox proportional hazards models were used to assess the association between patient and treatment characteristics and OS. **Results:** We identified 108 recurrent GBM patients treated after initial bevacizumab failure. Seventeen patients received a RT-based regimen and 91 patients received a non-RT regimen. Of the 17 patients who underwent some form of RT, 5 received RT alone and 12 received RT in combination with other chemo/targeted therapy (11 received RT with bevacizumab). Six patients underwent stereotactic radiosurgery, and 11 patients received fractionated radiation ranging 20 to 60 Gy (4 patients received standard fractionation of 2 Gy per fraction, 6 patients received a hypo-fractionated regimen of > 2 Gy per fraction, and 1 patient's regimen was unknown). At time of initial bevacizumab failure, both the RT and non-RT groups were similar in age, performance status, and extent of resection. Median OS and PFS for the entire cohort was 6.0 months (95% CI: 5.2, 6.6) and 2.6 months (95% CI: 2.3, 3.1) respectively. The group that received subsequent RT had a statistically significant increase in both OS (8.8 vs 5.4 mos; $p = 0.05$) and PFS (4.1 vs 2.3 mos; $p = 0.006$) when compared to the group that did not receive RT. In both univariate and multivariate analyses, only RT use after bevacizumab failure was predictive of OS. **Conclusions:** In this small cohort, use of salvage RT after bevacizumab failure in recurrent GBM was associated with improved survival. A prospective trial is warranted to confirm this finding.

2049 Poster Session (Board #38), Mon, 1:15 PM-4:45 PM

Graded prognostic assessment index for colorectal cancer with brain metastases. *First Author: Vidhya Karivedu, Fairview Hospital Cleveland Clinic, Cleveland, OH*

Background: Brain metastasis (BM) is a rare but serious neurologic complication of colorectal cancer (CRC). The Disease Specific Graded Prognostic Assessment (DS-GPA) which is based solely on Karnofsky performance scale (KPS) is a commonly used prognostic index in patients with BM. We evaluated DS-GPA and other potential prognostic factors for overall survival (OS) in CRCBM at our institution. **Methods:** With IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify CRCBM patients treated between 2002 and 2014. OS from the diagnosis of CRC BM was the primary endpoint. Cox proportional hazards models with stepwise variable selection were used to identify independent prognostic factors. **Results:** Ninety four patients with median age of 60 years (range; 32-87), were included for analysis. KPS was 90-100 in 35 patients (38%), 70-80 in 35 (39%) and <70 in 20 (23%) patients. Single BM was noted in 53 (56%), 2-3 BM in 25 (27%) and >3 BM in 16 (17%) patients. Eighty nine patients (95%) were symptomatic at diagnosis. Forty nine(52%) patients had supratentorial BM, 25(25%) had infratentorial BM and 20 (21%) had both supra-and infratentorial BM at diagnosis. Initial therapy included whole brain radiation (WBRT) in 31 (33%), stereotactic radiosurgery (SRS) in 22(23%), WBRT + SRS in 11(12%), surgery (S) in 2 (2%), S+SRS in 6 (6%), S+WBRT in 14(15%), S+SRS+WBRT in 1(1%), while 2 patients received only chemotherapy and 5 underwent observation. Median OS from diagnosis of BM was 5.5 months (95% C.I. 3.5-7.5). In multivariate analysis KPS and number of BM were independent predictors of OS. Combining these factors a revised GPA with three groups was defined: unfavorable (total points ≤3), intermediate (4-5), and favorable (≥6 points) with median OS of 2.8, 6.1 and 14.7 months, respectively. **Conclusions:** A revised DS-GPA for CRCBM based on KPS (performance status) and number of BM is proposed.

Factors	No. of points	Hazard ratio	P valve
Number of BM		1.27(1.02-1.59)	0.032
1	3		
2	2		
3	1		
>3	0		
Colon cancer specific GPA (KPS)		0.78(0.63-1.59)	0.015
100	4		
90	3		
80	2		
70	1		
<70	0		

Revised GPA	No. Points	Median OS (mo)
Unfavorable	≤3	2.8
Intermediate	4-5	6.1
Favorable	≥6	14.7

2050 Poster Session (Board #39), Mon, 1:15 PM-4:45 PM

Phase II trial of dovitinib in recurrent glioblastoma. *First Author: Manmeet Singh Ahluwalia, Cleveland Clinic, Cleveland, OH*

Background: Glioblastoma (GBM) is a vascular tumor and bevacizumab (a monoclonal antibody against VEGF-A) is FDA-approved in recurrence. Mechanisms of resistance to anti VEGF therapy include up-regulated FGF signaling and increased PDGF-mediated pericyte coverage. Dovitinibis an oral, small-molecule tyrosine kinase inhibitor of FGFR 1-3, PDGFR β, and VEGFR 1-3. **Methods:** This was a phase II trial in adults with GBM, stratified by prior anti-angiogenic therapy (naive – arm A, refractory – arm B). Arm A's primary endpoint (PE) was PFS6 with a 2-stage accrual design to test the hypothesis that PFS6 was 36% vs. 55%. Arm B's PE was time to progression (TTP) and a one-stage design to test the hypothesis that median TTP could be increased from 1.5 to 3 months. Type I and II error was 10% and 20%, respectively in both arms. Extracellular vesicles (EV) were measured at study enrollment, at the end of cycle 1 (day 28), and at progression (PD) to evaluate response to therapy. **Results:** Nineteen patients enrolled in Arm A and 14 in Arm B. Accrual in arm A was stopped after the first stage due to futility. Overall 64% (21/33) of patients were male, median age at on-study was 57 years (range 26-68), and median KPS was 80 (range 60-90). In Arm A, PFS6 was 5% (1/19), median PFS was 1.8 months (95% C.I. 1.3-2.8) and median OS was 7.9 months (95% C.I. 3.6-11.7). In arm B, median TTP was 1.8 months (95% C.I. 1.0-1.8); median PFS was 1.8 months (95% C.I. 0.7-1.8) and median OS was 3.0 months (95% C.I. 0.8-4.7). In arm A, patients with PD had significantly higher levels of CD14+ EV (median 83289 vs 27500, $p = 0.027$) and CD142+ EV (median 38855 vs. 4675 , $p = 0.042$) compared to stable disease at end of cycle 1. Overall 5 patients (15%) reported grade 4 toxicities and 22 (67%) reported grade 3 reactions, primarily elevated lipids/lipase (42%), fatigue (21%), thromboembolic events (18%), hypertension (9%), and lymphopenia (9%). Other toxicity seen were grade 4 appendicitis/colitis ($n = 1$), oral pain and proteinuria ($n = 1$), and delirium ($n = 1$). **Conclusions:** Dovitinib is not active in recurrent GBM, regardless of prior anti-angiogenic therapy. In arm A, elevated pre-treatment levels of CD14+ and CD142+ EV were associated with PD, suggesting their potential role as a predictor of poor response to Dovitinib. Clinical trial information: NCT01753713.

2051 Poster Session (Board #40), Mon, 1:15 PM-4:45 PM

Incidence of pseudo-progression in low-grade gliomas treated with radiotherapy. *First Author: Sophie E. van West, Erasmus MC, Rotterdam, Netherlands*

Background: Pseudo-progression (psPD) is a well-known phenomenon in high-grade gliomas (HGG) after treatment with radiotherapy/temozolomide. However the incidence of psPD in low-grade glioma (LGG) after radiotherapy (RT) is unknown. Therefore, we retrospectively investigated the occurrence of psPD in a cohort of low grade glioma patients treated with RT. **Methods:** All patients with histologically proven LGG treated with RT between 2000 and 2011 were reviewed. MRI scans were reviewed by two independent reviewers before and after RT in periods of 3-6 months until progression leading to the start of a new treatment as judged by the treating physician. Furthermore clinical data including dexamethasone dose and epileptic activity was taken into account. Pseudo-progression was scored when a new enhancing lesion occurred after RT, and this disappeared or remained stable for at least a year without therapy. **Results:** Seventy-one patients were treated with RT for LGG. Sixty-four patients were deemed eligible for evaluation (3 were lost to follow up and 4 patients were not evaluable, due to a missing scans). The median follow-up was 7 years (range 1- 22 years). The median progression free survival was 3.1 years. The median overall survival time was 5.3 years. Sixty-three patients were evaluable for psPD (1 patient was evaluated for response only, because of gadolinium allergy). psPD was seen in 13 patients (20.6%). In two of these patients epilepsy may have played a role. Pseudo-progression occurred after a median of 10 months in a period of 3 – 78 months. The median duration of psPD was 6 months with a range of 2 – 26 months. It always occurred within the RT fields. The area of the enhancement at the time of pseudo-progression was significantly smaller compared to the area of enhancement during 'true' progression (median size 54 mm^2 (range 12 – 340 mm^2) versus 270 mm^2 (range 30 – 3420 mm^2), respectively; $p = 0.009$). **Conclusions:** psPD occurs frequently in LGG patients treated with RT. This supports the policy to postpone a new line of treatment until further progression is evident, especially when patients have small contrast enhancing lesions in the RT field.

2052 Poster Session (Board #41), Mon, 1:15 PM-4:45 PM

Delineation of MGMT promoter hypermethylation as a predictive biomarker for the A071102 clinical trial of veliparib combined with temozolomide (TMZ) using patient-derived xenograft (PDX) GBM models. *First Author: Jann Nagina Sarkaria, Mayo Clinic, Rochester, MN*

Background: Poly-ADP-ribose polymerase inhibitors have potent sensitizing effects in pre-clinical models. This study was focused on identifying potential biomarkers of response to TMZ combined with veliparib in GBM. **Methods:** The efficacy of 3 cycles of TMZ alone or combined with veliparib (dosed days 1-5 every 28 days) was evaluated in 27 PDX models grown as orthotopic xenografts, with 8-10 mice randomized to each treatment group. **Results:** The combination of veliparib and TMZ was associated with significant survival prolongation ($p < 0.05$ by log-rank) in 8 of 20 MGMT methylated PDXs lines (range: 20 to 150 d increase vs. TMZ alone), as compared to 1 of 7 MGMT unmethylated lines (GBM6: 7 d increase). Comparing the survival ratios (median survival with treatment vs. placebo) across all lines, veliparib/TMZ was associated with a greater efficacy in MGMT methylated lines, as compared to TMZ alone, with an average survival ratio of 4.0 ± 2.0 and 3.0 ± 1.1, $p = 0.0002$ respectively, as compared to 2.4 ± 1.7 and 2.4 ± 1.5, $p = 0.41$ in unmethylated tumors. For the 8 responsive methylated lines, treatment with veliparib/TMZ resulted in an average median survival of 188 days (d) as compared to 121 d with TMZ alone. Exogenously expressed MGMT in GBM12 (MGMT methylated; 75 d prolongation in survival with veliparib/TMZ) resulted in a complete loss of TMZ efficacy with or without veliparib (36 d vs. 34 d, $p = 0.87$). Similar association between MGMT expression and lack of efficacy was observed in GBM28 sublines with an intact vs. homozygous deleted MGMT locus. In comparing in vivo DNA damage signaling, co-treatment with veliparib/TMZ, relative to TMZ alone, resulted in greater phosphorylation of Kap1 (S824), Chk1 (S345), Chk2 (T68), and H2AX (S139) only in MGMT methylated (GBM12, 39) lines. **Conclusions:** While veliparib combined with TMZ conferred profound sensitizing effect in MGMT hypermethylated tumors, the combination was ineffective in unmethylated tumors. Based on these data, MGMT methylation is a predictive biomarker and entry criteria for the randomized Phase II/III A071102 clinical trial testing this combination in newly diagnosed GBM.

2053 Poster Session (Board #42), Mon, 1:15 PM-4:45 PM

The role of temozolomide (TMZ) in the management of anaplastic astrocytoma (AA): A comparison of survival in the era prior to and following TMZ. *First Author: Inas Abuali, Saint Agnes Hospital, Ellicott City, MD*

Background: Adding TMZ to radiation therapy (RT) is common clinical practice for patients with AAs despite the lack of prospective studies documenting a survival advantage. Two retrospective studies, each with methodologic limitations, provide conflicting advice regarding the optimal treatment strategy. **Methods:** This single-institution retrospective study was conducted to determine survival trends in patients with AA. All patients > 18 years with newly diagnosed AA treated at Johns Hopkins from 1995-2012 were analyzed. As we incorporated TMZ into high grade glioma treatment regimens in 2004, patients were divided into pre-2004 and post-2004 groups for analysis. Clinical, radiographic, and pathologic data were collected. **Results:** A total of 196 patients were identified; 74 pre-2004 and 122 post-2004; mean age 47 years (+/-15); 57% male; 87% white, 69% surgical debulking. Baseline prognostic factors did not differ between groups. Chemotherapy was administered to 12% (TMZ = 1, PCV = 2, gliadel = 6) of the pre-2004 patients and 94% (TMZ in all, $p < 0.001$) of the post-2004 patients. The median OS was 32 months (95%CI 23-43 mo) with the post-2004 group faring better (37 mo, 24-64) than the pre-2004 group (27 mo, 19-40). Multivariate analysis controlling for age, Karnofsky performance status, and extent of resection revealed a 37% reduced risk of death (HR 0.63, 0.44-0.91, $p = 0.015$) in patients with AA receiving TMZ. **Conclusions:** This retrospective analysis suggests a significant improvement in the survival of patients with AA receiving TMZ with RT. Until prospective phase III data is available, our findings support the use of TMZ in the management of newly diagnosed AA.

2054 Poster Session (Board #43), Mon, 1:15 PM-4:45 PM

GLIOSTRY (GLIOblastoma regiSTRY) of the AINO (Italian Association of Neuro-Oncology): Analysis of factors influencing survival in glioblastoma patients receiving the nitrosourea fotemustine at first relapse following Stupp regimen. *First Author: Roberta Ruda, Department of Neuro-Oncology, University of Turin and City of Health and Science, Turin, Italy*

Background: patients with glioblastoma failing radiotherapy plus temozolomide are treated in Europe with nitrosourea-based regimens, but factors influencing survival are not entirely known.We investigated the factors influencing survival in a large cohort of Italian glioblastoma patients who received the nitrosourea fotemustine (FTM) at first relapse following the Stupp regimen. **Methods**: survival data and information on demographics, clinical, radiological, molecular and treatments factors were collected in 34 Italian Institutions. PFS and OS curves were constructed using the Kaplan-Meier method and both univariate and multivariate analysis were performed . **Results**: Since 2005, 921 (587 M 334 F, median age 56 yrs) patients were enrolled , and up to date 897 are evaluable. Median PFS following FTM was 103 days. Factors of prognostic significance in univariate analysis were: MGMT methylation (129 d methylated vs 90 d unmethylated tumors, $p < 0.001$) and association with bevacizumab (148 d the association vs 97 d FTM alone, $p < 0.0001$). Both MGMT status with an HR of 0.64 (0.52-0.79), $p < 0{,}001$, and association with bevacizumab with an HR of 0.71 (0.56-0.92), $p < 0{,}008$, remained significant after multivariate analysis. Median OS following FTM was 197 days. Factors of prognostic significance in univariate analysis were age (200 d < 65 yrs vs 182 d > 65 yrs, $p = 0.0102$), Karnofsky Performance Score (213 d KPS 90-100 vs 182 d KPS ≤ 80), extent of initial surgery (213 d gross total vs 184 d partial removal, $p = 0.0022$), MGMT status (246 d methylated vs 176 unmethylated tumors, $p < 0.001$) and association with bevaizumab (238 d association with bev vs 187 d FTM alone, $p = 0.0297$). MGMT status with HR of 0.60 (0.48-0.76), $p < 0.001$, and association with bevacizumab with HR of 0.73 (0.56-0.95), $p = 0.022$, remained significant after multivariate analysis. MGMT methylation was the strongest factor influencing OS from initial diagnosis. **Conclusions**: MGMT is a strong prognostic and predictive factor in GBM patients following FTM. The association of bevacizumab with FTM could be superior over FTM alone.

2055 Poster Session (Board #44), Mon, 1:15 PM-4:45 PM

Phase II trial of bevacizumab in patients with surgery and radiation refractory progressive meningioma. *First Author: Sean Aaron Grimm, Northwestern University, Feinberg School of Medicine, Chicago, IL*

Background: Systemic treatment options are limited for meningiomas that progress following surgery and radiotherapy. VEGF is associated with neovascularization, tumor growth, and edema in meningioma. This prospective phase II study was undertaken to determine the efficacy of bevacizumab (BEV), a VEGF ligand binding monoclonal antibody, in patients with progressive benign (BM), atypical (AM), and malignant meningioma (MM) as measured by median 6-month progression free survival (PFS-6). Secondary endpoints included median progression free survival (mPFS), median overall survival (mOS), and radiographic response rate. **Methods:** Patients with histologically confirmed BM, AM, or MM with radiographic progression were eligible. There was no limit on prior therapies. BEV was administered 10 mg/kg intravenously every two weeks. After 6 months of therapy, stable patients were eligible to switch to an every 3-week schedule of BEV (15 mg/kg). Clinical examination and imaging were performed every 4 and 8 weeks respectively for the first 6 months then every 6-12 weeks. Responses were graded using the Macdonald criteria. **Results:** 40 patients were treated: 15 BM, 22 AM, and 13 MM. Median KPS was 80. Median age was 54 (23-81) years. Median number of BEV infusions was 16 (2-62). Grade 3 toxicities included hypertension (10), proteinuria (2), hyponatremia (2), fatigue (1), bruising (1), nausea/vomiting (1), epistaxis (1), pancreatitis (1), perianal infection (1), ataxia (1), and thrombus/embolism (1). Grade 4 toxicities included anemia (1), wound infection (1), elevated lipase (1), and weakness (1). Best responses were stable disease (BM: 100%; AM: 85%; MM: 82%); partial response (BM: 0%; AM: 5%; MM: 0%); progressive disease (BM: 0%; AM: 10%; MM:18%). PFS-6, mPFS, and mOS were 87%, 22.5 months, 35.6 months for BM; 77%, 15.3 months, not reached for AM, and 46%, 3.7 months, 12.4 months for MM. **Conclusions:** Treatment of progressive meningioma with BEV commonly leads to disease stabilization. The results are promising compared to a contemporary meta-analysis, in which PFS6 was 29% and 27% for BM and AM/MM respectively, but require confirmation. Toxicity was minimal and expected for BEV notwithstanding prolonged drug exposure. Clinical trial information: NCT01125046.

2056 Poster Session (Board #45), Mon, 1:15 PM-4:45 PM

Can Diffusion and Perfusion Weighted Imaging predict 1p/19q codeled lower grade gliomas? *First Author: Marica Eoli, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy*

Background: Several factors influence prognosis of lower grade gliomas, including age, histological diagnosis, 1p/19q chromosome arm deletion (codel 1p/19q), isocitrate dehydrogenase (IDH1/IDH2) mutations. Diffusion and Perfusion Weighted Imaging (DWI and PWI) have been proposed as candidates for survival predictors in glioma patients. **Methods:** To assess the association between mean rCBV, rADC and Cho/Cr ratio values and prognostic biomarkers, we investigated 51 supratentorial grade II (36) and III (15) gliomas by advanced MRI (aMRI), including PWI and DWI, before surgery. Surgical sample histological subtypes and molecular variants (loss of heterozigosity on 1p, 19q, 17p, 9p, 10q; IDH1/IDH2 mutations, O6 methylguanine DNA methyltransferase methylation) were evaluated. **Results:** rCBV and rADC had significantly different values in gliomas with and without 1p/19q gliomas ($2.87 \pm 2{,}4$ vs. 1.29 ± 0.93, $p = 0.01$; $1.55 \pm 0{,}26$ vs. 1.81 ± 0.6, $p = 0.02$ respectively), but not in wild-type and mutated IDH1/IDH2 or grade II and III gliomas ($p > 0.05$). Cho/Cr ratios were similar in all subgroups. All 1p/19q codeleted patients had mutated IDH1/IDH2. Univariate analysis showed significantly longer PFS in patients with 1p/19q codeletion (84 *versus* 51 months, $p = 0.013$), and shorter PFS and OS in wild type IDH1/IDH2 patients (10 *versus* 60 months, $p = 0.0001$; 33 *versus* 80 months, $p = 0.0001$), after a median follow-up of 60 months. The ROC analysis showed that cut-off values of 1.33 for maximum rCBV and 1.77 for minimum rADC could predict the 1p/19q status with 63.4% sensitivity and 90% specificity (area under the curve 0.72, 95%CI 0.58-0.84) and 65.9% and 80% (area under the curve 0.78, 95%CI 0.62-0.87), respectively. **Conclusions:** Maximum rCBV and minimum rADC thresholds could help to predict 1p/19q codeletion and to identify lower grade gliomas with a favorable prognosis.

2057 Poster Session (Board #46), Mon, 1:15 PM-4:45 PM

Is Next Generation Sequencing (NGS) Ready for Routine Clinical Practice in Gliomas? Results of a Prospective Study Utilizing the MSK-IMPACT Assay *First Author: Antonio Marcilio Padula Omuro, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: NGS is becoming increasingly available but its relevance in clinical practice has been questioned. In this prospective, IRB-approved study (NCT01775072), we utilized the MSK-IMPACT assay to analyze gliomas in a routine practice setting. The MSK-IMPACT, performed in a CLIA-compliant laboratory, is a multiplexed assay (Illumina HiSeq) providing full exon coverage of 341 cancer related genes, detecting base substitutions, small indels, copy number and select gene rearrangements. **Methods:** After written consent, tumor and germline DNA were analyzed. Mutations were catalogued and compared to TCGA data. Comparison with other profiling methods, i.e. IHC (*IDH-1* R132H mutation), RT-PCR (*EGFRvIII),* Sanger sequencing *(IDH-1/2* mutations) and FISH (*EGFR* amplification, 1p/19q co-deletion) was performed. Participation in clinical trials was recorded. **Results:** N = 104 pts were enrolled (48 glioblastomas, 39 grade III, 9 grade II and 3 grade I gliomas). The mutational landscape was in line with TCGA, including mutations in *TERT* (59%), *TP53* (55%), *IDH-1* (35%), *ATRX* (27%), *PTEN* (22%) *EGFR* (17%), *PIK3CA* (12%) and *BRAF* (2%); four pts displayed a hypermutator genotype. MSK-IMPACT identified all *IDH1/2* mutations, including one *IDH2 R172K* in an IDH-1 R132H IHC-negative tumor. All pure oligodendrogliomas (N = 13) displayed 1p/19q codeletion on MSK-IMPACT. Three pts had 1p/19q codeletion on FISH but not on MSK-IMPACT, but mutational profile/ histology favored non-codeleted glioma, suggesting false-positive FISH results. All FISH *EGFR* amplifications were detected by MSK-IMPACT. Among *EGFR* amplified tumors, MSK-IMPACT disclosed *EGFRvIII* in 55%. To date, 33 pts have been enrolled in trials, including 4 extreme responders in whom results are guiding further drug development. **Conclusions:** NGS with MSK-IMPACT is a highly useful profiling tool, providing prognostic and therapeutically relevant information and guiding patient selection/ interpretation of clinical trials. Given lower cost, higher accuracy and wider range of information provided, this assay replaces with advantages other profiling tools, and is ready for incorporation into routine clinical practice. Clinical trial information: NCT01775072.

2058 Poster Session (Board #47), Mon, 1:15 PM-4:45 PM

Tumor profiling on 1245 gliomas and paired tumor study on 19 high grade gliomas. *First Author: Joanne Xiu, Caris Life Sciences, Phoenix, AZ*

Background: Gliomas are molecularly heterogeneous with genetic alterations driving the growth of recurrences different from the initial tumor. Previous reports showed molecular changes during progression of lower grade gliomas to GBM, driving tumor growth and treatment resistance; however changes during progression of high-grade gliomas have not been systematically reported. **Methods:** 1245 glioma tumors (934 GBM) were tested with multiple platforms including sequencing (SEQ), immunohistochemistry (IHC), fluorescent/chromogenic in-situ hybridization (FISH/ CISH), fragment analysis (FA) and promoter methylation (Me) assay. Metachronous paired tumors from 19 patients (pts) were assessed for biomarker changes over time. **Results:** EGFRvIII was seen exclusively in GBM (16% of GBM) while amplification was more common in GBM than grade II-III tumors (56% vs. 20%, $p < 0.001$). MGMT Me was seen in 47% of all, and was more common in grade II-III (64% vs. 42%, $p < 0.001$). PD-L1 expression on tumor cells was seen in 27% and was more common in tumors without MGMT Me (36% vs. 18%, $p = 0.01$). PD-1 expression on tumor-infiltrating lymphocytes was seen in 48% and was higher in GBM than grade II-III(54% vs. 30%, $p = 0.005$). 38 of 48 sequenced genes had mutations, including BRCA1 (8%) and BRCA2 (6%). 1p19q co-deletion was seen in 26% of grade II-III and 2.9% of GBM. Paired tumors from 19 pts (18 GBM and 1 grade III in both samples) taken at an average of 469 days apart (91-1400) showed that 17 pairs (89%) had one or more biomarker changes over time. 3 of 13 (23%) pairs lost MGMT Me, potentially indicating acquired resistance to temozolomide. EGFR aberrations including amplification (N = 1), mutations on the extracellular (EGFRvIII, N = 1) and intracellular domains (T790M, N = 1; Exon 20 insertion N = 1) were acquired in 3 pairs. One pt, presenting with a PTEN mutation, acquired three additional mutations: cKIT (E583K), PTPN11 (A72T) and PIK3CA (D434N). **Conclusions:** Multiplatform tumor profiling on a large cohort of gliomas confirms tumor heterogeneity. Changes in MGMT Me and EGFR of potential therapeutic importance are frequently observed in high grade gliomas at the time of recurrence, suggesting the need for a re-biopsy for tumor profiling to direct the next line of therapy.

2059 Poster Session (Board #48), Mon, 1:15 PM-4:45 PM

Tumor infiltrating lymphocytes associated with brain metastasis in breast cancer. *First Author: Nicole Olivia Williams, University Hosp/Case Western Reserve Univ, Cleveland, OH*

Background: Breast cancer represents the second most common cause of brain metastasis (BM). Though tumor-infiltrating lymphocytes (TILs) and immunotherapies have been studied in primary breast cancer, little is known about TILs in BM from breast cancer. The aim of this study is to characterize the immune response to BM in breast cancer. **Methods:** The cohort included 75 initial and recurrent BM samples and 20 matched primary breast tumors. Stromal (sTILs) were evaluated on H&E sections and scored according to international TILs working group guidelines and categorized as having no, low (1-5%), moderate (6-20%) or high (> 20%) TILs. Tumor DNA/RNA was extracted on corresponding archival FFPE material. Gene expression profiling was performed using Affymetrix Human Transcriptome Array 2.0 microarrays. PAM50 subtypes were assigned by clustering samples using median-subtracted PAM50 gene expression levels. Gene expression levels of programmed cell death 1 (PD1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte associated protein 4 (CTLA4), and forkhead box P3 (FOXP3) were compared in this cohort. **Results:** Of the 75 BM evaluated, 34 (45%) had no sTILs, 29 (39%) had low sTILs, 10 (13%) had moderate sTILS, and 1 (1%) had high sTILs. sTILs were significantly lower in the BM when compared with matched primary tumors ($p = 0.0025$). When comparing the level of BM sTILs in the PAM50 subtypes, the HER2-enriched subtype more commonly exhibited moderate to high sTILs compared luminal A, luminal B, and normal-like ($p = 0.065$). No association was seen between time to develop BM and % sTILs ($p = 0.68$). Though primary and BM were found to express both PD1 and FOXP3, only FOXP3 expression was found to be higher in primary tumors compared to BM ($p = 0.0025$). There was no association between PD1 and FOXP3 expression and PAM50 subtype or BM sTILS ($p > 0.05$). Significant PD-L1 and CTLA4 expression was not identified in primary tumors or BM. **Conclusions:** Overall, BM from breast cancer have relatively low sTILs expression. The expression of PD1 and FOXP3 in BM from breast cancer suggests that further investigation of the immune response in BM and clinical trials with immune checkpoint inhibitors should be considered for this poor prognosis population.

2060 Poster Session (Board #49), Mon, 1:15 PM-4:45 PM

Tumor profiles of brain metastases from NSCLC, breast cancer, and melanoma. *First Author: Santosh Kesari, UC San Diego, La Jolla, CA*

Background: An estimated 70,000 diagnoses of brain metastases (BM) occur each year in the U.S., with an incidence of 5-7% in breast and melanoma and 20% in lung cancer. Despite its prominence, the biology of BM remains poorly understood. Several theories of BM development exist, including the linear progression model, which suggests that the metastatic capabilities of tumor cells develop at primary sites following the accumulation of alterations. The parallel progression model argues that tumor cells disseminate early and accumulate changes independently at the secondary site. We compare the tumor profiles of BM from common cancers to understand the biology and to identify differential treatment strategies. **Methods:** Tumor samples were profiled using a multiplatform service (Caris Life Sciences, Phoenix, AZ), including sequencing (Sanger, NGS), protein expression (IHC) and amplification (ISH). **Results:** 5,391 NSCLC (293 BM, 5,098 lung), 3,595 breast cancer (99 BM, 3496 breast) and 761 melanoma (101 BM, 660 skin) unpaired samples were included. No significant differences were found in 48 genes between BM and the primary tumor sites, with the exception of PIK3CA in breast cancer, which was mutated less in BM vs. the breast samples (10% vs. 26%, p=0.02). In contrast, expression of TOP2A, TOPO1 and TS, and amplification of EGFR, were more prevalent in BM as compared to the primary sites (Table). **Conclusions:** A similar genetic landscape with limited differences was seen in BM of NSCLC, melanoma and breast cancer compared to primary tumors. The limited differences are more consistent with a linear progression model of cancer metastasis. Additionally ,this suggests that both primary tumor and BM would respond to similar chemotherapeutics with the consideration of effective blood-brain barrier-penetrant drugs. Small molecule inhibitors of EGFR could be considered due to increased EGFR amplification and the higher TOP2A, TOPO1 expression prompts consideration of topoisomerase inhibitors like etoposide or irinotecan.

	Brain met %	Primary met%	P
NSCLC			
TOPO2A	75	55	<0.01
TOPO1	64	55	0.02
TS	35	22	<0.01
EGFR FISH	36	28	ns
Breast			
TOPO2A	78	50	<0.01
TOPO1	78	63	<0.01
TS	39	28	0.04
EGFR FISH	31	14	<0.01
Melanoma			
TOPO2A	76	46	<0.01
TOPO1	61	57	ns
TS	56	45	ns
EGFR FISH	50	6	<0.01

2061 Poster Session (Board #50), Mon, 1:15 PM-4:45 PM

A phase I trial everolimus and sorafenib in patients with recurrent high-grade gliomas: Brain Tumor Treatment Collaborative trial 09-01. *First Author: Jeffrey J. Raizer, Lurie Comp Cancer Ctr of Northwestern Univ, Chicago, IL*

Background: Limited treatment options exist for patients with recurrent Malignant Gliomas (MG), especially after failing Bevacizumab (BEV). Signal transduction pathways involved in gliomagenesis provide therapeutic targets. Everolimus targets mTOR which is an important node downstream from PI3K and Akt. Sorafenib targets Raf, as well as VEGF and PDFG. The rationale for combining these agents is to inhibit two parallel pathways simultaneously. We performed a phase I trial of Everolimus and Sorafenib in patients with recurrent malignant gliomas in preparation for a phase II study. **Methods:** Patients with recurrent MG $>$ 18 yrs, KPS $\geq$ 60, adequate hematologic, renal and hepatic function and no history of HIV or hepatitis were eligible. No limit on prior relapses and BEV exposure was allowed. Enzyme inducing seizure drugs were not allowed. A 3 + 3 dose escalation was used to determine the MTD, defined as the highest dose combination resulting in 0/3 or 1/6 patients experiencing a DLT. The starting dose was Everolimus 5 mg a day + Sorafenib 400 mg twice a day with a plan to increase to a maximum dose of 10 mg a day and 800 mg twice a day over several defined dose levels. A de-escalation level was Everolimus 5 mg/day + Sorafenib 400 mg twice a day for 7 days on and 7 days off. **Results:** 11 men and 2 women were enrolled with a median age of 50 years (19-66) and median KPS of 80 (70-100). All patients had a GBM with 7 receiving prior BEV therapy. In cohort 1, 3 of 6 patients experienced a DLT which were grade 3: fatigue, chest pain, HTN, elevated ALT, hypercholesterolemia and hyperglycemia and one grade 4 hypertriglyceridemia. Dose de-escalation occurred with 1 of 7patients having a DLT of myositis, nausea, fatigue, hypertension and hypercholesterolemia-all grade 3. All patients have died due to disease progression with a median PFS of 4 weeks and OS of 20.9 weeks. **Conclusions:** This phase I study determined the phase II dose in patients with recurrent malignant glioma to be Everolimus at 5 mg daily and Sorafenib at 400 mg BID 7 days on and 7 days off. A phase II trial is on-going investigating this regimen in Bev naive recurrent anaplastic gliomas and GBMs as well as recurrent GBM who failed BEV. Clinical trial information: NCT01434602.

2062 Poster Session (Board #51), Mon, 1:15 PM-4:45 PM

Phase IB trial of carboxyamidotriazole orotate (CTO) and radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ) in newly diagnosed glioblastoma (GBM). *First Author: Alissa A. Thomas, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CTO is an oral inhibitor of non-voltage-dependent calcium signaling that results in simultaneous modulation of several receptor-mediated signaling pathways. A single-agent phase I trial determined the maximum tolerated dose (MTD) at 427 mg/m2, with a safe toxicity profile. A phase IB in combination with TMZ for recurrent malignant glioma found therapeutic brain tissue concentrations and early evidence of activity, with radiographic responses and median survival of 15 months, prompting this newly diagnosed disease study. **Methods:** Following a 3+3 design, pts were enrolled to receive escalating doses of daily CTO (219-481mg/m2) added to the standard GBM RT regimen (60 Gy concurrent with TMZ 75 mg/m^2 daily, followed by adjuvant TMZ 150-200 mg/m2 X5/28 days). **Results:** All enrolled pts (N = 15) had GBM (methylated MGMT: 33%; unmethylated: 67%). Next generation sequencing (N = 9) showed mutations involving *TERT* (56%), *EGFR* (33%), *IDH-1* (22%) and *TP53* (44%), among others. ChemoRT was well tolerated at CTO doses of 219-481 mg/m^2, with no dose-limiting toxicities (DLT) observed during the DLT period; adverse events included fatigue, nausea, constipation and headache. DLTs were however observed beyond the DLT observation period, and after RT: Gr 3 febrile neutropenia (N = 2), gr 4 neutropenia (N = 1), gr 4 platelets (N = 1) and gr 3 ALT/AST (N = 1). This prompted a halt in dose escalation at 481 mg/m^2 (declared the maximum administered dose, MAD) and expansion of a lower dose level (370 mg/m^2). Efficacy evaluation is ongoing, with one confirmed partial response and stable diseases for 7+ cycles. PK data confirmed therapeutic levels starting at 219 mg/m^2. Tissue and DCE-perfusion MRI correlates are ongoing. **Conclusions:** CTO in combination with RT and TMZ is safe and well tolerated. The MAD dose was 481 mg/m2 and recommended phase II dose is 370 mg/m2, although further evaluation of this dose level and longer follow up may be warranted. Further phase IB studies of CTO should consider designs such as continuous reassessment method, which better address late toxicities in comparison to a 3+3 design. Given encouraging signals of activity, a randomized study is warranted. Clinical trial information: NCT01107522.

2063 Poster Session (Board #52), Mon, 1:15 PM-4:45 PM

Decision support needs analysis in newly diagnosed malignant glioma. *First Author: Lara Kunschner Ronan, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: Standard treatment pathways exist for malignant glioma, but are largely palliative. Patients face difficult non-curative treatment decisions. Oncologists may misinterpret patient goals or communicate ineffectively the risks/benefits of treatments. Shared Decision Making in which the patients' values and goals are incorporated into informed consent is ideal in this situation. **Methods:** Ten patients, caregivers and two treating physicians completed questionnaire-based interviews exploring patient perceptions and understanding of standard of care treatment recommendations in the outpatient clinical setting after receiving a post-surgical diagnosis of malignant glioma. Cognitive dysfunction was evaluated with neurological examination, Trail Making Test and Hopkins Verbal Learning Test. Physical and emotional distress was scored with the FACT-BR and KPS. **Results:** Ten patients patients participated. Common themes in the patients' interviews were 1. Fear of "doing nothing", "chemotherapy", loss of function/QOL; 2. Misperception of improvement in prognosis with treatment; 3. Loss of autonomy in decision making to physician and family members; 4. Lack of perception of any options; 5. Need for validation in decision making; 6. Lack of perception of dis/advantages of treatment. All patients and caregivers desired more information than was provided. Patients and caregivers who expressed interest in a second opinion did so with the goal of validating what the treating physician was recommending to improve confidence that the patient was making the "right" decision. The physicians emphasized the expected advantages of improved survival. Physicians and caregivers perceived increased patient independence in decision making than did patient. **Conclusions:** Patients had difficulty formulating and discussing the treatment information provided in a verbal format. While the information given met criteria to form the basis for informed consent and the physicians believed that Shared Decision Making occurred, in fact there was poor understanding of prognosis, advantages and disadvantages of standard of care treatment and patients felt little autonomy. A decision tool to incorporate patients' concerns is under development.

2064 Poster Session (Board #53), Mon, 1:15 PM-4:45 PM

Clinical outcome of adult brainstem glioma treated with concurrent chemoradiotherapy: An institutional experience. *First Author: Haresh Kunhiparambath, All India Institute of Medical Sciences, New Delhi, India*

Background: Brainstem glioma (BSG) is an aggressive tumor of adulthood. Treatment outcomes remain dismal and role of concurrent chemoradiotherapy (CTRT) is not established in these patients .We intended to study the clinical characteristics along with outcome of adult BSG patients treated with CTRT. **Methods:** We retrospectively evaluated 29 patients, age more than 18 years, with BSG treated at our department in the period Jan 2007 to December 2012. Demographic and disease characteristics in this patient cohort were recorded, and their progression free survival (PFS) was analyzed with respect to sex, grade, use of CTRT and adjuvant chemotherapy. **Results:** Median age at presentation was 35 years (range 22-66 years), with a male: female ratio of 2:1.18 patients presented with gait ataxia and 16 presented with cranial nerve palsies.18 patients were diagnosed radiologically as low grade. None of the patient underwent surgery. Radiotherapy dose was 56-60 Gray over 5.5 -6 weeks at 1.8-2 gray/fraction. All patients completed their radiotherapy. 11 patients received concurrent Temozolomide (75 mg/m2), 10 patients received adjuvant Temozolomide (150-200 mg/m2 D1-5 q4 weeks for 3-6 cycles) and 6 patient received both concurrent and adjuvant Temozolomide. Median follow up duration was 9.77 months (range 0.3-54.82 months). At last follow up, 27 patients had progressive disease. Median PFS for the entire group was 64.19 months. PFS was significantly poorer in the patients who received concurrent Temozolomide than those who did not (Median PFS 64.19 vs. NR months; p = .016) on Univariate analysis. Sex, grade, and adjuvant chemotherapy did not statistically alter treatment outcomes. **Conclusions:** Outcome of adult BSG is better in our cohort compared to reported results. CTRT with Temozolomide has detrimental effect on survival and its use should be discouraged. Radiotherapy alone with standard fractionation remains the treatment of choice in inoperable adult BSG.

2065 Poster Session (Board #54), Mon, 1:15 PM-4:45 PM

A phase II study of the combination of BKM120 (buparlisib) and bevacizumab in patients with relapsed/refractory glioblastoma multiforme (GBM). *First Author: Kent C. Shih, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: BKM120 is an orally bioavailable, pan-class I PI3K inhibitor that is known to cross the blood brain barrier. The PI3K pathway is frequently dysregulated in GBM patients causing abnormal cell growth and proliferation. This phase II multicenter study evaluated the combination of BKM120 with bevacizumab in patients with relapsed/refractory GBM. **Methods:** Patients with relapsed/refractory GBM following 1st line radiation/chemotherapy and surgical resection were treated with BKM120 60 mg PO daily and bevacizumab 10 mg/kg IV every 2 weeks of each 4 week cycle. Following an amendment, responses were evaluated every 8 weeks per RANO criteria; prior to this amendment, responses were assessed by MacDonald criteria. Treatment continued until disease progression or intolerable toxicity. The primary endpoint was median PFS. Secondary endpoints included RR, OS and toxicity. **Results:** Sixty-eight patients were treated with a median age of 57 years (range, 19-77). 13 patients (19%) had received prior bevacizumab. Median treatment duration was 16 weeks (range, 1-120); 6 patients (9%) remain on treatment. Disease progression (51%) and toxicity (13%) were the most common reasons for treatment discontinuation. Overall RR was 32% (CR, 2; PR, 20); 18 patients (26%) had stable disease. In patients who received prior bevacizumab, 1 patient each experienced a CR and a PR and 4 experienced SD for a clinical benefit rate (CR+PR+SD) of 46%. Median PFS and OS (95% CI) were 5.3 months (3.8, 7.5) and 10.8 months (9.1, 22) respectively. Treatment-related toxicities included fatigue (37%), hyperglycemia (26%) and increased ALT (25%); 1 patient experienced grade 4 hyperglycemia. Forty patients (59%) experienced CNS symptoms while on study, 5 (13%) of which were treatment-related grade 3 toxicities: mood alteration, suicidal ideation, altered mental status, confusion, and psychosis (1 patient each). **Conclusions:** The combination of BKM120 and bevacizumab was well-tolerated and clinical activity was observed, including 6 patients who received prior bevacizumab. Accrual to this study in patients previously treated with bevacizumab continues. Clinical trial information: NCT01349660.

2066 Poster Session (Board #55), Mon, 1:15 PM-4:45 PM

The effect of regadenoson-induced transient disruption of the blood brain barrier on temozolomide delivery to rat brain parenchyma. *First Author: Sadhana Jackson, Johns Hopkins Univ, Baltimore, MD*

Background: The blood-brain barrier (BBB) poses a serious challenge of effective delivery of systemically administered agents to the central nervous system. Temozolomide is the only systemically delivered chemotherapy to significantly improve survival in patients with glioblastoma with brain concentrations of only 20% of that in blood. Regadenoson is an FDA approved adenosine receptor agonist used for cardiac stress testing, yet has demonstrated transient disruption of rodent BBB allowing dextran (70kD) brain entry. This study was conducted to determine if regadenoson could facilitate entry of temozolomide into normal rodent brains. **Methods:** Temozolomide (50 mg/kg) was administered by oral gavage to non-tumor bearing F344 rats. Two-thirds of the animals received a single dose of intravenous regadenoson 60-90 minutes later. All animals were sacrificed 120 or 360 minutes after temozolomide administration. Temozolomide concentrations were determined using HPLC/MS/MS. **Results:** At 120 minutes, brain temozolomide concentrations were significantly higher when given with regadenoson vs. alone (8.1 ± 2.7 μg/g and 5.1 ± 3.5 μg/g, $P < 0.05$), with a similar trend in brain:plasma ratios (0.45 ± 0.08 and 0.29 ± 0.09, $P < 0.05$). Brain and brain:plasma were increased without statistical significance 360 minutes after temozolomide administration. There was no difference in plasma temozolomide concentrations with or without regadenoson. **Conclusions:** These results suggest co-administration of regadenoson with temozolomide results in 60% higher temozolomide levels in normal brain without affecting plasma concentrations. This novel approach to increasing intracranial concentrations of systemically administered agents can potentially improve efficacy of therapeutic agents used for brain tumors and other neurologic disorders.

2067 Poster Session (Board #56), Mon, 1:15 PM-4:45 PM

Carboxyamidotriazole orotate (CTO) in combination with bevacizumab (BEV) for adult patients with recurrent malignant glioma post-BEV failure: Phase 1. *First Author: Annick Desjardins, Duke University Medical Center, Durham, NC*

Background: BEV is approved for the treatment of recurrent glioblastoma pts, but there is a lack of effective therapies once a tumor recurs on BEV. CTO, an oral inhibitor of non-voltage-dependent calcium signaling, modulates several pathways (EGFR, MEK, RAS, HDAC, HSP90, WNT/B-catenin, Akt, ERK, VEGF, Bcr-Abl). We postulated that combining CTO with BEV may result in greater VEGF inhibition and might allow salvage post-BEV failure. We are reporting on phase 1 of the study. **Methods:** Study objectives are to assess the maximum tolerated dose (MTD), dose limiting toxicity (DLT) and activity of CTO when combined with BEV among pts with recurrent WHO grade III or IV MG post-BEV failure. CTO dose escalation has followed a classical 3+3 design at a dose ranging from 225-642mg/m^2/day. BEV has been administered intravenously at 10mg/kg every 2 weeks. Pharmacokinetic (PK) sampling is performed during cycle 1 at each dose level. MRI of the brain is evaluated at baseline and every 8 weeks using RANO criteria. **Results:** To date, 15 pts have been enrolled on study. All pts have WHO grade IV MG. Median age at enrollment is 54 (32-66) years in eight females and seven males. Of the five pts treated at dose level 1 of CTO (225mg/m^2/day), three remained stable for 4 cycles and demonstrated CAI (the active moiety of CTO in plasma) levels of 2317 and 361 ng/ml. Of the six pts treated at dose level 2 (293mg/m^2/day), one pt remained stable for 7 cycles and one pt experienced a DLT, grade 3 hypertension and fatigue. Four pts were treated on dose level 3 (380 mg/m^2/day), but two pts were not eligible for MTD determination, as they discontinued CTO before the end of cycle 1 without experiencing a DLT. Grade 3 study-related adverse events included: fatigue (n = 1), soft tissue infection (n = 1), proteinuria (n = 2) and hypertension (n = 2). No grade 4 or 5 study-related adverse events have been observed. **Conclusions:** CTO, at a dose of 380mg/m^2/day, given in combination with BEV is safe thus far and tolerable. Non-evaluable pts for MTD are being replaced. Some pts having previously failed BEV have remained stable for a period of time on the combination. Further dose escalation is continuing to determine the Phase II dose. Clinical trial information: NCT01954030.

2068 Poster Session (Board #57), Mon, 1:15 PM-4:45 PM

Oncolytic polio/rhinovirus recombinant (PVSRIPO) against recurrent glioblastoma (GBM): Optimal dose determination. *First Author: Annick Desjardins, Duke University Medical Center, Durham, NC*

Background: The live attenuated oral (SABIN) serotype 1 poliovirus vaccine was modified to contain a heterologous internal ribosomal entry site stemming from human rhinovirus type 2, creating PVSRIPO. PVSRIPO recognizes nectin-like molecule-5, an oncofetal cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy. We report results of a dose finding study evaluating PVSRIPO delivered intratumorally by convection-enhanced delivery (CED). **Methods:** Eligible patients were adults with recurrent supratentorial GBM; solitary tumor 1-5cm in diameter; ≥ 4 weeks after chemotherapy, bevacizumab or study drug; adequate organ function; KPS > 70%; and positive anti-polio titer. The original two-step continual reassessment method dose escalation was amended to decrease to dose level -1 after observing prolonged steroid use in patients treated on higher dose levels. **Results:** Thus far, 20 patients have been treated (1 each at dose levels 1 and 3, 7 at level 2, 2 at level 4, 4 at level 5 and 5 at dose level -1). One dose-limiting toxicity was observed; a grade 4 intracranial hemorrhage at catheter removal (dose level 5). Adverse events possibly related to study include: pyramidal tract syndrome (grade 3, n = 5; grade 2, n = 1; grade 1, n = 1), seizure (grade 3, n = 1; grade 2, n = 1; grade 1, n = 8), lymphopenia (grade 3, n = 1), headache (grade 2, n = 4; grade 1, n = 4), dysphasia (grade 2, n = 3; grade 1, n = 6), paresthesia (grade 2, n = 3; grade 1, n = 5), concentration impairment (grade 2, n = 1; grade 1, n = 9), fatigue (grade 1, n = 7); one each of grade 2 diarrhea and hyperbilirubinemia; and one each of grade 1 fever, cough, nasal congestion, ataxia, eye pain, diplopia, homonymous hemianopia, thrombocytopenia, anemia, nausea and vomiting. Twelve patients remain alive, with pts #1 and #2 now more than 33 and 31 months post-PVSRIPO, respectively. **Conclusions:** Infusion of PVSRIPO via CED is safe thus far and encouraging efficacy results are observed. We are determining optimal phase II dosing. Clinical trial information: NCT01491893.

2069 Poster Session (Board #58), Mon, 1:15 PM-4:45 PM

Targeting dopamine receptor 2 (DRD2) signaling in combination with temozolomide chemotherapy as a novel therapeutic concept in glioblastomas. *First Author: Tor-Christian Aase Johannessen, Kristian Gerhard Jebsen Brain Tumor Research Centre, Department of Biomedicine, University of Bergen, Bergen, Norway*

Background: Glioblastomas are highly resistant to therapy and carry a poor prognosis. Novel therapeutic strategies are urgently needed to improve patient outcome. This study was designed to identify drugs that would sensitize glioblastoma cells to temozolomide (TMZ) chemotherapy. **Methods:** A genome-wide RNAi synthetic lethality screen was performed in glioblastoma cells to identify functional gene sets that would potentiate the effect of TMZ. The Connectivity Map database was then interrogated to identify potential drug candidates that would induce corresponding changes in gene expression. The highest ranked prospective compounds were validated in combination with TMZ in low-throughput cytotoxicity assays. Based on these findings, the most promising compound, the established anti-psychotic agent Thioridazine, was evaluated further in combination with TMZ *in vivo* in a clinically relevant orthotopic xenograft model. **Results:** Thioridazine significantly improved TMZ sensitivity in established glioblastoma cell lines as well as patient-derived cells. The specific chemosensitizing effect of Thioridazine was due to antagonism of dopamine receptor 2 (D_2 receptor; DRD2). Inhibition of D_2 receptor signaling by Thioridazine decreased MAPK and PI3K/AKT/mTor pathway activity through a DRD2/β-arrestin-2/AKT signaling complex. Inhibition of this complex induced non-apoptotic cell death caused by impaired autophagy leading to catastrophic vacuolization. The combination of TMZ and Thioridazine significantly decreased intracranial glioblastoma growth, and improved survival of tumor-bearing mice compared to treatment with TMZ alone. **Conclusions:** Our findings demonstrate that the DRD2/β-arrestin-2/AKT signaling complex connects dopamine signaling to tumor cell survival. We have also identified a novel strategy to inhibit autophagy in glioblastoma cells by antagonizing the D_2 receptor. Due to the low toxicity of Thioridazine and its advantageous pharmacological properties, the presented work suggests that Thioridazine plus TMZ could be used for glioblastoma treatment in an adjuvant setting.

2070 Poster Session (Board #59), Mon, 1:15 PM-4:45 PM

A phase 1b/2 study of the combination of the IDO pathway inhibitor indoximod and temozolomide for adult patients with temozolomide-refractory primary malignant brain tumors: Safety analysis and preliminary efficacy of the phase 1b component. *First Author: Howard Colman, Hunstman Cancer Inst Univ of Utah, Salt Lake City, UT*

Background: Indoleamine 2, 3-dioxygenase (IDO) is a key immune-modulatory enzyme within the IDO pathway that inhibits CD8+ T cells and enhances the suppressor activity of Tregs. IDO is expressed in a large proportion of solid tumors including 50 to 90% of glioblastomas (GBM). High IDO expression is correlated with poor prognosis in GBM. IDO pathway inhibitors such as indoximod (1-methyl-D-tryptophan / D-1MT) can improve anti-tumor T cell response slowing the tumor growth *in vivo*. We have demonstrated a synergistic effect of indoximod when combined with temozolomide (TMZ) and radiation in a syngeneic orthotopic brain tumor model. This phase 1b/2study is designed determine the safety profile and maximal tolerated dose (MTD) of indoximod in combination with TMZ in recurrent refractory malignant brain tumors with subsequent expansion into a phase 2 portion evaluating efficacy of the combination. **Methods:** After progression to standard front line-therapy with TMZ, patients were enrolled in a 3+3 dose escalation study of indoximod (600, 1000 or 1200 mg twice daily orally) with a standard dose of TMZ (150mg/m^2 x 5 days). Indoximod was administered for all 28 days of each treatment cycle. **Results:** 12 patients were required to fully enroll all three dose cohorts with no DLTs requiring cohort expansion at lower doses. Median age was 48.5 years (27-62) with 5 female and 7 male. 83% had a diagnosis of GBM. 6 patients remain on study, the longest on cycle 12. Best responses in these previously TMZ-refractory patients to date include SD in 3 patients lasting between 5 and 10 months duration (ongoing) with one patient demonstrating a progressive, ongoing substantial reduction in tumor size, approaching RANO criteria for PR. No patients to date have experienced a reduction or delay in temozolomide dosing due to the addition of indoximod nor an indoximod related serious adverse event. **Conclusions:** The MTD for indoximod in this combination and setting was 1200mg twice daily. Expansion into the phase 2 portion is proceeding to evaluate the exciting preliminary observations made in this trial. Clinical trial information: NCT02052648.

2071 Poster Session (Board #60), Mon, 1:15 PM-4:45 PM

Identification of glioblastoma patients who stand to benefit from PARP inhibitor therapy. *First Author: Kerrie Leanne McDonald, University of NSW, Kensington, Australia*

Background: The development of effective targeted drugs for the treatment of glioblastoma (GBM) represents a major unmet need. Veliparib (ABT-888; Abbvie) inhibits both PARP1 and PARP2 (poly[ADP-ribose] polymerase). The successful clinical application of veliparib and other PARP inhibitors (PARPi) will be assisted by the identification of predictive biomarkers. **Methods:** Efficacy of veliparib in combination with radiotherapy (RT) was tested on a panel of primary and recurrent GBM patient-derived cell lines (PDCLs). In order to screen for potential biomarkers for PARPi we performed whole genome sequencing (WGS) on sensitive and resistant PDCLs and also measured the expression of 96 candidate DNA repair pathway genes using the RT2 Profiler PCR Array (Human DNA Repair; Qiagen) **Results:** Differential sensitivity to veliparib and RT were observed amongst the panel of PDCLs. Three out of sixteen PDCLs showed hypersensitivity to veliparib/RT. PDCLs sensitive to treatment exhibited a large number of structural variation (SV) events ($>$ 200). The average SV events identified in the resistant PDCLs were $<$ 50. We detected mutations in genes involved in mismatch repair (MMR): *MLH1*, *MSH2*, *MSH6* and *PMS2*. We also detected mutations in other genes involved in DNA maintenance such as *XRCC4*, *FANCA*, *FANCD2*, *ATR*, *RPA1*, *REV3L* and *PARP1* only in the sensitive PDCLs. **Conclusions:** Mutations in DNA maintenance pathways may be a method for selecting patients for therapies involving the combination of DNA damaging agents such as radiotherapy, and PARP inhibitors. Additionally, the signature associated with genomically unstable GBM may be a method of identifying potential responders to PARP inhibitor therapy.

2072 Poster Session (Board #62), Mon, 1:15 PM-4:45 PM

Prospective validation of cerebrospinal fluid (CSF) circulating tumor cells (CTC) to diagnose leptomeningeal metastasis (LM) from epithelial tumors. *First Author: Xuling Lin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The diagnosis of LM remains challenging, as standard diagnostic tools such as CSF cytology and MRI have low sensitivity. We previously showed that detection of CSF CTC by rare cell capture technology (RCCT) may be a more sensitive technique to detect LM from epithelial tumors at early stages. To validate those findings, we evaluated the performance of CSF CTC analysis in a new cohort of patients with a suspicion of LM. **Methods:** In this IRB-approved prospective study, patients with epithelial tumors who had clinical symptoms suspicious for LM were enrolled. All patients underwent MRI and CSF analysis through conventional cytology and enumeration of CSF CTC in that same sample.CSF CTCs were enumerated through an FDA-approved, EpCAM-based enrichment, utilizing RCCT immunomagnetic platforms and antibody covered ferroparticles (Janssen Diagnostics, Raritan, NJ). For the present analysis, samples were considered positive for CSF CTCs when there was at least one CSF CTC detected in a 3 mL sample ($\geq$ 0.33 CSF CTC/mL). Diagnostic performance of CSF CTC was evaluated; the gold standard was either positive CSF cytology or unequivocal findings on MRI. **Results:** 62 patients were enrolled (27 breast, 20 lung, 7 GU, 3 GI, 2 renal and 3 other carcinomas). Among these patients, 21 (34%) had LM based on CSF cytology (n = 8), MRI findings (n = 4) or both (n = 9). CSF CTCs were positive in 27/62 samples (median 19.3 CSF CTC/mL, range 0.3 to 66.7), achieving a sensitivity of 95%, compared to 81% for CSF cytology alone and 62% for MRI alone. There were 7 false positive CSF CTCs, all of which with one or fewer CSF CTCs/mL; specificity was 83%. The one false negative sample also had negative CSF cytology but LM was seen on MRI. **Conclusions:** Detection of CSF CTCs by RCCT is a highly sensitive (95%) method to establish the diagnosis of LM, with superior diagnostic performance as compared to CSF cytology or MRI. However, results showing one or fewer CSF CTCs/mL are of uncertain significance and may correspond to false positive results. Larger studies with longer followup and ROC analysis are needed to investigate alternative CTC enumeration cut-offs to improve specificity.

2073 Poster Session (Board #63), Mon, 1:15 PM-4:45 PM

IDH1 mutation status and outcome in clinical trials for recurrent glioblastoma. *First Author: Jacob Joseph Mandel, Baylor College of Medicine, Houston, TX*

Background: IDH1 mutated glioblastoma (GB) has a better prognosis than IDH1 wildtype GB. Clinical trials for recurrent GB currently do not stratify patients (pts) based upon IDH status. It is not known if pts with IDH1 mutated GB on clinical trials are more likely to have a higher 6-month progression free survival (PFS6) or radiographic response (RR) rate. **Methods:** A retrospective review of GB pts treated at MD Anderson Cancer Center between 2006-2012 identified 330 pts enrolled in recurrent GB trials. 93 pts (28%) either had PFS6 or a complete or partial RR per RANO criteria. 49/93(53%) pts with PFS6 or a complete or partial RR were found to have tumor tissue available for IDH1 testing. A matched cohort of pts on the same recurrent GB clinical trials with tissue for IDH1 testing but no PFS6 or RR was identified based on the specific clinical trial, age and KPS. 49 pts were identified for comparison resulting in a total of 98 patients. **Results:** IDH1 status was obtained in 92 (94%) pts of which 17 (18%) had an IDH1 mutation. Recurrent GB trial was at 1^{st}-4^{th} recurrence with 62% at 1^{st}, 26% at 2^{nd}, 8% at 3^{rd} and 4% at 4^{th}recurrence. Median time from GB diagnosis to recurrent trial was 8.4 months (mo) for IDH1 wildtype GB vs. 10.9 mo for IDH1 mutated GB ($p < 0.66$). PFS6 was seen in 26/49 (53%) pts of which 2 pts IDH status was unknown. 5/24 (21%) pts with PFS6 had IDH1 mutations compared to 5/24 (21%) pts of their matched cohort without PFS6. RR was found in 46/49 (94%) pts of which 4 pts IDH status was unknown. IDH1 mutation was present in 7/42 (17%) pts with RR compared to 10/42 (24%) pts of their matched cohort without RR ($p < 0.49$). For all patients, median PFS on a recurrent trial was 3.68 mo for IDH1 wildtype GB vs. 3.52 mo for IDH1 mutated GB ($p < 0.72$). Median OS on recurrent trial was 8.64 mo for IDH1 wildtype GB vs. 9.59 mo for IDH1 mutated GB ($p < 0.49$). **Conclusions:** IDH1 mutation status does not appear to be predictive of PFS6 or RR in recurrent GB trials. However, further examination in larger randomized prospective studies is needed.

2074 Poster Session (Board #64), Mon, 1:15 PM-4:45 PM

Analysis of BRAF alterations and molecular profiling in glioblastoma and astrocytoma. *First Author: Nadia Faiq, UC San Diego Moores Cancer Center, San Diego, CA*

Background: Although well characterized in pilocytic astrocytoma and pleomorphic xanthroastrocytoma, the prevalence of BRAF alterations in glioblastoma (GBM) and astrocytoma is not well established. Characterization of BRAF mutations in glioblastoma and astrocytoma may identify a subgroup of patients with sensitivity to BRAF inhibitors. **Methods:** DNA was extracted from 95 diffuse gliomas (grade II-IV) at our institution and an independent set of 714 gliomas, and was subjected to hybrid capture for 315 or 265 cancer-related genes plus select intronic regions. Sequencing was performed to a mean coverage depth of $>$ 500x and analyzed for the presence of base substitutions, insertions/deletions, copy number alterations, and rearrangements. **Results:** 7 of 95 gliomas (7.4%) analyzed harbored BRAF alterations; 6 (6.3%) were identified with either a V600E mutation (3 GBM + 1 gliosarcoma) or a D594G mutation (2 GBM). One glioma with a BRAF rearrangement was identified (astrocytoma grade II). There were no alterations found in oligodendrogliomas. Molecular profiles in all 6 tumors with BRAF point mutations were similar; all were wild type for IDH1/2 and exhibited CDKN2A/B loss. Conversely, the BRAF rearrangement was IDH1 mutated and CDKN2A/B intact. To confirm the frequency of BRAF alterations, an independent database of 714 gliomas was queried. Thirty-four (4.8%) tumors were found to have BRAF alterations, including 24 BRAF point mutations. Of those, 96% ($n = 23$) were IDH1/2 wild type and 83% ($n = 21$) harbored CDKN2A/B loss. Conversely, BRAF rearrangements and amplifications ($n = 10$) did not share this profile. 40% harbored IDH1/2 mutations and only 40% displayed CDKN2A/B loss. In our patients, 5 of the 6 with BRAF point mutations are alive. The median overall survival is 28.8 months (10.7-40.6). One patient with recurrent GBM and V600E mutation was treated with the BRAF inhibitor vemurafenib with a PFS $>$ 12 months. **Conclusions:** BRAF alterations occur in GBM and astrocytoma. BRAF point mutations are associated with a specific molecular profile, specifically IDH1/2 wild-type and CDKN2A/B loss. This profile identifies a molecular subgroup of gliomas that may exhibit improved survival and are amenable to targeted therapy with BRAF inhibitors.

2075 Poster Session (Board #65), Mon, 1:15 PM-4:45 PM

Targeting PTBP1 as a therapeutic strategy to reverse lineage-specific splicing of ANXA7 and ensuing EGFR activation in glioblastoma. *First Author: Markus Bredel, University of Alabama at Birmingham School of Medcn, Birmingham, AL*

Background: Tissue-specific splicing involves evolutionarily conserved, alternative exons many of which have functional features that influence cell signalling. The membrane-binding tumor suppressor ANXA7 belongs to a family of proteins involved in endosomal organization and function. ANXA7 contains an alternative cassette exon that shows high prevalence in neurons, but its functional consequence is not well understood. PTBP1 is a ribonucleoprotein that is normally repressed during neuronal development. **Methods:** We used integrated molecular genetic and cell biology analyses, animal modeling, and clinical patient profiles to characterize the role of splicing of ANXA7 during glioblastomagenesis. We examined the cellular and kinomic effects of a new class of PTBP1 modulators and their effects on ANXA7 splicing. **Results:** Lineage-specific splicing of the cassette exon in ANXA7 diminished endosomal targeting of the EGFR oncoprotein and enhanced glioblastoma (GBM) progression. ANXA7 splicing was mediated by PTBP1, which was highly expressed in GBMs due to loss of brain-enriched microRNA miR-124 and to PTBP1 amplification. The alternative ANXA7 splicing trait was present in precursor cells, suggesting that GBM cells inherit the trait from a potential tumor-initiating ancestor. PTBP1 overexpression portended a poor clinical outcome in patients with GBM. Targeting PTBP1 with an FDA-approved compound, identified by a cell-based high-throughput assay that reports on the splicing activity of PTB, reduced PTBP1 levels and reversed ANXA7 splicing and ensuing EGFR activation. It revealed a significant inhibitory effect on GBM cell viability that was enhanced by the addition of radiation. Drug derivatives exerted even more potent effects on cell proliferation alone and when combined with radiation. **Conclusions:** PTBP1 mediates lineage-specific splicing of ANXA7 and eliminates its tumor suppressor function, thereby promoting GBM progression. Pharmacologic targeting of PTPB1 reverses the splicing event and exhibits anti-proliferative effects that are augmented by concurrent radiation, offering a potential new avenue for future therapeutic modulation in glioblastoma.

TPS2076 Poster Session (Board #66a), Mon, 1:15 PM-4:45 PM

A phase I study of TPI 287 concurrent with fractionated stereotactic radiotherapy (FSRT) in treatment of brain metastases from advanced breast and non-small cell lung cancer (NSCLC). *First Author: Solmaz Sahebjam, Moffitt Cancer Center, Tampa, FL*

Background: TPI 287, a member of taxanes diterpenoid (taxoid) family, is a microtubule-inhibitor with significant cytotoxic activity. TPI 287 is not a P-glycoprotein substrate and therefore is able to circumvent resistance associated with the expression of the multidrug-resistance-1 (MDR-1) gene. Preclinical studies have demonstrated that TPI 287 crosses the blood brain barrier and reaches a therapeutic concentration in brain tissue. In vivo models of human breast cancer brain metastasis show that TPI 287 significantly reduces the formation of large brain metastases. The radiosensitizing effect of taxanes is well established. This report describes an ongoing phase I trial of TPI 287 concurrent with FSRT in patients (pts) with 1-3 brain metastases from histologically or cytologically confirmed advanced breast or NSCL cancer. **Methods:** This phase I study employs a standard 3 + 3 dose escalation design exploring 6 sequential dose escalation cohorts (NCT02187822). Pts with up to 3 untreated brain metastases (maximum diameter of each brain lesion $\leq$ 5 cm, maximum tumor volume $\leq$ 120 cc) from breast cancer or NSCLC are eligible. Eligible patients will be treated with FSRT to target brain metastases (25 Gy in 5 daily fractions). TPI 287 is administered intravenously once per week, for total of 3 doses. The first dose of TPI 287 is given concurrently with the first fraction of FSRT. Once the recommended phase II dose (RP2D) is determined, an additional 10 patients will be enrolled in an expansion safety cohort, for a planned total enrollment of 36 patients. The primary study objectives are to determine safety and the RP2D of TPI 287 administered concurrently with FSRT to brain metastases. Secondary endpoints include determination of the pharmacokinetics of TPI 287, preliminary antitumor activity (local control rate, distant intra-cranial control rate, progression-free survival) and evaluating effect of treatment on measures of quality of life. Study Progress: At deadline for abstract submission, 2 patients have been enrolled onto this study. Clinical trial information: NCT02187822.

TPS2077 **Poster Session (Board #66b), Mon, 1:15 PM-4:45 PM**

Phase II study to evaluate the clinical efficacy and safety of MEDI4736 in patients with glioblastoma (GBM). *First Author: David A. Reardon, Dana-Farber Cancer Center Institute and Harvard School of Medicine, Boston, MA*

Background: Programmed cell death ligand-1 (PD-L1) is widely expressed on antigen presenting cells (APC) and other immune cells. PD-L1 binds two important regulatory receptors on T-cells: programmed cell death-1 (PD-1) and CD80/B7. Targeting Programmed Death-1 (PD-1) and its ligand, PD-L1, have demonstrated promising anti-tumor activity among other challenging solid tumors and growing data implicates PD-1/PD-L1 signaling as a significant contributor to immunosuppression in glioblastoma (GBM). PD-1 is expressed by many GBM infiltrating lymphocytes while PD-L1 is expressed by 61-100% of GBM tumors. Furthermore, loss of the PTEN tumor suppressor gene, which occurs in 40-50% of GBM tumors, leads to increased transcription and expression of PD-L1 in GBM. These findings indicate that PD-L1 is an attractive and important therapeutic target in GBM. MEDI4736 (M), a human IgG1κ blocking monoclonal antibody against PD-L1, represents a compelling immune-mediated anti-tumor treatment for GBM. **Methods:** Phase II, multicenter, open-label study (NCT02336165) is evaluating the clinical efficacy and safety of M in GBM patients. Eligible patients include those who are newly diagnosed with unmethylated MGMT GBM scheduled for standard radiotherapy (Cohort A); Bevacizumab-naïve patients with recurrent GBM (Cohort B); and Bevacizumab-refractory patients with recurrent GBM (Cohort C). Cohort A patients will receive M at 10 mg/kg i.v. Q2W for up to 12 months beginning with standard radiotherapy. Cohort B will receive M at 10 mg/kg i.v. Q2W for up to 12 months as monotherapy. Cohort C will receive M at 10 mg/kg i.v. Q2W for up to 12 months in combination with continued bevacizumab at 10 mg/kg Q2W. Primary endpoints include overall survival (OS) at 12 months (cohort A), progression free survival rate at 6 months (PFS-6) (cohort B) and OS-6 (cohort C). Secondary endpoints are safety/tolerability, PFS, median OS, radiographic response, and quality of life (QoL) by EORTC QLQ-C30/BN20. Exploratory endpoints are patient neurologic function using the Neurologic Assessment in Neuro-Oncology (NANO) scale, as well as immuno-correlative biomarkers and pharmacokinetics. Clinical trial information: NCT02336165.

TPS2078 **Poster Session (Board #67a), Mon, 1:15 PM-4:45 PM**

An oxygenation agent and radiation sensitizer, dodecafluoropentane, for the treatment of glioblastoma multiforme. *First Author: Jason D. Lickliter, Nucleus Network Limited, Melbourne, Australia*

Background: Post-resected glioblastoma multiforme (GMB) patients were treated with dodecafluoropentane emulsion (DDFPe) to evaluate the pharmacokinetics (PK), safety and potential survival benefit in combination with the current standard of care: radiation therapy (RT) and temozolomide (TMZ). DDFPe is an oxygen transport agent, which carries more than 100x more oxygen than other tested fluorocarbons. Studies in tumor xenografts show that DDFPe increases tumor pO2 by up to 400% and mitigates radiation resistance (J Biomed Nanotechnology, Vol 11, No 2, Feb2015, pp. 274-281). **Methods:** DDFPe is being dosed using an accelerated escalation design with one patient per dose level. Eligible patients have previously-untreated GBM with residual enhancing tumor on an early post-operative MRI scan, ECOG score 0-2, satisfactory blood counts and adequate renal and hepatic function. Since an increase in the frequency and extent of radiation necrosis is a theoretical risk of increased oxygenation, the location and size of the radiation field must be assessed as having a manageable risk should radiation necrosis occur. NVX-108 is infused intravenously prior to each fraction of radiation (total 60 Gray in 30 fractions), with patients breathing carbogen gas (2% CO2 and 98% O2) concurrently. Blood samples are drawn to evaluate DDFP PK. Objective tumor responses are assessed with serial gadolinium-enhanced MRI scans using RANO criteria. In addition, molecular analysis of tumor biopsies and tissue oxygen level dependent (TOLD) MRI measurement of tumor oxygenation are being used as exploratory predictive and pharmacodynamic biomarkers. The dose escalation schedule will study NVX-108 doses between 0.05 and 0.35 mL/kg in 5 planned dose levels. Dose levels 1 and 2 have been treated without dose-limiting toxicity. Data will be presented summarizing current safety, PK and preliminary efficacy results, as well as our progress in qualifying TOLD MRI as a potential biomarker of tumor hypoxia and re-oxygenation by DDFPe. Clinical trial information: 2014/007283.

TPS2079 **Poster Session (Board #67b), Mon, 1:15 PM-4:45 PM**

CoaGlio IV Trial: Randomized, controlled, triple-blind, multinational phase III study of adjuvant prophylactic anticoagulation in patients with glioblastoma WHO IV. *First Author: Susanne Antje Kuhn, Hospital Ernst von Bergmann, Potsdam, Germany*

Background: Venous thromboembolism (VTE) is a preventable complication in cancer and represents the second most frequent death cause, despite widely available anticoagulants. Further, VTE was proven as paraneoplastic syndrome of tumors, which use the coagulation to support their own aggressiveness. Currently, no guidelines recommend long-term prophylactic anticoagulation, since no data exists to support the use of any officially approved anticoagulant drug. None of the currently available anticoagulants has been adequately tested for its VTE prophylactic power in a cancer patient population. This study aims at providing a rationale for the generation of prophylaxis and treatment guidelines of VTE in cancer patients. This study finally aims to support the long needed completion of paradigm change in oncology since its initial description as Trousseau's syndrome 150 years ago. **Methods:** The controlled, triple-blind, multinational phase III study randomizes pts. in a 1:1 fashion to receive either postop prophylactic anticoagulation with the oral factor X blocker apixaban (2.5mg b.i.d) or placebo over a 12-month-period in addition to the international first line standard therapy (radiochemotherapy with temozolomide (TMZ) + adjuvant TMZ). The power calculation is based on a 10% difference in overall survival, power at 80%, two-sided alpha level of 0.05, 5% drop out, requiring 530 patients over a two year period, with analysis performed two years after last patient recruited. Eligibility includes: adults, good performance status, newly diagnosed glioblastoma WHO IV, no major co-morbidities and no pregnancy. The primary endpoint is overall survival. Secondary endpoints include: progression free survival (PFS) at 6 and 12 months, median PFS, objective tumor response rate, frequency and mortality of VTE, safety and health related quality of life.Pre-treatment bio-resourcing of tumor and blood will enable further correlative translational studies. Progress to date: Trial activation in Fall 2015 at more than 20 centers in Europe and the United States. Trial registration: European Clinical Trials Database EudraCT 2015-000425-37. Clinical trial information: EudraCT: 2015-000425-37.

TPS2080 **Poster Session (Board #68a), Mon, 1:15 PM-4:45 PM**

Phase I study of plerixafor and bevacizumab in recurrent high-grade glioma. *First Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA*

Background: Although anti-angiogenic therapy for high-grade glioma is promising, responses are not durable. The SDF-1/CXCR4 axis may help mediate resistance to VEGFR inhibition. Plerixafor is a reversible CXCR4 inhibitor that has demonstrated growth inhibition in glioblastoma xenografts. **Methods**: We are conducting a Phase I study to determine the safety and tolerability of plerixafor in combination with bevacizumab in patients with recurrent HGG. In Part 1 of the study, a 3 x 3 dose escalation design to a maximum planned dose level of plerixafor 320 μg/kg on Days 1-21 and bevacizumab 10 mg/kg on Days 1 and 15 of each 28 day cycle was used. DLTs were determined during the initial 4 weeks of therapy and included drug-related Grade $\geq$ 3 non-hematologic toxicities and Grade $\geq$ 4 hematologic toxicities. Part 2 of the study is a surgical study to determine if plerixafor penetrates tumor tissue. **Results**: Part 1 of the study has been completed with 23 patients enrolled. Part 2 of the study is now open with 3 patients enrolled to date. For all 26 patients, the median age is 59 (23-72), median KPS 90 (70-100), 11 women (42.3%). In Part 1, no DLTs were seen at the maximum planned dose level of plerixafor 320 μg/kg + bevacizumb. Treatment has been well tolerated to date with one grade 3 hypophosphatemia and one grade 3 rectal fistula. Preliminary pharmacokinetic data on plerixafor from the first two cohorts compares well with historical PK data. **Conclusions**: Combination treatment with bevacizumab and plerixafor is well tolerated in HGG patients. No DLTs were encountered at the maximum planned dose level. To date, 3 of 10 planned patients have enrolled in the surgical cohort to examine tumor tissue penetration. Updated results as well as preliminary circulating biomarker analysis will be presented. Clinical trial information: NCT01339039.

TPS2081 **Poster Session (Board #68b), Mon, 1:15 PM-4:45 PM**

A phase I study of convection-enhanced delivery of nanoliposomal irinotecan using real-time imaging in patients with recurrent high grade glioma.

First Author: Nicholas A. Butowski, University of California, San Francisco, San Francisco, CA

Background: Cytotoxic drug delivery to high grade glioma (HGG) is limited by the blood brain barrier (BBB). Convection-enhanced delivery (CED) improves chemotherapy delivery by utilizing fluid convection, obviating the challenges of crossing the BBB while minimizing systemic toxicity. CED of a highly concentrated formulation of nanoliposomal irinotecan (MM-398, nal-IRI) has been optimized in animal models of brain tumors and shows superior anti-tumor activity compared to systemic delivery. A major advance in the application of CED is the development of real time CED, which utilizes an interventional MRI suite to visualize the CED process with the aid of a co-convected contrast agent, and thus allows for real time monitoring of drug delivery to the target. **Methods:** With support from a R21 grant, a Phase I study of CED of concentrated nal-IRI using real-time imaging in patients with recurrent HGG is currently open for enrollment. This is a 3+3 dose escalation trial, with dose levels of 20 mg, 40 mg, 60 mg, and 80 mg of nal-IRI, given via up to 3 catheters surgically placed in an intra-tumoral location. The MRI contrast agent gadoteridol (2 mM) will be co-infused via the same catheters. Interim safety, efficacy, and imaging response results will be presented. From the imaging data, the correlation of pre-infusion modeling of drug distribution with post-infusion imaging will be analyzed. This will also allow for determination of the total volume of distribution to volume of infusion (Vd:Vi) ratio for each infusion. Clinical trial information: NCT02022644.

2500 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

A pharmacokinetically (PK) and pharmacodynamically (PD) driven phase I trial of the pan-AKT inhibitor AZD5363 with expansion cohorts in *PIK3CA* mutant breast and gynecological cancers. *First Author: Udai Banerji, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: AZD5363 is a novel potent pan-AKT inhibitor ($IC_{50}$of AKT1, AKT2 and AKT3 of 3, 7 and 7nM respectively) with preclinical activity across a range of models. **Methods:** The trial had an adaptive design that allowed changes in schedule based on toxicity, PK, and PD findings. AZD5363 was administered orally (PO) twice a day (BID). Three schedules were explored: continuous dosing (7/7), four days a week, (4/7) and two days a week (2/7). PD biomarkers including pAKT, pGSK3β, and pPRAS40 were measured by IHC in pre- and post-treatment tumor biopsies. Once a RP2D was established, two expansion cohorts of *PIK3CA*-mutant ER+ve breast (B) and gynecological (G) cancers were explored. **Results:** 47, 21 and 22 patients were treated on the 7/7, 4/7 and 2/7 schedules respectively, with a further 27 and 18 patients recruited to the B and G cohorts to date. The MTDs of 7/7, 4/7 and 2/7 were 320mg BID, 480mg BID and 640mg BID respectively. The dose limiting toxicities (DLTs) were rash and diarrhea for 7/7, and hyperglycemia for 2/7. No DLTs were identified for 4/7. The most common causally-related adverse events $\geq$ CTC Grade 3 were hyperglycemia (20%), diarrhea (10%), rash (10%), nausea (3%) and fatigue (1%). PK profiles at the RP2D of 480mg BID (4/7) showed a multi-dose $C_{ss,max}$ of 1426ng/mL and $AUC_{ss}$of 7952ng.hr/mL, which were consistent with exposures that gave tumor regression in preclinical models. Pre- and post-treatment biopsies confirmed target engagement in tumor tissue, with an increase in pAKT and reductions in pGSK3β and pPRAS40. Based on toxicity, PK and PD profiles 480mg BID (4/7) was chosen as the R2PD for single agent AZD5363, with the option of using 640mg BID (2/7) as a pharmacologically active dose for future combination studies. Target lesion shrinkage was observed in 7/15 and 4/14 in the B and G cohorts respectively to date, and with RECIST responses in evaluable patients of 3/15 (20%) and 1/14 (7%). **Conclusions:** Based on toxicity, PK and PD data two intermittent schedules of AZD5363 have been identified for further exploration. Promising single agent activity has been seen in *PIK3CA*-mutant breast cancer providing support for ongoing combination studies. Clinical trial information: NCT01226316.

2501 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

First-in-human, phase I, dose-escalation study of selective PI3Kα isoform inhibitor MLN1117 in patients (pts) with advanced solid malignancies. *First Author: Dejan Juric, Massachusetts General Hospital, Boston, MA*

Background: PI3K signaling is aberrantly activated in many solid tumors; isoform-selective targeting may enable robust inhibition of this pathway in PIK3CA mutant tumors while sparing signaling in normal tissues. This study (NCT01449370) evaluated the safety, MTD, preliminary antitumor activity and pharmacokinetics/pharmacodynamics (PK/PD) of an investigational PI3Kα isoform-selective inhibitor, MLN1117. **Methods:** Pts age $\geq$ 18 with advanced solid tumors (except primary brain tumors) and known *PIK3CA* mutation status received oral MLN1117 once daily (QD, 100–300 mg) or 3 days per wk (MWF, 200–1200 mg, or MTuW, 200–900 mg) in 21-d cycles. Dose escalation proceeded via a 3+3 design based on cycle 1 (C1) DLTs. Plasma concentrations of MLN1117 for PK analyses were evaluated in C1. PI3K pathway biomarkers were assessed in skin biopsies via immunohistochemistry. **Results:** At data cut-off, 76 pts had enrolled; 24/29/23 pts to QD/MWF/MTuW schedules; median of 3 cycles per group. C1 DLTs occurred in: 2 QD pts (ALT/AST elevation), 4 MWF pts (ALT/AST elevation, hyperosmolar state, nausea, vomiting, diarrhea, dehydration, hyperglycemia and anorexia), and 1 MTuW pt (nausea). MLN1117 MTDs were 150 mg QD and 900 mg for MWF/MTuW. Grade $\geq$ 3 AEs occurred in 54/41/57% of QD/MWF/MTuW pts; 17/14/13% discontinued due to AEs and 13/10/0% died on study. MLN1117 (100–900 mg) exhibited a median T_{max} of ~4 h and a dose-dependent increase in exposure with moderate-high PK variability (mean %CV on $AUC_{0\text{-}24h}$ ~50–70%); wkly exposures in MWF/MTuW pts were ~4 times higher than QD dosing. Mean plasma $t_{1/2}$ was ~11 h with no appreciable accumulation in plasma. MLN1117 200–900 mg suppressed p4EBP1 and pS6 in skin by up to ~100% and 70–90%, respectively, at ~3 h post-single dose. Per RECIST, there were 3/1/0 PRs (QD/MWF/MTuW) in breast and gastric cancers; 4/7/5 pts had stable disease lasting 105–466 d. **Conclusions:** In this first-in-human study (n = 76), the safety profile of MLN1117 was acceptable for MWF/MTuW dosing $\leq$ 900 mg. MWF/MTuW schedules enabled higher doses and weekly exposures vs QD dosing. PD data indicate PI3K pathway inhibition. Objective responses show antitumor activity in advanced solid tumors (n = 4). Clinical trial information: NCT01449370.

2503 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Phase I studies of anti-ENPP3 antibody drug conjugates (ADCs) in advanced refractory renal cell carcinomas (RRCC). *First Author: John A. Thompson, Seattle Cancer Care Alliance, Seattle, WA*

Background: ENPP3 is expressed in greater than 90% of clear cell (CC) and 70% of papillary (PAP) RCC and represents an interesting target in this disease. Hybridoma-derived AGS-16M8F and CHO-derived AGS-16C3F are fully human IgG2k monoclonal antibodies (mAbs), conjugated to microtubule disrupting agent MMAF via a plasma-stable linker, which bind to ENPP3. The 2 ADCs have similar pharmacokinetic and toxicologic profiles. **Methods:** Two phase I studies were conducted sequentially to test safety, PK, and antitumor activity (RECIST v1.1) of AGS-16M8F and AGS-16C3F in CC and PAP RRCC (median prior systemic therapies = 3). ADCs were given q3w until PD or unacceptable toxicity. **Results:** AGS-16M8F and AGS-16C3F studies treated 26 and 34 subjects in dose range 0.6 - 4.8 and 1.8 - 4.8 mg/kg, respectively. Fatigue was the most common adverse event (AE) in both studies. In the AGS-16M8F study, maximum tolerated dose (MTD) was not reached, but 3/8 subjects at 4.8 mg/kg discontinued for ocular toxicity (OT). OTs were most commonly reversible keratopathy. In the AGS-16C3F study, the initial dose of 4.8 mg/kg exceeded MTD; 2/2 subjects had dose-limiting toxicities (DLTs); 1 was grade 4 OT. OTs were also observed at lower doses, usually after 2 doses. This led to a successive de-escalation to 3.6, 2.7, and 1.8 mg/kg. Thrombocytopenia (TCP) was frequently reported but a DLT in only 1 subject at 3.6 mg/kg (AGS-16C3F). PK of both ADCs was comparable. Serum concentrations decreased multi-exponentially; exposure was dose proportional. In both studies, the mean terminal half-life was approx. 7-8 days for the intact drug and approx. 4 days for MMAF. **Conclusions:** Both ADCs tested had associated OT but it was more prominent with AGS-16C3F. However AGS-16C3F was well tolerated at 1.8 mg/kg and showed antitumor activity as evidenced by median disease control of 23+ weeks and durable PR in 2/10 of CC and 1/3 PAP RRCC. A phase II study is planned with AGS-16C3F at 1.8 mg/kg. Clinical trial information: NCT01672775.

	AGS-16M8F	AGS-16C3F	AGS-16C3F
	All	All	1.8 mg/kg
N	26	34	13
Median prior systemic therapies	3 (0-8)	3 (0-9)	3 (2-7)
Relevant AEs (All / $\geq$ grade 3)			
OT	8 / 1	29 / 10	12 / 2
TCP	8 / 3	11 / 6	2 / 1
Fatigue/asthenia	12 / 1	26 / 6	12 / 3
Median wks on therapy	12 (1-80)	9 (1-66)	18 (9-48+)
ORR	1 PR, 9 SD	3 PR, 17 SD	3 PR, 9 SD
Median Disease Control (PR+SD, wks)	21 (12-80)	18 (6 - 66)	23+ (9- 48+)

2504 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Therapy of advanced metastatic lung cancer with an anti-Trop-2-SN-38 antibody-drug conjugate (ADC), sacituzumab govitecan (IMMU-132): Phase I/II clinical experience. *First Author: Michael J. Guarino, Helen F. Graham Cancer Center at Christiana Care Health System, Newark, DE*

Background: Sacituzumab govitecan (IMMU-132) is a new ADC comprising SN-38, the active metabolite of the topoisomerase inhibitor, camptothecin (irinotecan), conjugated to an anti-Trop-2 antibody. In vitro and in vivopreclinical data suggest that IMMU-132 is a unique ADC, being most efficacious at a high drug-antibody ratio (DAR) of 7.6, and capable of delivering up to 136-fold more SN-38 than its parental drug, irinotecan, in a human cancer xenograft. Trop-2 is widely expressed in most epithelial cancers, including non-small and small cell lung cancers (NSCLC and SCLC). Therefore, the safety and efficacy of this new ADC is being examined in advanced metastatic lung cancers. **Methods:** A phase I/II clinical trial (ClinicalTrials.gov, NCT01631552) is ongoing in subsets of previously-treated patients with metastatic lung cancer, administering IMMU-132 on days 1 and 8 of 21-day treatment cycles. Treatment is continued based on tolerance or until progression, with safety and response assessments made every week and at 8-12 weeks, respectively. Dose reductions and delays allowed most patients to continue treatment until progression. **Results:** Thirty-four lung cancer (15 NSCLC and 19 SCLC) patients with a median of 3 (range, 1-7) prior therapies were given IMMU-132 doses at 8 mg/kg (N = 22), 10 mg/kg (N = 10), 12 mg/kg (N = 2). Tumor responses, including squamous and adenocarcinoma NSCLC types having PR, are summarized in the table below. Neutropenia was the only Grade 3/4 toxicity (G3, 15%; G4, 3%). Other drug-related G3 toxicities included diarrhea (9%), anemia (6%), leucopenia (3%), lymphopenia (3%), pneumonia (3%), vomiting (3%), dizziness (3%). No differences were found between 8 and 10 mg/kg dosing. No pt developed antibodies (ELISA) to the conjugate. **Conclusions:** Repeated cycles of IMMU-132 monotherapy are well tolerated. Objective responses in previously treated metastatic lung cancer encourage further study of IMMU-132 in these cancers. Clinical trial information: NCT01631552.

Tumor type	PR	Disease stabilization (PR+SD)	Clinical benefit (PR+ SD) > 6 mo	Median TPP (Mo)
NSCLC (N = 15)	27%	73%	42%	3.3+
SCLC (N = 19)	26%	53%	29%	2.8+

2505 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

A new anti-CEA-SN-38 antibody-drug conjugate (ADC), IMMU-130, is active in controlling metastatic colorectal cancer (mCRC) in patients (pts) refractory or relapsing after irinotecan-containing chemotherapies: Initial results of a phase I/II study. *First Author: Efrat Dotan, Fox Chase Cancer Center, Philadelphia, PA*

Background: Combination chemotherapies with 5-FU, irinotecan, oxaliplatin, anti-VEGF, and anti-EGFR agents have improved the outcome of mCRC pts. However, there is still an urgent need for better therapies to control this disease. IMMU-130 (labetuzumab govitecan), a conjugate of a humanized anti-CEACAM5 antibody, coupled site-specifically to SN-38 (7.6 moles SN-38/IgG) using a proprietary linker, is an attractive therapeutic option for mCRC pts. **Methods:** A phase I/II clinical trial (NCT01605318) was initiated in irinotecan- refractory/relapsed mCRC pts with an elevated CEA ($>$ 5 ng/mL), treated with IMMU-130 once- or twice-weekly at escalating 4-10 mg/kg dosages on weeks 1 and 2 of 3-week cycles. The primary objective of the study was determination of MTD, with secondary objectives of efficacy (by RECIST 1.1), PK and immunogenicity. Treatment was continued until disease progression or intolerance. **Results:** Between Feb 2013 and Nov 2014, 66 patients were enrolled. Median age was 57 years [39-82]. Median prior therapies were 5 [1-9], with 76% and 36% pts receiving prior bevacizumab and an EGFR inhibitor, respectively. Median number of cycles per pt was 2 [1-15]. Fifty-eight patients were evaluable for toxicity, with 3 DLTs (G3 typhlitis, G4 neutropenia and G3 nausea/vomiting $>$ 48h) in all pts. Grade 3/4 drug-related toxicities were found in 25% pts, including neutropenia (G3, 7%; G4, 3%), diarrhea (G3, 2%), anemia (G3, 3%) and lymphopenia (G3, 3%). The dose selected for further study was 10 mg/kg weekly or 6 mg/kg biw. No pt developed antibodies to the conjugate. Tumor reductions were seen in 23/66 (35%) pts, including one PR with 88% best tumor shrinkage still being treated for 52+ weeks, 6 pts with 20-30% tumor reductions, and 16 pts with 0-20% tumor reductions. **Conclusions:** Repeated cycles of IMMU-130 monotherapy had an acceptable toxicity profile. Tumor reductions were noted in 35% of patients despite prior relapse to irinotecan-containing therapies. These results encourage further evaluation of IMMU-130 in combination with other agents in mCRC. Clinical trial information: NCT01605318.

2506 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Dose escalation stage of a first-in-class phase I study of the novel oral ERK 1/2 kinase inhibitor BVD-523 (ulixertinib) in patients with advanced solid tumors. *First Author: Jeffrey R. Infante, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: Aberrant MAPK pathway signaling and resultant ERK kinase activity is evident in many oncogene-dependent cancers, and persistent or reactivated ERK signaling is common in intrinsic and acquired drug resistance to approved RAF or MEK inhibitors. This first-in-human trial of BVD-523 (ulixertinib), a selective ERK1/2 kinase inhibitor, was initiated based on its promising preclinical profile. **Methods:** Patients (pts) with advanced solid tumors were recruited into an accelerated 3+3 dose escalation protocol. Primary study objectives included determination of dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase II dose (RP2D); secondary objectives included pharmacokinetic, pharmacodynamic, and preliminary efficacy assessments. **Results:** The dose escalation phase included 27 pts treated with BVD-523 at dose levels of 10, 20, 40, 75, 150, 300, 600, 750, and 900 mg twice a day. DLTs were observed in 5 pts: two with grade 3 rash, one with grade 3 pruritus and elevated AST, one with grade 3 diarrhea, vomiting, dehydration and elevated creatinine, and one with grade 2 hypotension, elevated creatinine, and anemia. The MTD was 600 mg twice a day. The most common adverse events included diarrhea, nausea, vomiting or constipation (89%), rash (any form), dermatitis, or pruritus (78%), fatigue (70%), decreased appetite (37%), dyspnea (33%), and anemia (26%). Pharmacokinetics were generally linear and dose proportional up to 600 mg twice a day. Phosphorylation of the ERK substrates RSK1/2 was inhibited in peripheral blood samples starting at 75 mg twice a day. Metabolic response was observed in 5 of 16 evaluable pts assessed by FDG-PET. One (1) of 26 pts assessed by CT had a best response of partial response, and 7 had stable disease for at least 3 months. **Conclusions:** The ERK 1/2 inhibitor BVD-523 (ulixertinib) achieved pharmacologically relevant exposure and manageable tolerability at its MTD of 600 mg twice a day. Additional safety and preliminary efficacy assessments are underway in a cohort expansion stage of this study in patients with specific tumor genotypes and clinical characteristics treated at the RP2D, as well as in additional phase I and phase II studies. Clinical trial information: NCT01781429.

2507 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Phase II study with Wee1 inhibitor AZD1775 plus carboplatin in patients with p53 mutated ovarian cancer refractory or resistant (<3 months) to standard first line therapy. *First Author: Suzanne Leijen, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: AZD1775 (formerly MK-1775) is a potent and selective inhibitor of Wee1, a kinase that phosphorylates CDC2. Phosphorylation of CDC2 inactivates the CDC2/cyclin B complex and is therefore essential for normal G2 checkpoint function. As most p53-deficient tumors lack a functional G1 checkpoint, they rely on the G2 checkpoint for cell cycle arrest in response to DNA damage. G2 checkpoint abrogation, using a Wee1 inhibitor may therefore sensitize p53 deficient tumor cells to DNA-damaging anti-cancer agents. In a phase I study the maximum tolerated dose (MTD) of AZD1775 in combination with carboplatin demonstrated target engagement (NCT00648648). **Methods:** Patients (pts) with p53 mutated ovarian cancer refractory or resistant ($<$ 3 months) to standard first line therapy (carboplatin plus paclitaxel) were re-exposed to carboplatin (AUC 5), plus 5 bi-daily doses of 225 mg AZD1775 in a 21 day cycle (MTD) (NCT01164995). p53 mutation status was analyzed by both sequencing analysis (TP53 exons 2-10) and AmpliChip TP53 array (TP53 exons 2-11). Response evaluation was performed according to RECIST 1.0, volumetric tumor measurement (enhanced RECIST) and CA-125 blood levels. **Results:** Bone marrow toxicity, fatigue, diarrhea, nausea and vomiting were the most common adverse events. Out of 24 pts enrolled, 22 pts were evaluable for study endpoints. As best response (RECIST 1.0), 6 pts (27%) showed confirmed partial response (PR) with a median progression-free survival (PFS) of 10.9 months. Nine pts (41%) had stable disease and 7 pts (32%) had progressive disease as best response, with a median PFS of 5.3 and 1.3 months, respectively. **Conclusions:** AZD1775 is a first in class Wee1 inhibitor that in combination with carboplatin is well tolerated and shows promising anti-tumor activity in p53 mutated ovarian cancer refractory or resistant ($<$ 3 months) to standard first line therapy. Clinical trial information: NCT01164995.

2508 **Oral Abstract Session, Tue, 8:00 AM-11:00 AM**

Phase II multicenter proof of concept study of AZD4547 in *FGFR* amplified tumours. *First Author: Elizabeth Catherine Smyth, Royal Marsden, London & Surrey, United Kingdom*

Background: *FGFR*1/2 amplification acts as an oncogenic driver in multiple cancers. We investigated the efficacy of AZD4547, a potent orally available selective inhibitor of *FGFR* 1,2 & 3 receptor tyrosine kinases, in *FGFR1/2* amplified cancers. **Methods:** This is a phase II Simon 2 stage design for patients (pts) with *FGFR1* (HER2 negative breast/NSCLC) or *FGFR2* (gastroesophageal) amplified tumors treated with AZD4547 80mg twice daily on an intermittent (2 weeks (wks) on, 1 wk off) or continuous schedule. Eligible pts had progressed following $\geq$ 1 line of prior therapy. *FGFR1/2* amplification was determined centrally using FISH. Primary endpoint is centrally reviewed confirmed response rate (RR), with the study concluding efficacy if $\geq$ 3/17 patients in a cohort had a confirmed response. PET-CT was performed at baseline, D14 and 8 wks, biopsy at baseline and D14 and optionally on progression. Biomarker assessment included phospho-immunohistochemistry, *FGFR* copy number variation in tumor and plasma, and whole exome sequencing. **Results:** We screened 285 pts with advanced cancer, identifying *FGFR1* amplification in 18% (20/111) HER2 negative breast cancer (BC), 9.5% (4/42) NSCLC, and *FGFR2* amplification in 7.6% (10/132) gastroesophageal (GC). Confirmed RR was 33% (3/9) in *FGFR2* amplified GC, and 12.5% (1/8) *FGFR1* amplified BC. All 3 GC responders had a PET response on D14 PET. GC responses were durable; time on treatment was 45, 29 and 27 wks with the last pt ongoing. Common toxicities (all grades and schedules) included fatigue (71%), mucositis (41%), nausea (35%), and nail changes (24%). Asymptomatic retinal pigmented epithelial detachment occurred in 1 pt. Phosphate was elevated in most pts. Exploratory analysis revealed all GC pts with PR had *FGFR2* FISH ratio $>$ 8. Elevated *FGFR2* copy number was detected in free plasma DNA of all GC pts with PR, and no non-responding pt. Analysis of progression biopsies in a responding GC pt identified acquired *KRAS* amplification in progressing disease. **Conclusions:** AZD4547 demonstrated high activity in *FGFR2* amplified GC and lower activity in *FGFR1* amplified BC. Assessment of *FGFR2* copy number in cell free plasma DNA may provide a screening tool to identify *FGFR2* amplified GC. Clinical trial information: NCT01795768. Clinical trial information: NCT01795768.

2509 Poster Discussion Session; Displayed in Poster Session (Board #225), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Preliminary results of TATTON, a multi-arm phase Ib trial of AZD9291 combined with MEDI4736, AZD6094 or selumetinib in EGFR-mutant lung cancer. *First Author: Geoffrey R. Oxnard, Dana-Farber Cancer Institute, Boston, MA*

Background: AZD9291 is an irreversible, mutant-selective EGFR tyrosine kinase inhibitor (TKI) developed to have potency against EGFR mutations, including T790M, while sparing wildtype EGFR. In the previous phase I study of AZD9291, EGFR-mediated toxicity was reduced compared to available EGFR-TKIs. We hypothesized that the safety profile of AZD9291 would permit combinations with other targeted therapies in a tolerable fashion. **Methods**: TATTON (NCT02143466) is a multi-arm phase Ib trial studying AZD9291 in combination with MEDI4736 (anti-PD-L1 mAb), AZD6094 (MET inhibitor) or selumetinib (MEK1/2 inhibitor; AZD6244, ARRY-142886). Eligibility required advanced EGFR-mutant lung cancer, progression on any prior EGFR-TKI, measurable disease, adequate PS (0-1) and organ function, and tissue for correlatives. In each combination, AZD9291 was dosed at 80 mg daily and the 2nd agent was escalated from a dose below the phase II monotherapy dose. Using a rolling 6 design, patients (pts) were randomly allocated to a combination arm. Data included here are preliminary and will be updated for presentation. **Results**: As of 8 January 2015, 42 pts have been enrolled on combination therapy (MEDI4736 = 14 pts; AZD6094 = 7 pts, selumetinib = 21 pts). All 3 combination agents were escalated to their phase II monotherapy doses; an additional arm continues to explore intermittent dosing of selumetinib. Adverse event (AE) data is currently available for 20 pts from all arms and cycles and includes mild/moderate AEs in 16 pts (6 skin, 5 laboratory, 2 gastrointestinal, 3 other) and severe AEs in 4 pts (1 skin, 1 laboratory, 1 gastrointestinal and 1 metabolism); 2 DLTs were reported (fatigue – AZD6094 arm; transaminase elevation – selumetinib arm). To date, 3 partial responses (PR) have been seen with AZD9291/MEDI4736, 2 PR with AZD9291/AZD6094, and 2 PR with AZD9291/selumetinib. Combination dose finding is expected to complete by May 2015. **Conclusions**: The toxicity profile of AZD9291 makes rational combinations with potentially synergistic targeted therapies feasible at biologically active doses. Expansion cohorts are planned for pts with acquired resistance to third-generation EGFR-TKI. Clinical trial information: NCT02143466.

2510 Poster Discussion Session; Displayed in Poster Session (Board #226), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

ABT-414 in patients with advanced solid tumors likely to overexpress the epidermal growth factor receptor (EGFR). *First Author: Glenwood D. Goss, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

Background: Aberrant EGFR expression and signaling has been identified as a hallmark of cancer growth and survival. ABT-414 is an antibody-drug conjugate composed of the antibody ABT-806, targeting active EGFR/mutant EGFRvIII, linked to the anti-microtubule agent monomethylauristatin F. ABT-414 has shown potent antitumor activity in several EGFR-overexpressing tumor xenografts. This phase 1/2 trial evaluates the safety, pharmacokinetics (PK), and efficacy of ABT-414 in patients (pts) with solid tumors (NCT01741727). Herein, we report the ABT-414 maximum tolerated dose (MTD) and preliminary efficacy in an expanded cohort of pts with EGFR-amplified tumors. **Methods:** In the dose-escalation cohorts, pts (≥ 18 years) with advanced EGFR+ solid tumors received escalating doses of ABT-414 intravenously in 2 schedules, either on day 1 or on days 1 and 8 Q3W. Primary objectives included safety, determination of the MTD, the recommended phase 2 dose (RP2D), and the PK profile. In the EGFR-amplified cohort, pts received ABT-414 at the MTD to further assess ABT-414 safety and preliminary efficacy related to EGFR expression. **Results:** By 15 Dec 2014, 53 pts received ABT-414 (dose-escalation cohorts, n = 48; EGFR-amplified cohort, n = 5). Most common treatment-emergent adverse events (TEAEs) were blurred vision (49%, commonly due to transient microcystic keratopathy), fatigue (42%), nausea (42%), and dry eyes (36%). Most common grade 3/4 TEAEs were keratitis (8%), blurred vision (6%), dyspnea (6%), and hyponatremia (6%). Eye pain was the only DLT (n = 1 at 2 mg/kg Q3W). Due to several grade 3 ophthalmologic TEAEs in a single pt treated at 4.0 mg/kg, this dose was considered to exceed the MTD and the RP2D was set at 3 mg/kg Q3W. ABT-414 was the predominant circulating antibody with low levels of unconjugated ABT-806. PK exposure of ABT-414 appeared to be dose proportional. In the EGFR-amplified cohort, 1 partial response was observed (triple-negative breast cancer). Stable disease occurred in 11 of 53 pts (21%). **Conclusions:** The RP2D of ABT-414 (Q3W) is 3 mg/kg. The preliminary efficacy observed in pts with EGFR-amplified tumors suggests antitumor activity and warrants further investigation in this select population. Clinical trial information: NCT01741727.

2511 Poster Discussion Session; Displayed in Poster Session (Board #227), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Phase I expansion of S-222611, a reversible inhibitor of EGFR and HER2, in advanced solid tumors, including patients with brain metastases. *First Author: Sanjeev Deva, King's College London, London, United Kingdom*

Background: S-222611 is an oral, reversible ErbB tyrosine kinase inhibitor of EGFR and HER2 with potent pre-clinical activity. MTD was not reached during dose-escalation, even at the maximum dose of 1600mg QD. PK and efficacy data supported a daily dose of 800mg. A further cohort has been treated to further explore safety and efficacy. **Methods:** Subjects with advanced solid tumors expressing EGFR and/or overexpressing HER2 were enrolled. S-222611 was administered until disease progression or unacceptable toxicity. **Results:** 76 patients (33 male/43 female; median age 62 years [range 31-81], ECOG PS 0/1/2: 24/51/1), were included in this expansion phase, including breast (27), esophago-gastric (30), head & neck (12) and renal (7). Dose reduction was required because of adverse events in 11 patients (14%); the most frequent of such being diarrhea and elevated bilirubin. Only 2 patients discontinued treatment due to drug-related adverse events. Of the 41 patients with HER2-positive cancers (26 breast, 13 esophago-gastric, 2 head & neck), 1 complete response (gastric-esophageal junction cancer) and 5 partial responses (4 breast cancer, 1 gastric cancer) were observed; all these patients had received prior HER2-directed therapy. Prolonged stable disease (≥ 6 months) was observed in 3 additional patients with breast cancer. 6 of the 25 breast patients had brain metastases, in whom 1 intracranial response and 2 prolonged SD (≥ 6mo) were observed. In the EGFR+ve/HER2-ve cohort (n = 35), no RECIST responses were seen, however 4 patients had prolonged stable disease (≥ 6mo). **Conclusions:** S-222621 was well tolerated at a dose of 800mg once daily. Anti-tumour activity, including shrinkage of brain metastases, was evident in a heavily pre-treated population of patients with HER2-positive breast and esophago-gastric cancers. Clinical trial information: 2009-017817-31.

2512 Poster Discussion Session; Displayed in Poster Session (Board #228), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Safety and tolerability of increasing doses of CB-839, a first-in-class, orally administered small molecule inhibitor of glutaminase, in solid tumors. *First Author: James J. Harding, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Glutamine is required for the growth and survival of multiple tumor types. CB-839 is a highly selective, reversible, allosteric inhibitor of glutaminase, a choke point in the utilization of glutamine. CB-839 has broad in vitro and in vivo anti-tumor activity in solid and heme malignancies. **Methods:** CX-839-001 is an ongoing Phase 1 study of escalating doses of CB-839 in advanced and/or treatment-refractory solid tumor patients (pts) to evaluate safety and tolerability, and to identify the recommended Phase 2 dose (R2PD). CB-839 was administered orally continuously in 21-day cycles. Pharmacokinetics (PK) was monitored on Days 1, 15, and 22; pharmacodynamic (PD) assessment of glutaminase activity was measured ex vivo in platelets and tumor biopsies. Additional pts will be enrolled at the RP2D with triple negative breast cancer (TNBC), non-small cell lung adenocarcinoma (NSCLC), renal cell carcinoma (RCC), mesothelioma, and tumors with mutations in enzymes of the TCA cycle. **Results:** 35 pts were enrolled in dose escalation receiving CB-839 doses from 100 to 800 mg TID and 600 mg BID. Exposure increased less than dose proportionally but there was a clear PK/PD relationship with > 90% glutaminase inhibition in platelets when CB-839 exceeded 450 nM; target inhibition was confirmed in tumors. Radiographic stable disease (SD) was observed in 7 (28%) of 25 efficacy-evaluable pts (average duration 107 days; range 59-209) across all diseases and dose levels including TNBC (2/9 evaluable pts), NSCLC (2/4), mesothelioma (2/4) and RCC (1/3). Grade ≥ 3 treatment-related AEs occurred in 7 (20%) of pts, including ALT/AST (4 pts), creatinine, alkaline phosphatase, and GGT increases, lymphopenia, and hypoglycemia (1 pt each). A Grade 3 increase in creatinine considered unlikely related to CB-839 was a DLT at 250 mg TID. CB-839 was absorbed rapidly (T_{max} 1-2 hr fasted and 2-4 hr fed) and cleared with a half-life of about 4 hr. Plasma $C_{min}$was > 450 nM at steady state at the RP2D of 600 mg BID. **Conclusions:** Continuous CB-839 administration showed an acceptable safety profile, significant glutaminase inhibition and preliminary signs of clinical activity in multiple tumor types. Clinical trial information: NCT02071862.

2513 Poster Discussion Session; Displayed in Poster Session (Board #229), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A first-in-human dose-escalation study of the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of oral 2-hydroxyoleic acid (2-OHOA) in adult patients (pt) with advanced solid tumors including grade III/IV glioblastoma multiforme (GBM). *First Author: Desamparados Roda, The Institute of Cancer Research and The Royal Marsden, London, United Kingdom*

Background: 2-OHOA, is a synthetic hydroxylated lipid that activates sphingomyelin synthase (SGMS) and regulates the lipid content of cell membranes resulting in translocation of Ras to the cytoplasm and inactivation of Ras/MAPK, PI3K/Akt and PKC/cyclin/CDK signaling pathways. 2-OHOA reduces tumor growth in xenograft mice models of prostate, leukemia, breast, colon, breast cancer, and GBM, and also crosses the blood brain barrier. This first-in-human trial was designed to determine the safety, tolerability, and recommended phase 2 dose (RP2D), alongside the PK, PD and anti-tumor profile of 2-OHOA. **Methods:** Eligible pts with advanced solid tumors or grade (G) III/IV GBM received 2-OHOA as a PO suspension, BID in 21-d cycles using a '3+3' dose escalation design. Adverse events (AE) were assessed by Common Terminology Criteria for AE v4; tumor response was assessed every 2 cycles using RECIST 1.1/RANO criteria. **Results:** 17 pts (median age 59 years; range 19-71; 7 GBM and 10 solid tumors) were treated at 5 dose levels: 250-, 500-, 1000, 2000 and 4000-mg BID. Treatment was well tolerated with toxicities limited to grade 1-2 nausea (n = 4), vomiting (n = 6) and diarrhea (n = 6). The PK profile was dose-proportional with no accumulation up to 2000mg BID; t1/2 = 4h. No effect of food was observed. One pt with GBM treated at 500mg BID has a confirmed and ongoing partial response and is currently at cycle (C) 23 of treatment; a 2nd GBM pt has SD after 2 cycles and continues on study. A 3rd pt with progressive mesothelioma demonstrated SD lasting to C15. **Conclusions:** 2-OHOA can be safely administered up to doses of 4000mg BID. Clinical benefit was observed in 3 patients including 1 PR in a pt with GBM. Dose escalation continues to determine a RP2D, followed by a RP2D expansion in patients with both solid tumors and grade III/IV GBM. Clinical trial information: NCT01792310.

2514 Poster Discussion Session; Displayed in Poster Session (Board #230), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Final results of ProGem1, the first in-human phase I/II study of NUC-1031 in patients with solid malignancies. *First Author: Sarah Patricia Blagden, Ovarian Cancer Action Research Centre, London, United Kingdom*

Background: NUC-1031 is a first-in-class nucleotide analogue utilising phosphoramidate chemistry to enhance anti-cancer efficacy and safety. In preclinical studies NUC-1031 demonstrated potent anti-cancer activity, generating high intracellular levels of the active cytotoxic di-fluorodeoxycytidine triphosphate (dFdCTP) by overcoming key drug resistance mechanisms associated with nucleoside analogues. **Methods:** This study was comprised of 1) dose escalation part: 3–8 patients (pts) per cohort received 5-15 minute IV infusion of NUC-1031 starting at 500mg/m^2 once weekly on days 1, 8, 15 in 4 weekly schedule (q4w), or 375mg/m^2 twice-weekly on days 1 & 5, 8 & 12, 15 & 19 q4w and 2) expansion part at the recommended Phase II dose (RP2D). Endpoints were (primary) safety and tolerability, (secondary) pharmacokinetics (PK), pharmacodynamics and efficacy. **Results**: ProGem1 enrolled 68 pts, mean age 56 (20 - 83 yrs), average 2.7 prior lines of chemotherapy (range 1 - 6) with 16 primary cancer types. Dose-limiting toxicities occurred in 4 pts: G4 thrombocytopenia (2); G3 elevated ALT (2). 25 SAEs were 'possibly/probably related' to study drug, and 2 > G2: elevated ALT (4) and lung infection (3). Commonest AEs ≥ G3 'possibly/probably related' were: neutropenia (16), fatigue (13), elevated GGT (10). NUC-1031 was stable, with plasma half-life of 8.3 hours. High intracellular levels of the active anti-cancer agent dFdCTP (Cmax = 475.5 μM/L) were rapidly achieved and maintained for 24 hours. Notable efficacy results were observed: 5 RECIST Partial Responses (10%); 33 Stable Disease (67%) for an ITT disease control rate (DCR) of 56% and on treatment analysis (OTA) DCR of 78%. PRs and SDs were observed in pts refractory/relapsed to prior nucleoside analogue therapy and were durable, mean PFS 6.1 months (range 2 – 20 mths). The RP2D was 825mg/m^2 given on days 1, 8, 15, q4w. **Conclusions**: NUC-1031 has demonstrated impressive clinical activity with durable DCR (ITT 56%; OTA 78%) in a wide range of patients with advanced and rapidly progressing disease. NUC-1031 is well-tolerated at the RP2D. Phase III clinical studies in ovarian, pancreatic and biliary cancers are planned this year and combination studies are currently recruiting. Clinical trial information: NCT01621854.

2515 Poster Discussion Session; Displayed in Poster Session (Board #231), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

***TP53* mutations emerge in circulating cell-free DNA obtained from patients undergoing treatment with the HDM2 antagonist SAR405838.** *First Author: James Wilson Watters, Sanofi, Cambridge, MA*

Background: SAR405838 is an oral antagonist of HDM2 that results in p53 induction. In an ongoing Phase I study, p53 activation was demonstrated at doses that have an acceptable safety profile. We sought to develop a method for sequencing circulating cell-free DNA (ccfDNA) for the non-invasive monitoring of genetic changes in the tumor that may impact the activity of SAR405838 **Methods:** Baseline tumor and serially collected plasma samples were obtained from de-differentiated liposarcoma (DDLPS) patients undergoing treatment with SAR405838 at the maximum tolerated dose (300 mg QD). Tumor biopsies were sequenced using the Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies). A custom next-generation sequencing targeted gene panel was developed for ccfDNA. Sequencing libraries were prepared using custom xGen Lockdown probes (IDT). Sequencing was performed using the Illumina HiSeq 2500. Mutations were determined using a custom pipeline combining calls from MuTec and Lofreq. Mutation confirmation was performed using RainDance droplet digital PCR. **Results:** Tumor and plasma samples were available from 18 patients. All tumors were determined to be *TP53* wild-type at baseline. From ccfDNA, greater than 10,000X coverage of target sequence was achieved. No *TP53* mutations were identified at variant allele frequency (VAF) > 1% in the baseline ccfDNA samples. 27 non-synonymous mutations in *TP53* were identified at VAF > 1% in ccfDNA from patients undergoing treatment. All *TP53* mutations were previously reported in COSMIC, and all are located in the DNA-binding domain of p53. Mutation VAF increased during treatment, and multiple *TP53* mutations arose within individual patients. All patients undergoing 5 or more cycles of treatment showed evidence of *TP53* mutations in ccfDNA. A subset of mutations was selected for validation and all were confirmed using digital PCR. **Conclusions:** *TP53* mutations appear in the ccfDNA of patients during treatment with SAR405838. This may represent the selection of *TP53* mutant clones that are resistant to HDM2 inhibition. This finding suggests that HDM2 antagonists should be combined with other mechanisms including agents active in p53 mutant tumors.

2516 Poster Discussion Session; Displayed in Poster Session (Board #232), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Genomic mutation profiling (GMP) and clinical outcome of patients treated with buparlisib (PI3K inhibitor) in the "Signature" program. *First Author: Sarina Anne Piha-Paul, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pts included in the buparlisib (BKM120) module were analyzed by a tissue-agnostic genetic alteration–specific protocol that matches pts to treatments that target tumors harboring PI3K pathway–activated tumors. The pts are identified via standard of care physician-directed profiling. **Methods:** Pts with measurable advanced malignancies and no established standard therapy options were eligible. A local CLIA-certified test was sufficient for eligibility, and broad molecular profiling of pt tumors (confirmatory analysis of inclusion genetic alteration) was performed centrally post hoc. The primary objective was to assess clinical benefit (CB; CR + PR + SD at 16 weeks) by local investigator assessment. Buparlisib was given orally (100 mg once daily). Analysis correlating GMP with treatment outcomes will help determine the significance of these mutations. **Results:** GMP data were available for 76 pts across 19 tumor types (colorectal [14; 18%], sarcoma [11; 15%], ovarian [10; 13%], and head and neck [9; 12%]. Rare tumors included vaginal [1] and appendix [1]]. Median age: 60 years (range, 24-80), 49 women (65%), median number of prior therapies: 3 (range, 1-16). Baseline actionable alterations (local labs) included 38 PIK3CA mutations (50%), 17 PTEN mutations (22%), 16 PTEN losses (21%; IHC), 7 PIK3CA amplifications (9%), and 2 PIK3R1 mutations (3%). The concordance of baseline actionable alterations between local and central labs was 67%. Overall, 11 pts (15%) achieved CB. DNA from all pts was assayed by NGS, covering a panel of 288 cancer genes. Based on the assay, the tumors had a median of 4 mutations (range, 0-12) and tissue-specific patterns of mutation burden (lowest in cervix and sarcomas: 2; highest in colorectal and vaginal: 5+). The number of prior therapies did not correlate with the mutation load. Fewer mutations were noted in pts with CB. Most commonly altered genes (8+ pts): PIK3CA, PTEN, KRAS, TP53, APC, CDKN2A, RB1, and ERBB2. Aberrations in APC, BRCA2, CDKN2A, EP300, FBXW7, LRP1B, MLL2, PTEN, RB1, and SMAD4 were enriched in pts with no CB. **Conclusions:** Buparlisib showed activity in some pts, indicating that specific mutations may correlate with poor outcome. Clinical trial information: NCT01833169.

2517 Poster Discussion Session; Displayed in Poster Session (Board #233), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Alka-372-001: First-in-human, phase I study of entrectinib – an oral pan-trk, ROS1, and ALK inhibitor – in patients with advanced solid tumors with relevant molecular alterations. *First Author: Filippo G. De Braud, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: Entrectinib (formerly RXDX-101) is a potent and selective oral small molecule inhibitor of the TrkA/B/C, ROS1, and ALK kinases. Schedule A (fasted, 4d on/3d off for 3wks, 1 wk rest) demonstrated significant antitumor activity (ASCO 2014). This abstract reports completion of Sch A and two other ongoing dosing schedules (B and C). **Methods:** Pts with advanced solid tumors with molecular alterations in TrkA, ROS1 or ALK were treated in Sch B (QD) or Sch C (4d on/3d off), both in fed state. **Results:** 31 pts were treated in Sch A (N=19), B (N=6), or C (N=6). In Sch A, doses $>$ 800 mg/m^2 did not increase exposure significantly. Thus, accrual in Sch A was closed. Various dose levels (mg/m^2) were explored in Sch B [200 (n=3); 400 (n=3)] and Sch C [400 (n=3); 800 (n=3)]. 7 pts had objective responses: 6 PR, 1CR (see Table). We are the first to report clinical activity of a Trk inhibitor in a pt with *NTRK1*+ (encoding TrkA) CRC. Of 7 *ROS1*-rearranged evaluable/measurable NSCLC pts, 4 have had an objective response (ORR: 57%), with a median duration of 6+ months. Moreover, in *ROS1* pts treated at $\geq$ 400 mg/m^2, the ORR was 80% (4 of 5 pts). Entrectinib is well tolerated. The majority of pts reported G1/ G2 AEs. 13 pts reported $\geq$ G3 AEs. Asthenia and muscle weakness were possibly related $\geq$ grade 3 AEs (both reversible). No DLTs have been reported to date. In Sch A, entrectinib was readily absorbed and exposures increased dose-proportionally up to 800 mg/m^2. In fed state, entrectinib exposures were approx. 2x compared to fasted state. **Conclusions:** In this trial with entrectinib administered in 3 different dosing schedules, significant antitumor response was observed in pts with relevant molecular alterations, notably *ROS1*-rearranged NSCLC at doses $\geq$ 400 mg/m^2/day and the only *NTRK1* rearranged pt treated to date. Accrual in Sch B and C continues until RP2D is achieved, followed by dedicated studies in selected tumor types. Clinical trial information: NCT02097810.

Objective responses.

Tumor type (alteration)	Sch/Dose (mg/m^2)	Best Response	Duration of Response (cycles)
NSCLC (*ALK*)	A/800	PR	10
NSCLC (*ROS1*)	A/1200	PR	14+
	C/400	PR	7+
	C/400	CR	5+
	B/400	PR	3+
CRC (*NTRK1*)	A/1600	PR	3
Neuroblastoma (*ALK*)	A/800	PR	9

2518 Poster Discussion Session; Displayed in Poster Session (Board #234), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

First-in-human, phase I study assessing imalumab (Bax69), a first-in-class anti-oxidized macrophage migration inhibitory factor (oxMIF) antibody in advanced solid tumors. *First Author: Devalingam Mahalingam, Cancer Therapy and Research Center, The University of Texas Health Science Center at San Antonio, San Antonio, TX*

Background: MIF is a pleiotropic cytokine involved in tumor proliferation, invasiveness, angiogenesis, and the proinflammatory microenvironment. oxMIF is the pathogenic form mainly in tumor and its surrounding stroma. Imalumab (Bax69) is a novel recombinant, fully-human, monoclonal antibody that targets oxMIF, inhibiting tumorigenesis. Preclinical data demonstrated that Imalumab has antitumor activities and acceptable toxicities. **Methods:** The primary endpoint of this dose-escalation study (3+3 design) was to assess maximum tolerated dose (MTD). The secondary endpoints were to assess antitumor activity, safety, pharmacokinetics (PK), and pharmacodynamics (PD). Patients (pts) received intravenous (IV) Imalumab [28-d cycles; 2 dose schedules (DS)]: biweekly in all solid tumors (DS1); weekly in metastatic colorectal cancer (mCRC) (DS2). **Results:** As of Dec 2014, 28 pts were analyzed. DS1 = 19pts in 6 cohorts (1, 3, 10, 25, 37.5, and 50 mg/kg), and DS2 = 9 pts in 2 cohorts (10& 25 mg/kg). AUC and C_{max}increased with dose. Dose escalation was stopped at 50 mg/kg (DS1) and 25mg/kg (DS2). An MTD was not reached for either DS. One pt reported dose-limiting toxicities: hypersensitivity pneumonitis (DS1; 50 mg/kg). There were no other grade 3 & 4 treatment related adverse events (trAEs). Grade 2 trAEs include: fatigue (n = 2), peripheral edema (n = 1), infusion reaction (n = 1), urticaria (n = 1). About 86% of pts had no trAE $>$ G1. Stable disease (SD) $\geq$ 4 mo was seen in 7 heavily pre-treated pts, including 1 pt with NSCLC who achieved SD $>$ 13.4 mo. In DS2; Pre- and on-therapy tumor biopsies showed satisfactory tissue penetration of Imalumab with regulation of PI3K-AKT-mTOR downstream signaling, TNF-α signaling, anti-inflammatory cytokines (IL-1 and IL-10), and apoptosis in all 5 biopsy evaluable patients. Based on clinical PK & PD study, 10mg/kg weekly was considered a biologically active dose and sufficient to reach $\geq$ 95% target binding by the end of first cycle. **Conclusions:** Imalumab was well tolerated and showed single agent antitumor activity in heavily pretreated pts. An MTD was not reached. Recommended phase II dose (RP2D) is 10 mg/kg IV weekly. NCT01765790 Clinical trial information: NCT01765790.

2519 Poster Discussion Session; Displayed in Poster Session (Board #235), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

First-in-human phase I administration of YS110, a monoclonal antibody directed against the CD26 immunostimulatory molecule in advanced cancer patients. *First Author: ERIC ANGEVIN, Institut Gustave Roussy, Villejuif, France*

Background: YS110 is a recombinant humanized IgG1 monoclonal antibody that selectively binds with high affinity to the extracellular domain of the CD26 antigen. Preclinical evaluations of YS110 have demonstrated promising anti-tumor effects in cancer cell lines and xenografts expressing the CD26 antigen without significant side effects in toxicology studies (up to 100 mg/kg as single dose or 30 mg/kg for 5 weekly doses in monkeys). **Methods:** Escalating doses of YS110, using a standard 3+3 escalation scheme, were administered intravenously once every 2 weeks for 3 doses at 0.1, 0.4, 1 and 2 mg/kg and then based on PK data, once every week for 5 doses at 2, 4 and 6 mg/kg in solid tumors pts with confirmed CD26$^+$tumor expression ($\geq$ 20% of the tumor cells). This FIH study was designed to determine the MTD and RD, assess tolerance, PK and PDs of YS110. **Results:** 34 heavily pre-treated pts, including 23 pts with mesothelioma and 10 with renal cell carcinoma, were enrolled. A total of 232 infusions (median 3 [range 1-30]) of YS110 were administered across 6 dose levels ranging from 0.1 to 6 mg/Kg. MTD was not reached and 2 DLTs (1 pt with Gr 3 anaphylactic reaction at 1 mg/kg and 1 pt with Gr 3 allergic reaction at 2 mg/kg) were reported. Recovery was obtained with dose omission. Pts with a medical history of allergy were excluded and corticoids prophylaxis improved safety profile. No dose-dependent AEs were observed. Low grade asthenia (33.3%), hypersensitivity (30.0%), chills (13.3%), pyrexia (13.3%), nausea (13.3%), vomiting (10.0%), and headache (10.0%) were reported. Blood exposure PK parameters (AUC and Cmax) increased in proportion with the dose. Cytokines and immunophenotyping indicated CD26 target modulation. Prolonged stabilization was observed in 13 pts out of 25 evaluable pts. **Conclusions:** YS110 is well tolerated with preliminary evidence of activity. Combination with chemotherapy will be investigated. Clinical trial information: 2008-004407-56.

2520 Poster Discussion Session; Displayed in Poster Session (Board #236), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

First-in-human dose escalation, safety, and PK study of a novel EFNA4-ADC in patients with advanced solid tumors. *First Author: David S. Hong, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PF-06647263 is an anti-EFNA4 antibody drug conjugate (ADC) comprised of a humanized mAb (huE22), a hydrazine linker, and calicheamicin. Ephrin-A4 (EFNA4) is overexpressed in tumor versus normal tissue in a number of human tumors. PF-06647263 induced tumor regression in triple negative breast cancer (TNBC) and ovarian cancer (OVCA) xenograft models. **Methods:** Patients (pts) with solid tumors unseleceted for EFNA-4 expression are receiving escalating doses of PF-06647263 once every 3 weeks (Q3W) or weekly (QW) in 2-6 patient cohorts. The following doses have been evaluated: 0.015, 0.030, 0.050, 0.075, 0.100, and 0.134 mg/kg Q3W and 0.01 and 0.02 mg/kg QW. Once the maximum tolerated dose (MTD) is determined, expansion cohorts for patients with EFNA4-expressing TNBC and platinum-resistant OVCA are planned. Standard definitions are being used to classify hematological and non-hematological dose limiting toxicities (DLT). Serum pharmacokinetic (PK) and anti-drug antibody (ADA) development are also being assessed. **Results:** Data are available on 24 pts treated- 15 Q3W and 9 QW. Among the 24 pts (20F/4M), the mean age was 59 years (35-82). Total number of administered cycles is 55 (Q3W) and 26 (QW), and DLTs, were observed in 0 and 1 pts in the Q3W and QW regimens, respectively, during the first cycle. The most common adverse events (AE) were nausea (50%), fatigue (50%), decreased appetite (38%), diarrhea (33%), vomiting (33%), thrombocytopenia (TCP) (33%), abdominal pain (29%), and blood bilirubin increase (29%). One patient experienced Grade 4 neutropenia and the AEs with Grade 3 severity observed in more than 2 patients were mucosal inflammation (n = 3; 12%) and bilirubin increase (n = 2; 8%). Preliminary evidence of activity includes confirmed partial response (PR) in 2 pts (OVCA and TNBC). Two additional unconfirmed PRs (TNBC and peritoneal cancer) have also been recorded. **Conclusions:** PF-06647263 is a novel anti-EFNA4-ADC which to-date is well-tolerated in pts with advanced malignancies. Dose-escalation is continuing and updated safety, efficacy, and preliminary PK data will be reported at the meeting. Clinical trial information: NCT02078752.

2521 Poster Session (Board #237), Sat, 8:00 AM-11:30 AM

Phase I study of ontuxizumab, a humanized monoclonal antibody (mAb) recognizing endosialin in Japanese patients (pts) with hepatocellular carcinoma (HCC). *First Author: Masafumi Ikeda, National Cancer Center Hospital East, Chiba, Japan*

Background: Endosialin is a cell surface glycoprotein that is expressed on cells involved in the development of tumor vasculature, primarily pericyte and stromal fibroblast. Ontuxizumab is a humanized IgG1κ mAb that is the first clinical stage agent to target Endosialin. Based on the safety profile obtained in the dose escalation portion of this study, 3 dosage cohorts were expanded to further characterize the safety, pharmacokinetics (PK), and preliminary efficacy of Ontuxizumab in advanced HCC pts. **Methods:** HCC pts with Child-Pugh (CP) A who have no other appropriate treatment were enrolled at 4 study sites to 3 dosage cohorts; 4 and 8 mg/kg weekly, and 12 mg/kg biweekly as 4 weeks a cycle. Primary objective was safety. Efficacy endpoints were Response rate by RECIST v.1.1, Disease Control Rate (DCR) and Time to Progression (TTP). **Results:** Fifteen pts with advanced HCC pre-treated at minimum with sorafenib have been enrolled. Of these, 11 and 4 pts presented with ECOG 0 and 1 respectively, while 10 and 5 pts presented with CP A5 and A6 respectively. The PK profile from the HCC cohort was consistent with those of the dose escalation cohorts with other solid tumors. There were no significant differences for C_{max} and AUC of Ontuxizumab between HCC and other solid tumors. Mean $t_{1/2}$was 99.0 - 216 hours after multiple administrations. Safety profile was mainly characterized by Gr 1-2 events. Treatment related adverse events (AEs) were observed in 10 of 15 pts. The most common AEs were hiccups (20%), ALT increased, AST increased, blood bilirubin increased, hypoalbuminaemia and malaise (each 13%). There were 3 treatment related Gr 3-4 AEs (ALT increased, AST increased and hyperglycaemia), and no treatment related serious AEs. No CRs or PRs were reported; DCR was 60% with TTP ranging 1.4 to 12.9 months. Five pts (33%) showed tumor shrinkage and durable (over 6 months) SD was observed in 3 pts (20%). **Conclusions:** Ontuxizumab appears generally well tolerated in this HCC population with a PK profile consistent with the profile in other solid tumors. Preliminary efficacy results suggest that Ontuxizumab at minimum 4 mg/kg weekly warrants further investigation for clinical activity in HCC. Clinical trial information: NCT01773434.

2522 Poster Session (Board #238), Sat, 8:00 AM-11:30 AM

Phase I trial and pharmacokinetic study of Tanibirumab, a fully human monoclonal antibody to the vascular endothelial growth factor receptor 2 in patients with refractory solid tumors. *First Author: Su Jin Lee, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Tanibirumab is a fully human monoclonal antibody to the vascular endothelial growth factor receptor 2 (VEGFR-2). We conducted a first-in-human phase I study of Tanibirumab in patients with solid tumors which were refractory to standard chemotherapy. Primary endpoints are evaluating safety, pharmacokinetics (PKs), estimating maximum-tolerated dose (MTD) and recommended phase II dose (RP2D). **Methods:** We designed to escalate Tanibirumab at 9 different dose levels with 3+3 method and Tanibirumab (1-28mg/kg) was administered intravenously on D1, 8, 15 in 28-day courses. Dose limiting toxicities (DLTs) were assessed in only first cycle of treatment and response evaluation was performed every 2 cycles. The effects of Tanibirumab on serum VEGF, soluble VEGFR-2, PlGF and correlation between VEGF, VEGFR-2 expression in archival tumor tissue and efficacy were planned. **Results:** From October 2011 to September 2013, a total of 26 patients with refractory solid tumors were enrolled. The median age was 58 years (range, 27-75) and 20 patients were male. Most common tumor type was colorectal cancer (N = 18) and 7 patients had history of previous bevacizumab treatment. As hemangioma continued to occur, last dose level, 28m/kg was not performed. DLTs were not found, and MTD was confirmed as 24mg/kg. Hemangioma was observed in 50% of patients, but most of those were grade 1-2 which disappeared after discontinuation of study drug. Among 18 patients of efficacy set, no objective response was observed, but 11 patients showed stable disease. PKs were characterized by dose-dependent linear exposure and mean trough concentrations exceeded biologically relevant target levels at 12mg/kg and above. Serum VEGF, soluble VEGFR-2, PlGF increased at 4mg/kg dose level and above. **Conclusions:** Treatment with Tanibirumab showed tolerable toxicity profile and modest clinical efficacy in patients with refractory solid tumors. We have a plan to conduct phase II trial in patients with glioma. Clinical trial information: NCT01660360.

2523 Poster Session (Board #239), Sat, 8:00 AM-11:30 AM

Molecular characteristics in breast cancer tumors treated with neoadjuvant chemotherapy with and without bevacizumab: Results from NeoAva—Randomized phase II study. *First Author: Olav Engebraaten, Oslo University Hospital, Oslo, Norway*

Background: The molecular characteristics of responding and non-responding breast cancers when treated with antiangiogenic therapy are largely unknown. **Methods:** To investigate molecular alterations in tumors treated with antiangiogenic therapy, the NeoAva study included patients with HER2 negative primary tumors of $\geq$ 25 mm that were randomized (1:1) to receive chemotherapy (4 x FEC100 + 12 weeks of taxane-based therapy) with or without bevacizumab. Tumor material was obtained at screening, 12 weeks into treatment and at surgical removal at 25 weeks. mRNA expression profiling was performed (Agilent). In this study, 131 patients were evaluable for tumor response. **Results:** pCR in breast and axilla were obtained in 14 (21.1%) patients in the chemo+bev arm, and in 7 (10.6%) patients in the chemo-only arm. The overall pCR rates were higher in the ER negative tumors compared to ER positive tumors ((9 of 23) vs (12 of 108)). Addition of bevacizumab seemed to improve pCR in the ER positive patient group (9 vs 3) and not in ER negative patient group (5 vs 4). Tumors that achieved pCR showed a significant higher expression of genes (n = 362) enriched for immune response related pathways, compared to the tumors that did not achieve pCR in the ER positive group. The identified immune gene signature predicted response independent of the PAM50 proliferation signature and VEGF pathway signature, particularly in the bevacizumab treated group ($p < 0.001$). Proliferation scores regressed across time-points in response to therapy ($p < 0.001$), and bevacizumab treatment accelerated the reduction of the proliferation score in the ER positive tumors. In response to therapy, tumors achieved a better prognosis profile, i.e. Luminal A or Normal-like profile. ER positive tumors, particularly Luminal B showed significant differences in gene expression and associated pathways between two treatment arms (chemo only and chemo+bev), while minimal change was observed for ER negative/Basal-like tumors. **Conclusions:** The immune signature was found to be a strong predictor of response in ER positive tumors, particularly in tumors treated with chemotherapy combined with bevacizumab. Clinical trial information: NCT00773695.

2524 Poster Session (Board #240), Sat, 8:00 AM-11:30 AM

Bevacizumab plus Letrozol (LEA clinical trial phase III). Using hypertension for finding biomarkers of efficacy. *First Author: Juan de la Haba-Rodriguez, Medical Oncology Department University Reina Sofia Hospital. Biomedical Research Institute Maimonides, Cordoba, Spain*

Background: The LEA study compares the combination of endocrine therapy plus bevacizumab (ET-B) against endocrine therapy (ET), as first line treatment in patients (pts) with advanced breast cancer. It failed to demonstrate superiority for the combination (JCO 2015 in press). Some retrospective studies have shown that pts developing hypertension (HT) whilst on antiangiogenic treatment have a better outcome. Polymorphisms in several HT-related genes might contribute to inter-individual differences in response to these treatments. The aim of this study is to analyze the predictive value of HT for bevacizumab efficacy. Associations between polymorphisms in genes related with HT and bevacizumab efficacy were assessed. **Methods:** The LEA study randomized 380 pts in two treatment arms, ET-B (191 pts) and ET (189 pts). We collected Grade 1-4 HT in all pts and genotyped eleven polymorphisms in HT-related genes (ACE, AGTR1, AGT, VEGF, ADRB1, ADRB2, GNB3, NOS3) in germinal DNA from 117 of these pts (ET-B:67/ ET:50). **Results:** A higher rate of HT was associated with the bevacizumab combination arm (17% vs 62% pts ET vs ET-B arm, $p < 0.001$). Pts developing HT had a better response rate (45% vs. 27% in pts with HT vs no HT, $p < 0.001$), as well as a longer progression free survival (PFS) (21.9 vs 12.0 months, HR = 0.55 (95%CI:0.43–0.71), $p < 0.001$) and overall survival (OS) (48.6 vs 41.6 months, HR = 0.55 (95%CI:0.38–0.79), $p = 0.0010$). The association found between HT and ET-B, and between HT and efficacy was maintained in the genotyped subpopulation. The variant in the angiotensin converted enzyme (ACE) rs1799752 (287pbIN/DEL) and in the angiotensin receptor type 1 (AGTR1) rs5186 (M235T) were associated with HT ($p < 0.05$). In the ET-B arm, we found a correlation between rs1799752 ACE IN/DEL and PFS ($p = 0.04$), and between VEGF2578 and OS ($p = 0.0045$). **Conclusions:** HT is correlated with better clinical outcomes in pts treated with the ET-B combination. These results provide preliminary evidence of the predictive role of polymorphisms in HT-related genes in bevacizumab efficacy. The real interest of these polymorphisms should be further elucidated in larger prospective studies.

2525 Poster Session (Board #241), Sat, 8:00 AM-11:30 AM

A phase 1 trial of a potent and selective VEGF receptor inhibitor, apatinib, in patients with advanced solid tumors. *First Author: Sunil Sharma, University of Utah Huntsman Cancer Institute, Salt Lake City, UT*

Background: VEGF-mediated signaling pathways are critical to tumor growth. Apatinib mesylate is a novel, oral angiogenesis inhibitor that potently and selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR-2). **Methods:** Apatinib mesylate was administered once daily as oral monotherapy starting at 100 mg/day and escalating to 250, 500, 750, or 850 mg/day, with dose expansion at the up to 850mg/day or maximum tolerated dose levels. The primary objective was to determine the safety and tolerability of continuous oral Apatinib mesylate in patients with recurrent solid tumors. A secondary endpoint was response to treatment. **Results:** In this Phase 1 trial, 25 patients were treated and evaluated for safety and tolerability**.** The dose levels were: 100 mg/day (n = 5); 250 mg/day (n = 9); 500 mg/day (n = 4); 750 mg/day (n = 4); and 850 mg/day (n = 3). Median age was 62 years (range, 33–76 years), and median prior number of therapies was 3.5 (range, 0-8 therapies). There was 1 dose-limiting toxicity (malignant hypertension, 250mg/day). Among 19 evaluable patients, after 2 cycles, there was 1 (5.3%) partial response, 11 (57.9%) stable disease, and 7 (36.8%) disease progression. Pharmacokinetic data will be presented. **Conclusions:** Apatinib mesylate monotherapy was well tolerated in patients with recurrent solid tumors in this phase 1 trial with preliminary evidence of promising antitumor activity. The recommended phase 2 dose for further development was 850 mg/day. Clinical trial information: NCT01497704.

2526 Poster Session (Board #242), Sat, 8:00 AM-11:30 AM

Phase I study of the combination of alisertib (MLN8237) and gemcitabine in advanced solid tumors. *First Author: Edward Jae-hoon Kim, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Aurora Kinase A (AKA) is a key mitotic regulator overexpressed in multiple solid tumors. This open-label dose escalation phase I study evaluated the safety and tolerability of alisertib (MLN8237), an oral AKA inhibitor, in combination with gemcitabine. **Methods:** Patients (pts) > 18y with refractory solid tumors received 28-day cycles of gemcitabine on days 1, 8, 15 and alisertib twice daily on days 1-3, 8-10, and 15-17. Gemcitabine was given at a standard dose of 1000mg/m^2. Four dose levels (DL) of alisertib (20-50mg) were planned following a conventional 3+3 design to investigate the occurrence of dose limiting toxicities (DLT) over cycle 1, and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D). Anti-tumor activity was assessed by response rate (RECIST 1.1) and progression-free survival. **Results:** Twenty-one pts were treated with median age 57 y [42-75]; 48% male; PS 0 (7 pts), 1 (13 pts), or 2 (1 pt); median prior therapies was 2 [0-7]; tumor types were NSCLC (7); colorectal (3); poorly differentiated neuroendocrine (3); small cell lung (2); head and neck (2); 1 each of pancreatic, gallbladder, small bowel, and mesothelioma. A median of 4 cycles [1-13] were administered. Two pts experienced DLTs: 1 pt at DL3 had grade 3 urinary tract infection; 1 pt at DL4 developed grade 3 oral mucositis, hyponatremia, and dehydration. The maximum administered dose (DL4) achieved 900 mg alisertib per cycle and was tolerated (1 DLT in 6 pts). Grade 3–4 hematologic toxicities observed included neutropenia (57%), leukopenia (48%), anemia (24%), and thrombocytopenia (14%). Hyponatremia (19%) was the only non-hematologic toxicity observed in > 10% of the pts. Ten of 14 evaluable pts (71%) had stable disease as their best response with remaining 4 pts having disease progression. **Conclusions:** Alisertib can be safely administered with gemcitabine and the R2PD for alisertib is 50 mg PO BID on days 1-3, 8-10, and 15-17 in combination with full dose gemcitabine. Further clinical evaluation of this combination is warranted and a pre-planned expansion is ongoing in pts with pancreatic adenocarcinoma including evaluation of pharmacokinetic interaction of the combination at the MTD. Clinical trial information: NCT01924260.

2527 Poster Session (Board #243), Sat, 8:00 AM-11:30 AM

First-in-human Phase 1 safety, PK, and PD study of the CDK4/6 inhibitor G1T28. *First Author: Renger G. Tiessen, PRA Health Sciences, Groningen, Netherlands*

Background: G1T28 is a highly potent and selective CDK4/6 inhibitor being developed as an IV agent for targeted bone marrow chemoprotection and as an oral antineoplastic agent. The CDK4/6 pathway is critical in regulating cell proliferation of certain tumors. In addition, hematopoietic stem and progenitor cells (HSPCs) are dependent upon CDK4/6 for proliferation. Transient G1T28-induced G1 cell cycle arrest of HSPCs renders them resistant to the cytotoxic effects of chemotherapy. Thus, G1T28 could be used for chemoprotection (reduction of chemotherapy-induced myelosuppression) in patients with CDK4/6-independent tumors, or as an antineoplastic agent in patients with CDK4/6-dependent tumors. **Methods:** The objective of this study was to assess the safety and tolerability of G1T28, as well as to characterize PK and PD (NCT02243150). Part 1 was a double blind, placebo-controlled, single escalating dose study in healthy volunteers of both sexes, where subjects were randomized (3:1) to receive G1T28 or placebo as a single 30-minute IV infusion. In Part 2, 8 subjects will receive single escalating oral doses of G1T28 in three dosing periods. PD assessments included evaluation of *ex vivo* stimulation of lymphocytes and bone marrow cell cycle analysis. **Results:** 45 subjects have enrolled in the study to date. In Part 1, G1T28 was administered at doses of 6, 12, 24, 48, 96 and 192 mg/m^2. G1T28 was well tolerated, with no dose limiting toxicities or serious adverse events reported. In Part 1, G1T28 exposure (Cmax and AUC) increased proportionally with dose, while clearance was relatively constant. G1T28 at 96 and 192 mg/m^2 demonstrated a robust pharmacodynamic effect with a dose-dependent decrease in phytohemagglutinin (PHA)-stimulated lymphocyte proliferation *ex vivo*. **Conclusions:** G1T28, a novel CDK4/6 inhibitor, is well tolerated and demonstrates predictable PK and robust PD activity. Based on these results, IV G1T28 will be investigated in Phase 1b/2a studies in patients with CDK4/6-independent tumors to evaluate its potential as a targeted bone marrow chemoprotectant. In addition, the oral formulation will be assessed as an antineoplastic agent in patients with CDK4/6-dependent tumors. Clinical trial information: NCT02243150.

2528 Poster Session (Board #244), Sat, 8:00 AM-11:30 AM

Overcoming the proliferation rate paradox: Clinical evaluation of a continuous dosing scheme of the novel oral Eg5 inhibitor 4SC-205. *First Author: Klaus B. Mross, Klinik für Tumorbiologie, Freiburg, Germany*

Background: Mitotic proteins, like Eg5, are exclusively expressed during mitosis. Targeted therapy directed against such proteins prevents side-effects like peripheral neuropathies. However, mitosis is a timely restricted event and doubling times of human solid tumours (~120d) largely exceed the ones observed in preclinical models. Therefore, continuous exposure at the target site is mandatory. Here we present a clinical dosing scheme for the Eg5i 4SC-205 to address these challenges **Methods:** Time-dependent anti-proliferative effect of 4SC-205 on spindle check point (SAC) deficient (H929, HT29) and proficient (HCT116, NCCIT) cell lines was investigated. Apoptosis induction was assessed by western blot analysis for Noxa, Mcl-1 and caspase 3. 59 patients (pts) with solid tumours were enrolled in a Phase I study and dosed either once weekly (ow) at days 1 and 8 or twice weekly (tw) at days 1, 4, 8, and 11 or continuously (con) within a 21-day cycle. **Results:** Effects on proliferation and apoptosis inductionin SAC deficient/proficient cell lines was time-dependent. SCA deficient cells required up to 96h incubation to establish the full IC_{50}. 46 pts were enrolled in the discontinuous dosing arms with either once weekly (ow) or twice weekly (tw) (dose levels: 25mg (N = 3), 50mg (N = 3), 100mg (N = 6), 150mg (N = 6) and 200mg (N = 13) ow; at 50mg (N = 3), 75mg (N = 7), and 100mg (N = 5) tw). 13 patients were evaluated for con. dosing at 10mg (N = 3), 20mg (N = 6), and 30mg (N = 4). Response acc. to RECIST was not observed. Overall, 22% of pts. were stabilized into follow-up after 6 weeks. One patient is still on treatment at 20mg daily. The median time on study of pts receiving continuous dosing of 20 mg was 162 days. In contrast, the overall median time on study was 42 days under ow or tw dosing. **Conclusions:** Prolonged exposure is needed for 4SC-205 to inhibit proliferation and to induce apoptosis in SAC deficient cell lines. This requirement was translated into the clinic utilizing a continuous dosing scheme. 4SC-205 can be safely administered at an oral daily dose of 20mg (= RP2D). Promising long-term disease stabilization is observed under continuous dosing. Clinical trial information: NCT01065025.

2529 Poster Session (Board #245), Sat, 8:00 AM-11:30 AM

Evaluation of targeted bone marrow arrest by G1T28, a CDK4/6 inhibitor in clinical development to reduce chemotherapy-induced myelosuppression. *First Author: Patrick J. Roberts, G1 Therapeutics, Inc, Research Triangle Park, NC*

Background: Myelosuppression is the major dose-limiting toxicity of chemotherapy, which limits dose intensity. G1T28 is a highly potent and selective CDK4/6 inhibitor in development as an IV agent to provide targeted bone marrow chemoprotection in patients with CDK4/6-independent tumors. Hematopoietic stem and progenitor cells (HSPCs) are dependent upon CDK4/6 for proliferation; G1T28 induces a transient G1 cell cycle arrest that renders HSPCs resistant to the cytotoxic effects of chemotherapy. In preclinical models, this results in faster recovery of all blood cell counts following chemotherapy and preservation of long-term hematopoietic function. **Methods:** To rationally design tolerable and active chemotherapy combination regimens with reduced multi-lineage myelosuppression, the magnitude and duration of G1T28-induced HSPC G1 arrest in human bone marrow was characterized. Data from 3 species (mouse, rat, dog) were used to evaluate dose response relationships for HSPC G1 cell cycle arrest and to construct a cross-species allometrically-scaled PK/PD model. Model simulations and human PK/PD data from a Phase I trial (NCT02243150) were used to predict the biologically effective dose (BED) in humans. In this trial, the BED was assessed by obtaining bone marrow aspirates and evaluating G1 arrest of HSPCs by flow cytometry. **Results:** Preclinical PK/PD modeling outputs and clinical data predicted the BED in humans to be 192 mg/m^2. Specifically, a 15mg/kg dose of G1T28 in dogs produced robust and sustained bone marrow arrest for ~24 hours and had a similar PK exposure to the predicted human BED. A single bone marrow aspirate from 12 subjects following 192 mg/m^2 (baseline, n = 5; 24 h post-G1T28, n = 3, or 32 h post-G1T28, n = 4) demonstrated a robust G1 arrest of multiple progenitor subsets at 24 h, with early progenitors persisting in G1 arrest to 32 h. **Conclusions:** A single IV administration of G1T28 at the BED of 192 mg/m^2 produced robust inhibition of HSPCs within the bone marrow for > 24 hours. Based on these results, Phase 1b/2a studies are planned to evaluate the potential of G1T28 in reducing multi-lineage chemotherapy-induced myelosuppression. Clinical trial information: NCT02243150.

2530 Poster Session (Board #246), Sat, 8:00 AM-11:30 AM

SLC1A5 to predict outcome with chemotherapy in early triple-negative breast cancer. *First Author: Anna Maria Affan, St Vincent Charity Medical Center, Cleveland, OH*

Background: TNBC are high grade tumors which have a poor prognosis. SLC1A5 is a neutral amino acid transporter found in these tumors and high levels correlate with aggressive biological behavior. By targeting SLC1A5 function, tumor cell growth can be inhibited and autophagy activated which should result in improved survival benefit for patients with TNBC. We evaluated the role of SLC1A5 on tumor death rate in patients who were treated with chemotherapy for early TNBC. **Methods:** A retrospective, cohort study of patients with TNBC was performed to evaluate survival compared with the level of expression of SLC1A5. A histogram was constructed to determine a median point which could be used to define a "high" versus "low" score. Five was used as the average cut-point. Thereafter to determine overall survival, Kaplan-Meier product-moment technique (K-M) was used, with comparisons between groups made by using the log rank test. Statistical significance was taken as $p < 0.05$. **Results:** The cohort consisted of 171 patients with TNBC. The median age was 51 years with similar distribution between node positive and node negative cases. Survival information was available for 112 patients with data available on the SLC1A5 score. There was a significant association of the outcome of interest, overall survival, with the SLC1A5 score with a worse outcome noted in tumors with higher expression ($p = 0.00189$). Furthermore, 80 patients with TNBC who received chemotherapy with higher levels of SLC1A5 showed worse survival ($p = 0.0005$). Additionally, the relationship between SLC1A5 and hypoxia-induced upregulation of Carbonic Anhydrase IX (CAIX), was explored using the Welch Two Sample t-test. There was a significant association with higher levels CAIX associated with higher SLC1A5 ($p = 0.0189$). **Conclusions:** This study suggests that SLCA15 is associated with tumor hypoxia and worse outcome in chemotherapy treated patients. The results emphasize the importance of evaluating proteins involved in cell metabolism and autophagy, to aid in the development of novel targets. The relationship of CAIX with SLCA15 implies that the latter may be involved in tumor hypoxia that needs further exploration in additional cohorts and clinical trials.

2531 Poster Session (Board #247), Sat, 8:00 AM-11:30 AM

Phase I dose-escalation study with extended daily administration of Debio1143, an oral inhibitor of apoptosis protein inhibitor, in patients with solid tumors. *First Author: Henry C. Pitot, Mayo Clinic, Rochester, MN*

Background: Inhibitors of apoptosis proteins (IAPs) play a critical role in modulating multiple processes, including caspases activation and NF-κB signaling. Because high expression of IAPs represent a frequent oncogenic event in human cancers, therapeutic targeting of IAPs is considered as a promising approach. The small molecule Debio 1143 is a potent orally-active IAP antagonist able to promote apoptosis in tumour cells by restoring caspase activity, and modulating NF-κB signaling and TNFα effects in various preclinical models. A shorter schedule of Debio1143 (daily x 5, every 21 days) was well tolerated in cancer patients up to 900 mg QD. **Methods:** Oral Debio1143 was administered to patients with advanced solid tumors according to a novel extended schedule: daily x 14, every 21 days. The starting dose was 200 mg QD. The MTD was exceeded when any two patients within the same cohort experienced dose-limiting toxicity (DLT). Serial blood samples and urine were collect on cycle 1 for PK and PD assessments. **Results:** Six-teen patients received doses from 200 to 400 mg QD. Only one DLT (G3 reversible ALT and ALP elevation) was reported at 200 mg. Most common AEs of any grade deemed related to study drug were fatigue (31%), nausea (29%), decreased appetite (20%), vomiting (16%), diarrhea (14%) and rash (14%). Average tmax and t½ were about 2 and 7 h, respectively. Exposure increased in a relatively dose- proportional manner without accumulation over 14 days. The exposure of the main metabolite Debio1143-MET1 increased in a greater than dose proportional manner. Renal excretion of Debio 1143 was less than 15% of dose. Rapid and sustained degradation of cIAP-1 in surrogate tissue was observed at all doses. Debio1143 induced plasma MCP-1, TNFα, M30 and M65 increase. No changes were observed for IL-8. No responses were seen in 16 evaluable patients. **Conclusions:** The MTD was not reached and 400 mg was the highest tested dose. The extended schedule administration of oral Debio 1143 was well tolerated with significant PD activity at the doses investigated. A phase Ib trial of this extended schedule of Debio1143 in combination with concurrent chemo-radiation in LA-SCCHN is ongoing. Clinical trial information: NCT01078649.

2532 Poster Session (Board #248), Sat, 8:00 AM-11:30 AM

First-in-human study of TAS-115, a novel oral MET/VEGFR inhibitor, in patients with advanced solid tumors. *First Author: Nobuaki Matsubara, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Aberrations in the MET receptor tyrosine kinase pathway occur in various human malignancies (via MET amplification, mutation, or overexpression) driving cell proliferation, survival and metastasis. TAS-115 is a novel oral MET/VEGFR inhibitor with preclinical activity in human tumor models. This dose escalation study evaluates TAS-115 in patients (pts) with advanced solid tumors. **Methods:** In this Phase I study, the primary objective is to determine the MTD and RD of TAS-115, secondary objectives included safety and tolerability, antitumor activity, and PK. Eligible pts (aged ≥ 20 years, ECOG PS ≤ 1) had tumors that are refractory to standard therapy. The accelerated titration and 3+3 design are used in this study. TAS-115 is administered continuously 21 days in one cycle. **Results:** Phase I was begun in Oct 2011. The drug formulation has been changed because of the saturation of absorption. Phase I using the new formulation was restarted from Dec 2013. As of Jan 15 2015, 18 pts were enrolled in the dose escalation phase of new formulation (67% male, median age 61 years, 55% PS 0). The numbers of types of tumors were gastrointestinal stromal tumor in 3, gastric in 3, colorectal in 2, bile duct in 2, breast in 2, and others in 6 pts. Pts were treated in 5 dose cohorts of 200-800 mg. DLTs occurred at 800 mg in the 2 pts, which included grade 3 thrombopenia with hemorrhage and grade 3 rash. The frequent drug-related AEs (all grade ≥ 35%) were edema (67%), AST increase (61%), fatigue (56%), ALT increase (50%), rash (50%), leucopenia (44%), neutropenia (39%), thrombopenia (39%). TAS-115 exposure was generally increased with dosage. Mean C_{max} and AUC_{last} at 800 mg were 4,910 ng/mL and 39,400 ng*h/mL, respectively, with a mean T_{max} of 1.3 hrs and apparent $T_{1/2}$of 13.7 hrs. Preliminary efficacy was observed in 5 pts. 2 pts maintained SD more than 12 and 24 weeks, respectively, and reduction of SUV in PET was observed in 5 pts. Biomarker analysis including MET status is also evaluated and will be presented. **Conclusions:** TAS-115 was well tolerated and the safety profile was confirmed up to 800 mg. The ongoing dose escalation is still under evaluation and RP2D will be determined. Clinical trial information: JapicCTI-111645 and 132333 Clinical trial information: JapicCTI-111645 and JapicCTI-132333.

2533 Poster Session (Board #249), Sat, 8:00 AM-11:30 AM

First-in-human study of LY3039478, a Notch signaling inhibitor in advanced or metastatic cancer. *First Author: Christophe Massard, Gustave Roussy Cancer Campus, Villejuif Cedex, France*

Background: LY3039478 (LY) is an orally bioavailable, potent, and highly selective Notch inhibitor (Notch 1-4). We report on safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of LY. **Methods:** Eligible pts (ECOG $\leq$ 1) had relapsed solid tumors, adequate hematologic, renal, and hepatic functions. Using a predictive pre-clinical PK/PD model and non-clinical toxicology data, a dose range of 2.5-100 mg was selected. LY was given three times a week (TIW) on a 28-day cycle until disease progression. Dose escalation used 3+3 design with probability toxicity band modelling. Safety assessments were based on CTCAE V4.0. Primary objective: to define the recommended phase 2 dose of LY; additional objectives: PK, PD (Aβ in plasma and a panel of 46 genes expressed in skin), and preliminary antitumor activity. **Results:** 55 pts were treated. The most common related toxicities ($\geq$ 10% of pts) included diarrhea (42%); vomiting (40%); nausea (36%); asthenia (33%); decreased appetite (25%); hypophosphatemia (18%); mucosal inflammation (16%); weight decreased (15%); hair color changes and dry skin (13% each); dry mouth (11%). 5 dose-limiting toxicities were observed in cycle 1: thrombocytopenia grade 4 in 3 pts (20mg, 30mg, and 60mg), nausea and asthenia grade 3 in one patient (100mg) and colitis grade 3 (100mg). Other observed grade 3/4 toxicities related to LY in $>$ 1 patient included hypophosphatemia (5 pts) and vomiting (2 pts). Maximum tolerable dose (MTD) was defined as 75 mg TIW. AUC and C_{max} appeared to increase in a dose proportional manner. There was no accumulation with multiple dosing with an elimination half-life of approximately 6-8h. Dose dependent inhibition of plasma Aβ and target genes (in skin) was observed. At the recommended dose of 75mg TIW, preliminary data indicate approximately 80% inhibition of Aβ, $>$ 50% inhibition of HES1, NRARP, and CCND1. Additional inhibited genes included HES2, HES4, HES5, HEYL and MYC. 6 pts received $\geq$ 6 cycles (range 6-18). Best observed response is PR in a patient with ER+/PR+ HER2-breast cancer. **Conclusions:** The recommended dose for LY monotherapy is 75 mg TIW with manageable toxicities and significant target inhibition. Further exploration of LY monotherapy is ongoing. Clinical trial information: NCT01695005.

2534 Poster Session (Board #250), Sat, 8:00 AM-11:30 AM

Trends in the characteristics, dose-limiting toxicities and efficacy of phase I oncology trials: The Cancer Research UK experience. *First Author: Han Hsi Wong, Cancer Research UK Centre for Drug Development, London, United Kingdom*

Background: Phase I oncology trials are crucial in cancer drug development and have evolved over the years. We examined the trends in trial characteristics, dose-limiting toxicities (DLTs) and efficacy, and questioned whether the concepts of DLT and maximum-tolerated dose (MTD) were still helpful. **Methods:** Cancer Research UK Centre for Drug Development (CRUK CDD) sponsors phase I trials across the UK. We reviewed our experience of adult trials between 1995 and 2013. **Results:** Forty-nine trials were divided into two groups based on the starting date for recruitment: 1995-2003 (24 trials, n = 603) and 2004-2013 (25 trials, n = 750). From 1995-2003 to 2004-2013, there was a shift towards studying biological and targeted agents. Patients in the later years tended to be older, had a greater disease burden and were more likely to have received prior treatment, although baseline haematology and biochemistry test results were no worse. The incidence of DLTs was similar in both year groups (10.1% vs 11.5%; risk of death 0.7% vs 0.3%). DLTs such as neuropathy, stomatitis and thrombocytopenia were less common in the later trials, while the frequency of elevated liver enzymes was greater. Non-classical DLTs also emerged in the later trials, including hypertension, hypophosphatemia, cardiac and ophthalmic toxicities. Of a total of 219 DLT events, only four fell outside the protocol-defined criteria for a DLT. The overall disease control rate increased from 27.9% in 1995-2003 to 36.0% in 2004-2013 (P = 0.0033) due to improved disease stabilisation, and there was a trend towards a lower rate of progressive disease as best response (51.0% vs 46.3%, P $>$ 0.05). Objective response rates as high as 33.3% (radioimmunotherapy in lymphoma) were observed, and were both disease- and agent-dependent. Doses at or above the MTD were associated with response to cytotoxics and radioimmunotherapy but not to other targeted agents. **Conclusions:** CRUK CDD phase I oncology trials continue to provide clinical benefit to participants while minimising toxicities, and DLT remains a helpful concept. However, pharmacodynamic rather than MTD endpoints are becoming increasingly important in defining the dose for subsequent trials.

2535 Poster Session (Board #251), Sat, 8:00 AM-11:30 AM

A phase I study of intravenous artesunate (IV AS) in patients with solid tumors. *First Author: John F. Deeken, Inova Comprehensive Cancer and Research Institute, Mclean, VA*

Background: Although the artemisinin class of anti-malarial drugs has shown significant anti-cancer activity in preclinical models, no prospective clinical trials have so far been performed. Proposed anticancer mechanisms include: DNA damage, inhibition of angiogenesis, TRAIL-mediated apoptosis, and inhibition of several signaling pathways. We performed a phase I clinical study to determine the maximum tolerated dose (MTD), and the dose limiting toxicities (DLTs) of IV AS. **Methods:** Patients (Pts) with refractory solid tumors were enrolled in this accelerated titration dose escalation study with planned dose levels of 8, 12, 18, 25, 34 and 45 mg/kg given on days 1 and 8 of a 21 day cycle. One patient would be treated at each dose level until a $\geq$ level 2 toxicity occurred during cycle 1, then a traditional 3+3 dose escalation rule would apply until 2 of 6 patients experienced DLTs on a dose level. Intensive PK was performed. Archived tumor blocks were obtained for correlative studies. **Results:** Between 01/2013 and 04/2014, 19 pts were enrolled, 17 of whom were evaluable for toxicity; 16 were evaluable for efficacy. The median age was 59, 12 (63%) were female, and 10 (52%) were Caucasian. The first pt on 8mg/kg had a Gr 3 non-DLT toxicity, so 3+3 dose escalation was then initiated. DLTs were seen at dosages of 12 (1 of 6 patients), 18 (1 of 6) and 25mg/kg (2 of 2), and were neutropenic fever (Gr 4), hypersensitivity reaction (Gr 3), AST elevation (Gr 4), and nausea/vomiting (Gr 3), respectively. The MTD was determined to be 18mg/kg. Grade 3/4 AEs seen in 2 pts each (12%) were: LFT abnormalities, anemia, neutropenia, and febrile neutropenia. One pt died on study related to disease progression and was deemed to not be drug related. No responses were observed; 3 patients had prolonged stable disease for 8, 10, and 11 cycles with ampullary, renal, and ovarian cancer, respectively, for a disease control rate of 19%. Tumor expression of transferrin and ABCB6 did not correlate with disease control. PK results will be presented. **Conclusions:** The MTD of IV AS is 18mg/kg on this schedule. Treatment was well tolerated at that dose level. Modest clinical activity was seen.

2536 Poster Session (Board #252), Sat, 8:00 AM-11:30 AM

Phase Ib study of afatinib plus standard-dose cetuximab in patients (pts) with advanced solid tumors. *First Author: Anas Gazzah, Drug Development Department, Gustave Roussy, Villejuif, France*

Background: Afatinib combined with cetuximab has shown activity in pts with *EGFR*mutation-positive NSCLC and acquired resistance to EGFR tyrosine kinase inhibitors. Targeting the ErbB pathway may also be beneficial in other tumor types; for example, squamous cancers have high levels of EGFR overexpression. This Phase Ib study assessed afatinib plus standard-dose cetuximab in pts with other advanced solid tumors. **Methods:** In Part A, a 3+3 design was used to determine the maximum tolerated dose (MTD) of afatinib (from 30 to 40 mg daily) plus cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^{2}weekly). Treatment was administered until disease progression or unacceptable toxicity. Dose-limiting toxicities (DLTs) in cycle 1 were used to determine MTD. In Part B, MTD was assessed in 3 expansion cohorts (squamous NSCLC, squamous cell carcinoma of head and neck [HNSCC], other tumors). **Results:** In Part A, 3 pts received afatinib 30 mg in cohort 1, and 6 received afatinib 40 mg in cohort 2. No DLTs were observed in either cohort; MTD was defined as afatinib 40 mg once daily plus standard-dose cetuximab. In Part B, 39 pts have been treated to date at MTD (7 squamous NSCLC, 9 HNSCC and 23 other). Pts were heavily pre-treated (median 3 lines of prior therapy). Among the 45 pts receiving afatinib 40 mg, the most frequent drug-related adverse events (AEs; all grades [G], n [%]) were rash/acne (37 [82%]), diarrhea (28 [62%]), stomatitis (16 [36%]) and fatigue (13 [29%]). 12 pts had drug-related G3 AEs (most commonly rash/acne (5 [11%]) and fatigue (2 [4%]). There were 2 drug-related G4 AEs (hyperlipasemia and hypersensitivity) and no drug-related G5 AEs. Preliminary efficacy results showed that 38% of pts in the expansion cohort had stable disease (SD); 4/7 (57%) in squamous NSCLC, 3/9 (33%) in HNSCC, 8/23 (35%) in other tumors; no objective responses have been reported to date. Median duration of disease control was 12 weeks. **Conclusions:** MTD was defined as afatinib 40 mg once daily plus cetuximab 250 mg/m^2 weekly (after 400 mg/m^2 loading dose). At MTD, AEs were mild-to-moderate with no unexpected AEs. SD was observed in 38% of heavily pre-treated pts with squamous NSCLC, HNSCC, and other tumor types. Updated efficacy results will be presented. Clinical trial information: NCT02020577.

2537 Poster Session (Board #253), Sat, 8:00 AM-11:30 AM

Phase I trial of the HSP-90 inhibitor PU-H71. *First Author: John F. Gerecitano, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: PU-H71 (PU) is an HSP-90 inhibitor that can be labeled with ^{124}I without altering its biochemical properties. Intratumoral drug concentration can be calculated based on ^{124}I-PU-H71 (*PU) PET imaging, leading to a surrogate marker of intratumoral pharmacokinetics. **Methods:** Patients (pts) with previously treated solid tumors, lymphoma and myeloproliferative neoplasms (MPN) on ruxolitinib were eligible. PU was given days 1, 4, 8, 11 each 21 days at escalating dose levels using a Continuous Reassessment Method (CRM). The primary objective was determination of the MTD. Secondary objectives included plasma and intratumoral PKs measured by pre- and on-treatment core needle biopsies (CNB) and by *PU PET imaging. **Results:** To date, 40 pts have received PU at doses from 10-400mg/m^2. 37 are currently evaluable for DLT, and the last 3 pts needed (per CRM) are being enrolled. Five pts experienced DLTs: 1 (of 2) at 400 mg/m^2 - grade 3 mucositis; 4 (of 7) at 350 mg/m^2 – 1 pt grade 3 AST and ALT, 1 pt grade 3 nausea/vomiting + grade 2 intolerable myalgia, 1 pt grade 3 anemia, 1 pt grade 2 intolerable headache. Related grade 3 toxicities seen in more than one pt include: AST (n = 2), atrial fibrillation (n = 2), diarrhea (n = 2), hypertension (n = 2), hyponatremia (n = 3), lymphopenia (n = 6) and WBC decrease (n = 2). Grade 4 toxicities include lymphopenia (n = 2), amylase (n = 1), and urine output decrease (n = 1). Intratumoral concentrations of 0.5 – 8 μM (greater than the IC50 for most cancer cells) were consistently achieved 24h after first dose at doses of 50 - 300 mg/m^2, suggesting that target saturation may be achieved below DLT-related doses. Tumor regressions included: 22.6% in a cervical SCC pt (140 mg/m^2), 8.3% in a triple negative breast cancer pt (300 mg/m^2), 25.6% in an ER positive breast cancer pt (400 mg/m^2), 20.8% in a penile SCC (350 mg/m^2) pt and 20.6% in a Marginal Zone Lymphoma pt (50 mg/m^2). One MPN pt decreased WBC and increased hemoglobin > 1 unit. 23 pts had *PU PET imaging. 13 of these had CNBs. Intratumoral concentrations measured both ways were in close concordance. **Conclusions:** PU is a well tolerated HSP-90 inhibitor with signals of activity seen in several tumor types.*PU can be used to visualize PU uptake and *PU PET scans can be used to estimate intratumoral concentrations of PU. Clinical trial information: NCT01393509.

2538 Poster Session (Board #254), Sat, 8:00 AM-11:30 AM

Safety and pharmacokinetics (PK) of cabazitaxel (C) in patients (pts) with hepatic impairment (HI). *First Author: John Sarantopoulos, Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio, TX*

Background: C studies excluded pts with HI. A Phase I dose-escalation study (NCT01140607) assessed the effect of HI on C PK and safety in pts with advanced solid tumors. **Methods:** Pts with normal hepatic function (NHF; bilirubin [B] ≤ ULN; aspartate aminotransferase [AST] ≤ ULN), mild (MiHI; B > 1– ≤ 1.5 x ULN or AST > 1.5 x ULN), moderate (ModHI; B > 1.5– ≤ 3 x ULN) or severe (SHI; B > 3–10 x ULN) HI received C dose escalation starting at 25, 20, 10 or 10 mg/m^2, respectively. Endpoints were cycle 1 (C1) dose-limiting toxicities (DLTs), safety and PK. Plasma PK were derived by non-compartmental analysis. HI effect was assessed by linear mixed-effects modeling on clearance normalized to body surface area (CL/BSA) and exposure normalized to dose. **Results:** Pts (43 [6 NHF, 18 MiHI, 12 ModHI, 7 SHI]) had a median age of 60 years (range 18–79); 52% were male; 81% had ECOG performance status 1. Colon and liver tumors were most common (19%; prostate 7%). Maximum tolerated doses (MTD) were 20 (MiHI) and 15 mg/m^2 (ModHI). The SHI cohort was discontinued early (first pt treated at 20 mg/m^2 died). Median number of C cycles (range) at MTD were: NHF 3 (1–4); MiHI 2 (1–31); ModHI 2 (1–3). In evaluable pts, C1 DLTs were seen in 3/4 NHF, 3/11 MiHI and 1/6 ModHI pts at MTD, and 0/6 SHI pts at 10 and 15 mg/m^2. The most frequent DLT was grade 4 febrile neutropenia (FN). The most frequent C-related, grade 3–4 toxicities were neutropenia (42%), FN (16%) and anemia (12%). PK was assessed in 36 pts (6 NHF, 15 MiHI, 9 ModHI, 6 SHI). CL/BSA was lower (geometric mean 13.4 L/h/m^2) than typical values (26.4 L/h/m^2) in NHF, but similar in MiHI (23.5 L/h/m^2) and ModHI (27.9 L/h/m^2). CL/BSA in SHI was 18.1 L/h/m^2. Compared with MiHI, CL/BSA increased 19% in ModHI (geometric mean ratio 1.19; 90% CI 0.74−1.91), but decreased 23% in SHI (0.77; 0.39−1.53) (39% with erratic PK profiles excluded [0.61; 0.36–1.05]), and AUC_{last}/dose decreased 14% in ModHI (0.86; 0.50−1.46) and increased 17% in SHI (1.17; 0.63–2.14). No change in C free fraction was seen. A pt with cholangiocarcinoma on study had stable disease at cycle 32. **Conclusions:** Cabazitaxel tolerability was similar in pts with MiHI, ModHI or NHF, and consistent with prior reports. There is no evidence that MiHI or ModHI results in a substantial decline in C CL. Clinical trial information: NCT01140607.

2539 Poster Session (Board #255), Sat, 8:00 AM-11:30 AM

Phase 1 study of BPM 31510 (Ubidecarenone) in patients with advanced solid tumors (ST): Use of multiomics platform to evaluate reversal of Warburg effect. *First Author: Ralph Zinner, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BPM 31510 is a small molecule that targets the metabolic machinery of the cancer microenvironment to create a hallmark shift from lactate dependency towards mitochondrial oxidative phosphorylation, reversing the Warburg effect. Preclinical data indicate BPM 31510 causes this shift resulting in tumor regression and enhances the antitumor activity in combination with chemotherapy agents in a priming schedule. This is the first clinical study to evaluate BPM 31510 at a 4-days (d) continuous infusion in four arms; as a single agent, and in combination with Gemcitabine, 5-FU or Docetaxel. **Methods:** Eligible patients (pts) (aged ≥ 18 y) had previously treated relapsed/refractory ST. Pts in the monotherapy arm received IV BPM 31510 for 4 d in continuous infusion in 28-d cycles. Pts in the combination arms were primed for 3 wks and then started in a weekly dosing (either gemcitabine, 5-FU or docetaxel) after the BPM 31510 infusion in a 6-wk cycle. Doses were escalated in a 3+3 schema. Phase I endpoints were safety, PK and Multi-Omics based pharmacodynamics. Tumor response is evaluated at wk 2 and every 4 -6 wks. **Results:** As of 01 Dec 2014, 56 pts have been enrolled. Pts have been treated at 3 dose levels up to 137 mg/kg. No DLTs or treatment-related SAEs have been reported. MTD has not yet been established. Most frequently reported related AEs in all 4 arms were grade 1-2 INR prolongation that resolved after Vitamin K administration. No bleeding reported. Grade 1-2 thrombocytopenia has been seen in the Gemcitabine arm requiring dose modification. PK data indicated linear distribution. 12/25 pts (48%) that are evaluable for efficacy after cycle 2 showed various responses including: tumor reductions, decrease FDG, arrested tumor progression, stable disease, decrease in tumor markers, QOL improvements. Integrated multi-omics technology showed reversal of the Warburg effect in selected pts. **Conclusions:** Emerging data from this study suggest that BPM 31510 is well tolerated in monotherapy or in combination with chemotherapy agents. Early anti-tumor activity is seen. Dose-escalation on a 6-day infusion schedule is ongoing to determine the recommended phase II dose Clinical trial information: NCT01957735.

2540 Poster Session (Board #256), Sat, 8:00 AM-11:30 AM

Preliminary clinical pharmacokinetics and pharmacodynamics of Debio 1347 (CH5183284), a novel FGFR inhibitor. *First Author: Claudio Zanna, Debiopharm International SA, Lausanne, Switzerland*

Background: Deregulated fibroblast growth factor receptor (FGFR) signaling is associated with tumorigenesis. Debio 1347 is an orally-available ATP competitive inhibitor of FGFR 1, 2 and 3 with preclinical data showing high target-specificity and antitumor activity across models of FGFR amplified, mutated or translocated tumors for various human malignancies. Debio 1347 is currently investigated in selected patients harboring FGFR genetic alterations. **Methods:** The first-in-human, phase I dose-escalation study enrolls patients with advanced solid tumor malignancies harboring defined activating alterations of FGFR 1, 2, or 3. Patients receive Debio 1347 orally once daily. With a starting dose level of 10 mg the study follows a 3+3 dose-escalation scheme on a modified Fibonacci sequence (MH Voss et al, abstr TPS2629^, ASCO 2014). Debio 1347 plasma levels are measured after single and repeated dosing using a validated LC-MS/MS assay. The PD profile of Debio 1347 is also assessed by measuring plasma levels of several biomarkers including FGF23 and phosphate. PK/PD relationships are explored graphically. **Results:** Preliminary data from 22 patients treated with 10-40 mg/day during the dose escalation phase of the trial indicate that Debio 1347 is rapidly absorbed with a median tmax occurring at 3 hours post-dose. Apparent oral clearance (CL/F) and volume of distribution (Vz/F) are on average 8 L/hour and 130 L, respectively. Plasma levels generally decrease mono-exponentially with an average half-life of 11 hours. Debio 1347 plasma exposure is dose-proportional and accumulation after 28-day repeated dosing is in general insignificant. Plasma PD markers show time-dependent changes in several patients, particularly on higher dose levels enrolled to date, and appear correlated with Debio 1347 plasma levels. Hyperphosphatemia starts to be observed after 8 days of treatment in several patients and returns to normal values in few days in case of treatment withdrawal. **Conclusions:** The PK and PD properties of Debio 1347 suggest a once daily oral dosing regimen is appropriate and preliminary PD findings are indicative of Debio 1347 target engagement in patients with FGFR gene alterations.

2541 Poster Session (Board #257), Sat, 8:00 AM-11:30 AM

A phase I study of BI 853520, an inhibitor of focal adhesion kinase (FAK), in patients with advanced or metastatic solid tumors. *First Author: Alona Zer, Princess Margaret Cancer Center, Toronto, ON, Canada*

Background: BI 853520 is a potent and highly selective inhibitor of FAK. In the dose-finding part of this study in patients (pts) with advanced or metastatic solid tumors, the maximum tolerated dose (MTD) was determined as 200 mg in a continuous oral daily dosing schedule in 28-day cycles. Dose limiting toxicities included proteinuria grade 3 and fatigue grade 3. Preliminary pharmacokinetic (PK) data support the once-daily dosing schedule. BI 853520 is now evaluated at the MTD in expansion cohorts of selected tumor types. **Methods:** Pts with metastatic or advanced-pancreatic adenocarcinoma (PAC), platinum-resistant ovarian cancer (OC), esophageal cancer (EC) and soft tissue sarcoma (STS) are treated with 200 mg of BI 853520. Selection criteria: radiologically demonstrated progressive disease in 6 months before study entry and consent for tumor biopsies for biomarker assessment. Endpoints include further determination of safety profile (NCI Common Terminology Criteria for AEs (v4.03)), PK, pharmacodynamics (PD) and efficacy, determined according to RECIST v1.1 criteria. **Results:** To date, 41 pts have been treated: 8 PAC, 11 OC, 8 EC, 14 STS. Male/female ratio: 12/29, median age 62 years (range, 21–78 years), ECOG PS 0/1:10/31. Drug-related adverse events (AEs) in $>$ 10% of pts included proteinuria (58.5%), nausea (58.5%), diarrhea (48.8%), vomiting (36.6%), fatigue (19.5%), decreased appetite (14.6%), dyspepsia and dysgeusia (both 12.2%), in the majority of grade 1–2. Proteinuria grade 3 was reported in 8 pts and reversible upon treatment interruption. Ten pts underwent dose reduction. Three drug-related serious AEs have been reported of which none were fatal. Preliminary PD analysis in fresh tumor biopsies (pFAK) shows target engagement. Preliminary efficacy: of 30 evaluable pts 8 pts had stable disease lasting 2-6 cycles in PAC (3 pts), OC (1 pt), EC (1 pt) and in STS (3 pts), and 22 progressed. **Conclusions:** The safety profile of BI 853520 is favorable. Preliminary analysis shows anti-tumor efficacy in pts with progressive disease. Recruitment is ongoing and an update on all study endpoints will be provided at the meeting. Clinical trial information: NCT01335269.

2542 Poster Session (Board #258), Sat, 8:00 AM-11:30 AM

Phase I study of the safety and tolerability of the Exportin 1 (XPO1) inhibitor Selinexor (SXR) in Asian patients (pts) with advanced solid cancers. *First Author: David Shao Peng Tan, National University Cancer Institute, Singapore (NCIS), Singapore, Singapore*

Background: SXR is an orally administered potent XPO1 inhibitor that forces nuclear retention and activation of multiple tumor suppressor proteins resulting in tumor cell death. SXR was evaluated in Asian pts with advanced cancer to assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PDn) and efficacy. **Methods:** SXR dose escalation was initiated in a 3+3 design on a twice weekly continuous 28 day cycle, schedule 1 (S1), but stopped due to persistent drug-related adverse events (AEs). Two further schedules were explored: S2, once weekly continuously every 28 days, and S3, twice weekly for 2 weeks of a 21 day cycle. Serial tumor biopsies were performed pre- and 6-8 weeks post SXR. RECIST/ Cheson lymphoma criteria for response was evaluated every 2 cycles. **Results:** 18 pts (median age 61 yrs; ECOG 0-1) received escalating doses of SXR across 3 schedules. In S1 no dose-limiting toxicity (DLT) occurred at expanded dose-level (DL) 1 (40mg/m^2, 6pts), but was stopped due to persistent $\geq$ G2 AEs (fatigue [50%], hyponatremia [50%], anorexia [17%]) post cycle 1. In S2, at DL1 (50mg/m^2, 3pts) and DL2 (60mg/m^2, 3pts), G1/2 AEs were hyponatremia (67%), nausea (33%), fatigue (50%) and anorexia (50%) with no $\geq$ G3 AEs. In S3, at DL1 (40mg/m^2, 3 pts) and DL2 (50mg/m^2, 3 pts); AEs were hyponatremia G1/2 (50%) and $\geq$ G3 (50%), nausea G1/2 (33%) and $\geq$ G3 (17%), fatigue G1/2 (67%) and $\geq$ G3 (33%), anorexia G1/2 (67%). No DLTs occurred in S2/S3. PK analysis demonstrated SXR exposure with no accumulation and comparable half-life and clearance when compared with non-Asian pts. At 40mg/m^2, $AUC_{0\text{-}inf}$ (5,222 ng*h/mL) was comparable to the anti-tumor exposure observed in mice and dogs. Mean T_{max} = 2hrs and $T_{1/2}$ = 5.7 hrs. Reduced cellularity and proliferation with increased fibrosis and apoptosis was seen in tumors post-SXR administration. Of 13 evaluable pts, best responses were PR in 2pts with refractory diffuse-large B-cell lymphoma, SD in 8 pts (colorectal [n = 2], pancreas, squamous cell tongue, non-small cell lung, ovarian and hepatocellular carcinoma [n = 2]), and PD in 3pts. **Conclusions:** Dose-escalation of SXR is ongoing on S2 and S3 with more G3 AEs seen in S3. Promising antitumor activity was observed. Clinical trial information: NCT02078349.

2543 Poster Session (Board #259), Sat, 8:00 AM-11:30 AM

Predicting outcomes in patients with advanced malignancies treated on Phase 1 clinical trials. *First Author: Kit Man Wong, University of Colorado, Denver, CO*

Background: Appropriate selection of patients fit for Phase 1 trials is critical to avoid harm and maximize the potential for benefit, yet this can be challenging. Previous studies of prognostic factors demonstrated mixed results and many were limited by small cohorts. There is no consensus on the optimal prognostication strategy. We analyzed outcomes and prognostic factors of a large cohort of Phase 1 patients treated at an academic center. **Methods:** 779 patients with advanced solid malignancies enrolled on Phase 1 trials from 2001-2009 at the University of Colorado were included. Baseline patient, disease and lab parameters, trial characteristics and outcomes were extracted from a prospective IRB-approved database. Associations between clinical factors and 90-day mortality (90DM), overall survival (OS), progression-free survival (PFS) and response rate (RR: CR+PR) were analyzed by multivariate Cox or logistic regression. **Results:** The study population had a median age of 59 (18-87) years and 49% males. Gastrointestinal (GI) cancers were most common (30%). 151 (19%) patients had $\geq$ 3 metastatic sites, mainly lungs (37%) and liver (33%), while 350 (45%) had $>$ 2 prior lines of therapy. The experimental regimen consisted of: 88% targeted, 1% cytotoxic, 11% both. Median PFS and OS were 8.0 (95% CI 7.6-8.4) and 31 (95% CI 27-34) weeks, respectively. The 90DM rate was 31% and RR was 3.1%. The likelihood of 90DM was associated with high LDH ($>$ 2.5x upper limit of normal (ULN) vs. $<$ ULN: adjusted odds ratio (aOR) 4.6, 95% CI 1.7-12.2) and low albumin ($<$ 30 vs. $>$ 35g/L: aOR 5.1, 95% CI 3.0-8.7). Independent factors for poor OS included breast, gynecologic and GI tumors, LDH $>$ ULN, ALP $>$ ULN, albumin $<$ 35g/L, and Hb $<$ 80g/L. Shorter PFS was also predicted by these factors (except ALP), as well as $>$ 2 prior treatments, use of targeted therapy alone and $\geq$ 2 agents. Addition of cytotoxics to a targeted agent significantly increased response (aOR 6.5, 95% CI 2.5-16.8). **Conclusions:** This single-center cohort of Phase 1 patients is characterized by a unique set of prognostic factors, some of which are consistent with prior studies. Tumor type, LDH, ALP, albumin and Hb are potential determinants of OS. Further validation of these prognostic factors is warranted.

2544 Poster Session (Board #260), Sat, 8:00 AM-11:30 AM

First-in-man combination phase I study of TAS-114 and S-1 in patients (pts) with advanced solid tumors. *First Author: Toshihiko Doi, National Cancer Center Hospital East, Chiba, Japan*

Background: TAS-114 is a first-in-class oral deoxyuridine triphosphatase inhibitor, which acts as a modulator of the pyrimidine nucleotide metabolic pathway. We are conducting a first combination phase 1 dose escalation and expansion study of TAS-114 and S-1 to investigate the safety, maximum-tolerated dose (MTD), pharmacokinetics (PK), pharmacogenomics and preliminary antitumor efficacy in pts with advanced solid tumors refractory to standard therapy. **Methods:** TAS-114 was administrated orally BID for 14 days followed by 7 days rest at the starting dosage of 5 mg/m^2 with the fixed dosage of S-1 (30 mg/m^2). Dose-limiting toxicity (DLT) was evaluated during the 1st cycle in dose escalation cohort (DEC), using a 3 + 3 design. Expansion cohort (EC) is conducted in parallel with DEC at the dosage which was confirmed tolerable in DEC. **Results:** As of 25 September 2014, 56 pts were enrolled with 36 pts in the DEC and 20 pts in the EC. In DEC, dosage of TAS-114 was escalated up to 240 mg/m^2 with a MTD not yet reached. In EC, TAS-114 was administrated at the dosage of 120 and 160 mg/m^2 with the fixed dosage of S-1 (30 mg/m^2). Currently, we are planning the dose escalation of TAS-114 with Japanese approved fixed dose of S-1 (36 mg/m^2). A recommended phase 2 dose is expected to be reached soon. Two pts at the dosage of 10 and 240 mg/m^2 developed DLTs, including grade 2 platelet count decreased and grade 3 aspartate aminotransferase increased. The most common treatment related adverse events were white blood cell decreased, anemia and rash. TAS-114 exposures tend to increase dose-dependently with large inter-individual variability. Preliminary antitumor efficacy was observed with acceptable safety in pts with NSCLC, gastric cancer and pancreatic neuroendocrine tumor. Especially, partial responses were confirmed in 2 of efficacy evaluable 6 pts with NSCLC. Further safety, PK and efficacy data will be presented. **Conclusions:** The combination therapy of TAS-114 and S-1 was well tolerated in pts with severe treated advanced solid tumors, resulting in the promising antitumor efficacy. Further safety and efficacy of this combination therapy will be investigated in this phase 1 and subsequent phase 2 study. Clinical trial information: NCT01610479 Clinical trial information: NCT01610479.

2545 Poster Session (Board #261), Sat, 8:00 AM-11:30 AM

Phase 1, first-in-human study of ARQ 087, an oral pan-Fibroblast Growth Factor Receptor (FGFR) inhibitor, in patients (pts) with advanced solid tumors. *First Author: Kyriakos P. Papadopoulos, START Center for Cancer Care, San Antonio, TX*

Background: ARQ 087 is a novel, orally bioavailable, ATP-competitive inhibitor of multiple kinases, including FGFR1-3. It has potent *in vitro* and *in vivo* inhibitory effects on a variety of human tumor cell lines and xenograft models dependent on FGFR signaling. **Methods:** This first-in-human 2-step study was initiated in pts with advanced solid tumors. Step 1: dose escalation/food-effect to characterize PK, safety, maximum tolerated and recommended Phase 2 Dose (RP2D; unselected for FGFR aberration). Step 2: expansion cohort to to assess safety and clinical activity of ARQ 087 in selected tumor types, including FGFR gene amplification, translocation and mutation. Assessments included tumor molecular status, response by RECIST v.1.1 every 8 weeks (wks), plasma concentrations of FGF19, 21, 23, fasting glucose and phosphate. **Results:** 61pts were treated (dose range 25-425mg QOD or QD) in Step 1; the majority were female (61%), mean age 64 yrs (34 -78). The RP2D was defined as 300 mg QD continuous dosing. Dose-limiting toxicities included increased liver enzymes (reversible Grade (G) 3 AST increase). Common drug-related adverse events (AEs; mostly G $\leq$ 2) were fatigue (53%), elevated LFTs (45%), nausea (45%), vomiting (20%) and diarrhea (20%). Only 2 pts (3%) experienced G1 drug-related hyperphosphatemia. Drug $t_{1/2}$ was 2-11 days, PK was unaffected by food. FGF 19/21/23 concentrations post-treatment were increased 1.5-6 fold. Ten pts in Step 1 had confirmed stable disease (SD) $\geq$ 16 wks (adrenocortical [2], endometrial, ovarian, NSCLC, choroidal melanoma, carcinoid, sarcoma [3]). A squamous NSCLC pt with Src amplification had SD (24% tumor reduction) for 32 wks. One adrenocortical carcinoma pt with FGFR1 amplification remains on study $>$ 22 months. Two ongoing pts with intrahepatic cholangiocarcinoma with FGFR2 fusions demonstrated a partial response and SD $>$ 24 wks with 26% decrease in target lesions, respectively. **Conclusions:** ARQ 087 has manageable, mostly G $\leq$ 2 AEs. It has demonstrated preliminary antitumor activity in pts with FGFR-pathway aberrations. Further evaluation of ARQ 087 in pre-defined tumor types is ongoing. Clinical trial information: NCT01752920.

2546 Poster Session (Board #262), Sat, 8:00 AM-11:30 AM

Dermatologic toxicities of 3,517 solid tumor patients on phase I clinical trials of the National Institutes of Health Cancer Therapy Evaluation Program (CTEP). *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Dermatologic adverse events (AEs) can be key determinants of overall drug tolerability, and the maximum tolerated and recommended phase II doses of therapy on phase I trials. We present the largest dedicated analysis of dermatologic AEs on phase I trials to date. **Methods:** Data from a prospectively maintained database of solid tumor patients (pts) enrolled onto CTEP-sponsored phase I trials from 2000 to 2010 was analyzed. Cumulative incidence, site, type, and timing of drug-related dermatologic AEs were described and compared between pts who received molecularly targeted agents (MTAs), cytotoxic therapy, or a combination of both. **Results:** 3,517 solid tumor pts and 6,165 unique drug-related dermatologic AEs were analyzed: 1,545 pts on MTA only trials, 671 on cytotoxic only trials, and 1,392 on combination MTA and cytotoxic trials. Percent grade 1, 2, 3, and 4 dermatologic drug-related AEs were 75.5%, 22.6%, 1.9% and $<$ 0.1%, respectively. Most common drug-related dermatologic AEs were alopecia (23%) and maculopapular rash (21%). Of 1,270 pts with drug-related dermatologic AEs, timing of worst drug-related toxicity was: 743 pts (cycle 1), 303 (cycle 2), and 224 (cycle 3 or later). While cumulative incidence of $\geq$ grade 3 drug-related dermatologic AEs increased to 2.4% by cycle 6, it was only 1.6% at the end of cycle 1. Cumulative incidence of drug-related dermatologic AEs was highest in pts with MTA only therapy, and significantly differed by dose level ($p < 0.001$). In pts who received MTA only therapy, drug-related dermatologic toxicity was most common for combination kinase inhibitor-containing therapy ($p < 0.001$). **Conclusions:** A substantial proportion of drug-related dermatologic AEs occurs after the traditional DLT monitoring period. Future phase I trial designs should account for delayed toxicities to avoid defining intolerable doses of study therapy.

2547 Poster Session (Board #263), Sat, 8:00 AM-11:30 AM

A first in human Phase I/II study of NUC-1031 in patients with advanced gynecological cancers. *First Author: Sarah Patricia Blagden, Ovarian Cancer Action Research Centre, London, United Kingdom*

Background: Acquired resistance to chemotherapy hampers patients'survival from many gynecological malignancies. NUC-1031, a first-in-class nucleotide analogue, utilises phosphoramidate chemistry to overcome key drug resistance mechanisms and enhance anti-cancer activity. **Methods:** NUC-1031 was given as a single injection either 1) on days 1,8, & 15 of a 28 day cycle (q4w) in doses ranging from 500mg/m^2 to 1000mg/m^2, or 2) as a twice weekly schedule on days 1 & 5, 8 & 12, 15 & 19 q4w at 375mg/m^2. Primary endpoints were safety and tolerability, and secondary endpoints were pharmacokinetics (PK), pharmacodynamics and efficacy. **Results:** Of 68 patients (pts) enrolled in this study, 18 had primary gynecological cancers: 13 ovary/fallopian tube (comprising high grade serous (HGS) (10), G2 endometrioid (2), mixed clear cell/serous (1)), 3 endometrium (comprising G3 serous (2), MMMT (1)), and 2 cervix (SCC). Pts had a mean age of 59 years (age range 42-78 yrs) and received an average of 3.5 prior chemotherapy regimens. All pts with HGS cancers were platinum resistant with average platinum-free interval 3.7 months (range 0.3 – 6.9 mths). NUC-1031 was well tolerated. In total 9 SAEs were reported in 7 pts. The most common AEs of grade $\geq$ 3 considered 'possibly/probably related' to the study agent were: myelosuppression (8); fatigue (6); GGT (3). The PK profiles revealed high and sustained intracellular levels of the active metabolite dFdCTP (AUC of 2.1 nmol/million cells/hr) over 24 hrs. Fourteen of the 18 pts had received at least 2 cycles of NUC-1031 and were evaluable for RECIST assessment of response. Significant disease control rate (DCR) was observed: 2 Partial Responses (14%); 11 Stable Disease (79%) for an ITT DCR of 72% and on treatment analysis (OTA) DCR of 93%. The mean PFS was 7.5 months (range 3 – 15 mths), with 3 pts showing ongoing disease control. **Conclusions:** NUC-1031 showed clear signs of clinical activity in patients with gynecological cancers, OTA DCR 93%. The agent was well tolerated, with durable SD and PR observed, PFS 7.5 months. A Phase Ib study of NUC-1031 in combination with carboplatin is ongoing. Phase III studies are planned in both platinum sensitive and refractory gynecological cancers. Clinical trial information: NCT01621854.

2548 Poster Session (Board #264), Sat, 8:00 AM-11:30 AM

Biomarker analysis from a Phase I study of copanlisib with expansion cohorts in solid tumors with and without PIK3CA mutations and NHL. *First Author: Carol Elaine Pena, Bayer HealthCare Pharmaceuticals, Whippany, NJ*

Background: Copanlisib is a novel, selective, reversible, pan-Class I phosphatidylinositol-3-kinase (PI3K) inhibitor with potent activity against both the δ and α isoforms. Safety and tumor response data from the first-in-man phase I trial have been reported (Patnaik et al., 2012, ASH), with two patients with follicular lymphoma ongoing as of January 2015, with partial responses lasting 1380 and 909 days. A secondary objective of the study was to identify biomarkers associating with copanlisib response. **Methods:** After dose escalation, expansion cohorts were enrolled and treated at the maximum tolerated dose (0.8 mg/kg, iv, on days 1, 8 and 15 of a 28-day cycle), including solid tumors (n = 25) with and without PIK3CA mutations, and non-Hodgkin lymphoma (NHL; n = 9). PIK3CA, BRAF, and KRAS mutations were tested using digital PCR on archival tumor samples and circulating tumor (ct) DNA from plasma (BEAMing). Next generation sequencing (NGS) of tumor genes and IHC for PTEN were performed on archival tumor samples. **Results:** Ten of 25 solid tumor patients (40%) had mutations in PIK3CA in tumor (BEAMing: 5/22; NGS: 4/9) and/or ctDNA (7/25), of which 8 had breast cancer; 2 of 22 tested (9%) had KRAS mutations. None of the NHLs tested had PIK3CA or KRAS mutations. PTEN loss was identified by IHC in 9 of 18 (50%) solid tumors, and in 1 of 7 (14%) NHLs tested. PTEN mutations were detected in 2 of 11 cases; both had PTEN loss. Of the 9 solid tumor patients with PTEN loss, 1 had a complete radiological response (CR) lasting more than one year and 2 had extended stable disease (SD) ($\geq$ 4 cycles); conversely, of the 9 without PTEN loss, none had an objective response (OR) or extended SD. The CR was in an endometrial cancer patient with PTEN loss and both PTEN and PIK3CA mutations. However, PIK3CA mutations alone did not seem to enrich response rate, as 3 of 10 (30%) patients with PIK3CA mutations and 4 of 15 (27%) without had either an OR or extended SD. **Conclusions:** PTEN loss, but not PIK3CA mutations alone, may enrich for response to copanlisib in this mixed solid tumor expansion cohort. The CR to copanlisib in the presence of both PTEN and PIK3CA aberrations may be due to multiple mechanisms leading to PI3K pathway activation. Clinical trial information: NCT00962611.

2549 Poster Session (Board #265), Sat, 8:00 AM-11:30 AM

Phase I trial of tivantinib in combination with carboplatin and pemetrexed as first-line treatment in patients with advanced nonsquamous non small cell lung cancer or malignant pleural mesothelioma. *First Author: Paolo Andrea Zucali, Department of Oncology, Humanitas Research Hospital - Humanitas Cancer Center, Rozzano, Italy*

Background: Tivantinib (T) is a selective non-ATP competitive oral inhibitor of MET receptor. Preclinical data showed that MET inhibition blocks Malignant Pleural Mesothelioma (MPM) and Non Small Cell Lung Cancer (NSCLC) cell growth and migration. Adding T to standard first-line chemotherapy may improve efficacy. **Methods:** Patients (pts) with advanced MPM or non-squamous NSCLC were eligible to receive escalating doses of T combined with carboplatin (C) AUC 5 i.v. d1-q21 and pemetrexed (P) 500 mg/m2 i.v. d1-q21 as first-line treatment. After 6 cycles of CP, T is continued as maintenance therapy until progression. Pts must be chemo-naïve with ECOG Performance Status (PS) < 2 and adequate bone marrow, liver, and kidney functions. A standard 3+3 dose-escalation design was employed starting from dose level 0 (T 240 mg BID). The primary endpoint of the phase I study was to assess the maximum tolerated dose (MTD), defined as the highest dose level at which no more than 1 of 6 pts experiences a dose limiting toxicity (DLT) during the first cycle. To evaluate the anti-tumor activity (MPM pts: 3-month PFS%; NSCLC pts: 5-month PFS%) and the pharmacokinetics of the combination, a phase Ib trial is still ongoing. **Results:** From April 2013 to September 2014, 12 pts were enrolled in the phase I study; mean age was 69 years (range, 37-73 years), M/F: 9/3, ECOG PS 0/1: 5/7, MPM/NSCLC: 6/6. The MTD was reached at dose level 0 (T 240 mg BID). DLTs (2 neutropenia G4, 1 thrombocytopenia G4) were observed in 2 pts, both at dose level 1 (T 360 mg BID). The most common all-grade toxicities were nausea/vomit (67%), anemia (58%), neutropenia (50%), and asthenia (50%). G3/4 treatment-related AEs were reported in 6 pts (50%) and all were hematological (neutropenia, thrombocytopenia, anemia). All pts received 6 cycles of CT. Among 12 evaluable pts, 1 had CR, 4 PR, and 7 SD as best response. **Conclusions:** Adding T to CP is safe with preliminary evidence of antitumor activity. T 240 mg BID in combination with C AUC 5 i.v. d1-q21 and P 500 mg/m2 i.v. d1-q21 represents the recommended dose for phase II trials. Clinical trial information: NCT02049060.

2550 Poster Session (Board #266), Sat, 8:00 AM-11:30 AM

SORAVE: A phase I trial to evaluate safety and efficacy of combination therapy with everolimus and sorafenib. *First Author: Christian Mattonet, Lung Cancer Group Cologne, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany*

Background: Combined inhibition of signaling pathways interfering with angiogenesis and cell proliferation may overcome mechanisms of drug resistance in tumors. We evaluated the combination of the multikinase inhibitor sorafenib (S) and the mTOR inhibitor everolimus (E) and assessed pharmacodynamic (PD) activity of E by PET. **Methods:** Patients with relapsed solid tumors received escalating doses of E 2.5-10.0mg/d in a 14 days monotherapy run in phase followed by combination therapy with a fixed dose of S 800mg/d from day 15. Further patients were treated with the MTD in an extension phase. The primary aim was to define a safe and feasible combination treatment regimen. DLT was defined as any drug related toxicity of CTC IV° or requiring hospitalization or interruption of therapy for > 2 weeks within the first 29 days of treatment. Pharmacokinetic (PK) analyses were performed on days 5, 14 and 29 combined with explorative PD assessment of E by FDG-PET on days 1, 5 and 14 of treatment. Efficacy was assessed by CT (RECIST 1.1) every six weeks of combination treatment. **Results:** 31 patients (mean age 58.5 years) were enrolled and evaluable from October 2009 to December 2013, of which 16 (51.6%) had NSCLC. DLT was not observed according to protocol definition in the dose finding phase (18 patients), however the MTD for treatment of further patients was defined at 7.5mg/d E + 800mg/d S due to toxicities at 10mg E occurring after the DLT-defining interval (leucopenia / thrombocytopenia III° and pneumonia III°). The median PFS of all treated patients was 99 days (95% CI 85.7 - 112.3), the median OS was 178 days (95% CI 116.9 - 239.1). In 24 of 29 evaluable patients (82.8%) a decrease in SUVmax of the hottest lesion could be observed in PET, the best response as by PERCIST criteria was PR in 7 (21.4%) and SD in 21 (72.4%) patients. No patient reached PR in CT scan whereas 8 of 21 (38.1%) evaluable patients showed confirmed SD over at least 14 weeks. **Conclusions:** Treatment of patients with relapsed solid tumors with a combination of 7.5mg/d E and 800mg/d S is safe and feasible. Most tumors show a moderate metabolic decrease in PET, however this seems to reflect more a pharmacodynamic effect than long term disease control observed in this group of patients. Clinical trial information: NCT00933777.

2551 Poster Session (Board #267), Sat, 8:00 AM-11:30 AM

Phase 1 study of the folic acid (FA) and tubulysin B hydrazide (TubBH) small molecule drug conjugate (SMDC) EC1456 in patients (pts) with advanced cancers (CA). *First Author: Daniela Matei, Indiana Univ Simon Cancer Ctr, Indianapolis, IN*

Background: The folate receptor (FR) is expressed in many cancers, with limited expression in most normal tissues. EC1456, a potent SMDC of FA and the anti-tubulin cytotoxic TubBH, targets delivery of TubBH to FR-expressing cells. EC1456 demonstrated potent activity in paclitaxel- and cisplatin-resistant FR expressing cells. In murine models of FR-expressing xenografts, EC1456 caused complete tumor regression without significant toxicity. Enhanced anti-tumor activity was observed when EC1456 was combined with platinum, taxanes, and topotecan in preclinical models. These data led to this clinical evaluation of EC1456 in advanced CA pts. **Methods:** The primary objective is to determine the MTD of EC1456 administered on 2 schedules (BIW: days 1, 4, 8, 11 q 21 or 28 days [dosages: 0.5-6.0 mg/m^2)], or QW: days 1, 8 q 21 days (dosage: 1.5-6.0 mg/m^2). Key inclusion criteria: age $\geq$ 18 years, ECOG PS 0–1, and adequate organ function. ^{99m}Tc-etarfolatide scan to evaluate FR status is to be obtained on enrolled pts. Dose escalation follows the "3+3" protocol for BIW cohort, and continuous reassessment method for QW cohort. Cycle 1 DLT evaluation must be completed for each schedule cohort prior to dosing a new cohort. **Results:** 16 pts have been treated: median age: 67.5 (48-86), M/F: 7/16. 11 pts have received 50 cycles of EC1456 BIW (median 2; range: 1-16), and 5 pts have received 19 cycles of EC1456 QW (median 4; range: 1-8). The only DLT and treatment related (TR) SAE occurred at 4.5 mg/m^2 QW schedule (Grade 3 infusion reaction). There have been no TR-deaths, Grade 4 toxicity, or toxicity causing dose delay, omission or reduction. Most TR-AEs have been Grade 1-2. Stable disease $>$ 14 cycles has been observed in 2 pts with FR expression on ^{99m}Tc-etarfolatide SPECT scan (mesothelioma; GEJ CA) on BIW schedule, and SD $>$ 6 cycles in 1 pt (leiomyosarcoma) on QW schedule. **Conclusions:** Due to the DLT on the QW schedule, cohort expansion is ongoing at 3.5 mg/m^2. Dose escalation of EC1456 BIW is ongoing. EC1456 is generally well tolerated. PK data are anticipated in May 2015. Clinical trial information: 001999738.

2552 Poster Session (Board #268), Sat, 8:00 AM-11:30 AM

ANG1005 for brain metastases from breast cancer: 18F-FLT-PET and MRI as complementary approaches to response assessment. *First Author: Susan Elaine Bates, Medical Oncology Branch, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: ANG1005 is a novel drug conjugate consisting of 3 molecules of paclitaxel covalently linked to Angiopep-2, designed to cross the blood brain barrier (BBB) via endocytosis after binding to LRP-1. A multi-center Phase II study with the primary endpoint of intra-cranial response in patients with brain metastases from breast cancer is ongoing. At the NCI a biomarker substudy is evaluating ^{18}F-FLT (3'-Fluoro-3' deoxythymidine)-PET for response assessment. **Methods:** ANG1005 was administered IV at 550 mg/m^2 q21d to patients with measurable brain metastases from breast cancer. All patients underwent imaging before and after cycle 1 with ^{18}F-FLT, a thymidine analog and novel imaging agent; its retention reflecting DNA synthesis. We compared FLT PET images with Gd-MRI contrast scans for brain metastasis detection and response assessment. Both dynamic and static images were obtained. The % change after ANG1005 was determined, with 20% considered significant. Nine of 10 planned patients have been accrued. **Results:** Eighteen metastatic brain lesions in 8 patients were analyzed. The maximum standard uptake value (SUVmax) ranged from 0.8 to 4.0 in the baseline scan, mean 1.8. Twelve of the 18 lesions showed a $>$ 20% change post therapy. The average % change was -24.8% (range: 11 to -66.8%) using SUVmax, and -7.7% using tumor to normal ratios. The FLT-PET uptake reduction exceeded the MRI result in 4 patients. Two patients had confirmed partial responses lasting 6 and 14 cycles, respectively. Six patients had stable disease, receiving a median 6 cycles. The best tumor reductions, as determined by MRI per CNS RECIST v1.1 ranged from -5% to -60% in lesion size, compared to baseline. **Conclusions:** CNS metastases from breast cancer require new CNS-directed therapies designed to cross the BBB, such as the paclitaxel conjugate ANG1005. Given that contrast-enhanced MRI detection of brain metastases represents gadolinium leakage through the BBB, rather than actual tumor volume, better approaches are needed to assess drug efficacy. Pilot evaluations of FLT-PET imaging of brain metastases suggest that it is a promising tool that may serve as a complementary assessment method for CNS disease. Clinical trial information: NCT01480583.

2553 Poster Session (Board #269), Sat, 8:00 AM-11:30 AM

Pharmacologic advantage (PA) of intraperitoneal (IP) nab-paclitaxel in patients with advanced malignancies primarily confined to the peritoneal cavity. *First Author: Mihaela C. Cristea, City of Hope, Department of Medical Oncology and Therapeutics Research, Duarte, CA*

Background: *nab*-Paclitaxel is albumin-bound paclitaxel that achieves higher intratumoral concentrations and undergoes receptor-mediated transcytosis across cell membranes. Previous clinical trials have demonstrated an advantage to IP chemotherapy. A phase I study was undertaken to evaluate the safety, tolerability and pharmacokinetics of IP *nab*-paclitaxel. **Methods:** Eligible pts received IP *nab*-paclitaxel on D1, 8, 15 of a 28-day cycle with a 3+3 dose-escalation design. Plasma and peritoneal pharmacokinetic (PK) samples were drawn prior to dose, immediately upon completion of infusion, 1, 2, 4, 6, 8, 12, 24 and 48 hours post-dose on C1D1 and C1D15. **Results:** The trial is complete with 27 pts with peritoneal carcinomatosis secondary to GYN (n=14), GI (n=12) malignancies and 1 pt with peritoneal mesothelioma. The starting dose level was 35mg/m^2 and escalated to 170mg/m^2. The MTD of IP *nab*-paclitaxel was established at 140 mg/m^2. DLTs included grade 3 neutropenia resulting in treatment delay >15 days, grade 3 abdominal pain and grade 4 neutropenia > 7 days. Plasma and IP PK data are summarized below in the Table. Over the four dose levels, the data show a ~150-fold PA to IP *nab*-paclitaxel with low intra-pt variability. The lowest PA was 50-fold. **Conclusions:** PK results suggest a significant PA to IP *nab*-paclitaxel (i.e. higher peritoneal exposure compared to plasma).The inter- and intra-patient variability appears to be low. The plasma AUC's resulting from IP *nab*-paclitaxel at the MTD of 140 mg/m^2 are similar to plasma AUC's associated with IV *nab*-paclitaxel at 100 mg/m^2. In addition to achieving high local drug levels in the peritoneum, patients are also exposed to therapeutic systemic drug levels. This study was funded by the National Comprehensive Cancer Network (NCCN) with support from Celgene Corporation. Clinical trial information: NCT00825201.

nab-Paclitaxel Dose (mg/m^2)	N	Treatment Day	Plasma AUC (mg/L x hr)	Peritoneal AUC (mg/L x hr)	Ratio (%)
35	1	Cycle 1 Day 1	0.6	89	160
		Cycle 1 Day 15	0.5	93	172
70	1	Cycle 1 Day 1	1.5	299	194
		Cycle 1 Day 15	1.6	321	199
90	1	Cycle 1 Day 1	1.1	207	94
		Cycle 1 Day 15	1.1	194	72
112.5	3	Cycle 1 Day 1	3.0 (0.8-4.2)	305 (210-427)	134 (50-389)
		Cycle 1 Day 15	2.5 (0.6-3.2)	290 (230-358)	118 (88-403)

2554 Poster Session (Board #270), Sat, 8:00 AM-11:30 AM

A phase I study of ARQ 197 in combination with temsirolimus in advanced solid tumors. *First Author: Christos Kyriakopoulos, University of Wisconsin Carbone Cancer Center, Madison, WI*

Background: A wide variety of human cancers exhibit dysregulated c-Met activity that has implications in oncogenesis. Phosphorylation of c-Met results in activation of the PI3K/AKT/mTOR pathway. Combined blockade of c-Met and mTOR pathways has shown efficacy in preclinical studies. ARQ 197 (tivantinib) is a c-Met inhibitor and temsirolimus is a selective mTOR inhibitor. We aimed to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), adverse events (AEs), clinical activity and pharmacokinetic (PK) parameters of the above combination. **Methods:** This open-label phase I study used a 3 + 3 dose escalation design. Patients (pts) in cohorts of 3 were treated with escalating doses of ARQ 197 (120-360 mg tablets orally twice daily) and temsirolimus (20 mg IV weekly) followed by dose expansion at MTD. Separate cohorts were planned for poor and extensive ARQ 197 metabolizers based on CYP2C19 genotypes. Cycles were 28 days besides cycle 1 that was 35 days to allow for PK analysis. **Results:** 21 pts (median age 57 [range 29-71]) were enrolled for dose escalation. All were extensive CYP2C19 metabolizers. The most common types of cancer were colorectal (6 pts), ovarian (4 pts), renal (2 pts) and pancreatic (2 pts). In the dose escalation cohort, 16/21 pts were evaluable per protocol. They remained on study for a median of 73.6 days (range 15-296). The MTD was ARQ 197 240 mg bid and temsirolimus 20 mg once weekly. DLTs included grade (gr) 4 neutropenia (2 pts; 1 with gr 3 febrile neutropenia) and gr 3 abdominal pain (1 pt). The most common AEs at least possibly related to therapy included: fatigue (62%; gr 1-2 in 12 pts, gr 3 in 1 pt), anemia (48%; gr 2 in 9 pts, gr 3 in 1 pt), nausea (48%; gr 1-2 in 9 pts, gr 3 in 1 pt), vomiting (48%; gr 1-2 in 9 pts, gr 3 in 1 pt) and diarrhea (48%; gr 1-2 in 9 pts, gr 3 in 1 pt). 1 pt with ovarian cancer had a confirmed partial response and remained on study for 9 months. A second pt with ovarian cancer has stable disease and remains on study at 5 months. 4 of 6 pts have been enrolled to the dose expansion cohort and are in cycle 1. Data from the dose expansion will be presented. **Conclusions:** The combination of ARQ 197 with temsirolimus appears to be well tolerated with evidence of clinical activity. The MTD expansion and PK analysis are ongoing. Clinical trial information: NCT01625156.

2555 Poster Session (Board #271), Sat, 8:00 AM-11:30 AM

First-in-human phase I study of the DNA repair inhibitor DT01 in combination with radiotherapy in patients with in transit melanoma. *First Author: Christophe Le Tourneau, Institut Curie, Department of Medical Oncology, Paris, France*

Background: DT01 is a double stranded DNA oligonucleotide conjugated to cholesterol, which mimics "false" double strand breaks (DSB). DT01 triggers DNA repair proteins trapping, thereby inhibiting their repair activity. In non-clinical studies, DT01 showed antitumor activity as a single agent and in combination with radiotherapy (RT) in several tumor types including melanoma. No NOAEL could be defined. **Methods:** Subcutaneous peritumoral and intratumoral injections of DT01 were evaluated in combination with RT in a first-in-human phase I trial in patients (pts) with unresectable in-transit metastases of melanoma. Each pt received RT at a standard dose (3Gy/d 5 days/week for 2 weeks) on all selected tumor lesions, while only one or two tumor lesions were treated with DT01 3 times a week during both weeks of RT. A 3+3 dose escalation design was used. DT01 dose levels explored were 16, 32, 48, 64, and 96 mg. RT was given using a rectangular field by a linear accelerator. Tolerance was assessed using NCI CTCAE v4.3 and efficacy using modified RECIST criteria 1.1. **Results:** Seventeen pts (16 eligible) were included in the trial, of whom received RT alone in 31 and RT + DT01 in 31 tumor target lesions. As no dose-limiting toxicity was observed, the maximum tolerated dose was not reached. Most frequent adverse events were reversible grade 1 and 2 injection site reactions. PK analyses suggested a systemic passage of DT01 in a non-linear fashion. Overall response rates (ORR) were 68% and 48% in tumor lesions treated with RT + DT01 and RT alone, respectively. Notably, ORR correlated with blood AUC ($p = 0.01$), suggesting 1) an anti-tumor activity of DT01, and 2) a systemic effect of DT01. **Conclusions:** DT01 in combination with RT is safe in patients with metastatic in-transit melanoma, and provides antitumor activity in DT01-treated and non-treated lesions possibly explained by a systemic distribution of the drug. Clinical trial information: NCT01469455.

2556 Poster Session (Board #272), Sat, 8:00 AM-11:30 AM

Rationale for the combination of veliparib with platinum-based chemotherapy. *First Author: David Maag, AbbVie, North Chicago, IL*

Background: Owing to the role of PARPs in DNA damage repair, PARP inhibitors (PARPi) are under clinical investigation as anticancer therapies with a focus on tumors with impaired homologous recombination or regimens containing DNA damaging chemotherapies. Pre-clinical evidence indicates that PARPi potentiate the cytotoxicity of platinums. A recent Phase II study suggested evidence of a benefit in both progression and survival when veliparib was added to carboplatin and paclitaxel in the treatment of advanced NSCLC. **Methods:** *In vitro*efficacy was evaluated in GFP-overexpressing cell lines cultured as 3D spheroids. *In vivo* efficacy was determined in xenograft tumor-bearing SCID mice. PARP1 trapping was evaluated by cellular fractionation and immunoblotting. Bone marrow toxicity was determined with CFU assays. **Results:** We have developed a method to monitor the growth of 3D spheroids *in vitro* in real time. In this system, veliparib potentiated the activity of platinums in numerous models. Likewise, veliparib potentiated the activity of platinums in multiple xenograft models *in vivo*. PARP trapping was undetectable when PARPi were combined with cisplatin. PARPi differed in the extent to which catalytic inhibition and trapping could be resolved. PARPi with more potent trapping activity induced greater cytotoxicity in bone marrow CFU assays than equipotent inhibitors with weaker trapping activity. **Conclusions:** Veliparib potentiates the activity of platinum agents *in vitro* and *in vivo*; however the mechanisms underlying this activity remain unclear. PARP trapping is a recently characterized mechanism central to the synergistic cytotoxicity of PARPi and temozolomide. In contrast, our results suggest that PARP trapping is not required for the combination activity of PARPi and cisplatin. Our observation that potent trapping activity is associated with cytotoxicity towards myeloid and erythroid progenitors suggests that trapping may contribute to the anemia and myelosuppression observed in patients treated with PARPi. As such, PARPi capable of catalytic inhibition at concentrations where trapping is undetectable may be more suitable for combination regimens in which trapping is not required for activity.

2557 Poster Session (Board #273), Sat, 8:00 AM-11:30 AM

Genomic landscape of DNA repair genes in cancer: Mutation and copy number variation (CNV) frequencies. *First Author: Jonathan Anker, Northwestern University, Chicago, IL*

Background: DNA repair genes are frequently mutated in cancer, with different cancers linked to specific repair pathways. However, much remains unknown, including whether these mutations drive cancer or are a result of the disease. We have reviewed genome sequencing data of tumor samples to identify DNA repair genes that are frequently mutated or display high CNV. **Methods:** We created a comprehensive list of DNA repair genes and indirectly involved caretaker genes. The mutation and CNV frequencies of these genes were recorded from the COSMIC database (cancer.sanger.ac.uk). **Results:** Of the 193 genes analyzed, 24 had a mutation frequency of greater than 1.0% across all cancers. Table 1 lists the 10 genes most frequently mutated (overall and by common cancer types; n > 19,778 for each gene overall) or with CNVs (n > 4,118 for each gene). Colorectal, skin, lung, and breast cancer were most associated with DNA repair mutations. There was an inverse correlation as genes with a high CNV gain displayed a low CNV loss frequency, and vice versa ($p < 0.001$). **Conclusions:** Multiple DNA repair pathways were affected in each cancer type. Interestingly, genes with high frequency CNVs were either predominantly CNV gain or loss, but not both, providing evidence that these are functional alterations. This study provides comprehensive lists of candidate genes to be further studied as biomarkers for genomic instability or novel therapeutic targets. Table 1: Direct (bold) and indirect DNA repair genes most frequently mutated or with CNV gain or loss in cancer.

Overall	%	Lung	%	Breast	%	CRC	%	Skin	%	CNV gain	%	CNV loss	%
TP53	26.9	TP53	33.0	TP53	22.9	TP53	43.7	TP53	24.5	**RRM2B**	7.0	**NEIL2**	2.3
MLL3	4.3	MLL3	10.1	MLL3	6.8	**ATM**	22.5	MLL3	12.0	**RECQL4**	6.8	**WRN**	2.1
ATM	4.2	**ATM**	4.7	**ATM**	2.3	**MSH6**	12.0	**ATM**	7.0	**RAD54B**	6.0	**FANCB**	1.5
DNA-PKcs	2.1	POLQ	4.7	CENPE	1.9	**DNA-PKcs**	11.8	POLQ	6.6	**NBS1**	6.0	POLI	1.2
BRCA2	2.1	**DNA-PKcs**	3.9	**BRCA1**	1.9	MLL3	11.7	**BRCA2**	5.9	SPO11	5.0	**RPA4**	1.1
BAP1	2.0	**FANCM**	3.5	**BRCA2**	1.7	**BRCA2**	11.1	TP53BP1	5.7	**RFC4**	4.3	**TREX2**	1.0
POLQ	1.7	CENPE	3.1	TP53BP1	1.6	**MLH1**	10.1	**ATR**	5.6	**RAD1**	4.2	**CETN2**	0.9
ATR	1.6	**BRCA2**	3.0	**POLE**	1.5	**LIG1**	9.6	**DNA-PKcs**	5.3	**RNF168**	4.2	**UBE2A**	0.9
MSH6	1.6	SHPRH	2.8	**DNA-PKcs**	1.5	**ATR**	8.5	**FANCP**	5.2	**POLB**	4.1	**APEX2**	0.8
CHEK2	1.5	**MDC1**	2.7	**ATR**	1.5	**MSH2**	8.1	**POLE**	4.7	CDK12	4.0	**FAN1**	0.7

2558 Poster Session (Board #274), Sat, 8:00 AM-11:30 AM

Phase I clinical trial of temozolomide and methoxyamine (TRC-102) in patients with advanced solid tumors. *First Author: Jennifer Rachel Eads, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: Temozolomide (TMZ) is an alkylating agent that generates DNA adducts that are repaired by direct DNA and base excision repair mechanisms. Methoxyamine (MX, TRC-102) is a small molecule that potentiates TMZ by binding to apurinic and apyrimidinic sites after removal of N3-methyladenine and N7-methylguanine, inhibiting site recognition of apurinic/apyrimidinic (AP) endonuclease. We conducted a phase I trial to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of intravenous MX when given with oral TMZ. **Methods:** Patients (pts) with advanced solid tumors, progression on standard treatment, and no CNS involvement were enrolled. A standard 3+3 design was used to assess TMZ (150-200 mg/m^2 orally) and MX (15-150 mg/m^2 IV). Dose Levels (DL) 1-3: TMZ day 1, MX day 4 in first 14 day cycle (C), TMZ days 1-5, MX day 1 in subsequent 28 day C; DL 4-7: TMZ days 1-5, MX day 1 of 28 day C. DLT period was 42 days for DL 1-3 and 28 days for DL 4-7. Tumor response assessed per RECIST and AEs by CTCv4. Pharmacokinetics (PK) of 1-hour MX infusion and comet assays on peripheral blood mononuclear cells were performed. **Results:** 38 pts were enrolled: 45% male, 82% white, 16% African American, 2% Asian, median age 59.5 years (38-76), mean number of C 2.9 (1-13). No DLTs were observed. Grade 3 AEs: fatigue (n = 2), lymphopenia (n = 2), anemia (n = 1), INR (n = 1), leukopenia (n = 1), neutropenia (n = 1), allergic reaction (n = 1), constipation (n = 1), psychosis (n = 1) and paranoia (n = 1). Late grade 4 AEs: thrombocytopenia (n = 2) and confusion (n = 1). Partial response was seen in 1 pt with pancreatic adenocarcinoma (PAC) (8 mo); prolonged stable disease in 1 pt with PAC (4 mo), pancreatic neuroendocrine tumor (NET) (9 mo), small bowel NET (5.5 mo), ovarian cancer (12.5 mo) and non-small cell lung cancer (5.5 mo). MX PK was linear with dose and was not affected by concomitant TMZ. Geometric means (SD) were: t½ 45.6 (11.5) h, Cl 31.7 (15.6) L/h/m^2 (n = 31). **Conclusions:** TMZ 200 mg/m^2 may be safely administered with MX 150 mg/m^2 with minimal toxicity. Evidence of antitumor activity was observed, particularly in pancreatic adenocarcinoma and neuroendocrine tumors. Further studies assessing this drug combination are warranted. Clinical trial information: NCT00892385.

2559 Poster Session (Board #275), Sat, 8:00 AM-11:30 AM

Using gamma-H2AX and H2AX quantitative ELISA for monitoring DNA damage induced by chemotherapeutic agents and irradiation exposure. *First Author: Jiuping Jay Ji, National Clinical Target Validation Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD*

Background: Gamma-H2AX (γH2AX) is a biomarker for DNA double-strand breaks and programmed cell death, but variable relative amounts of H2AX in different samples causes ambiguity in the meaning of the γH2AX level unless it is related to total H2AX levels. We developed a 96-well plate-based ELISA for quantifying γH2AX and H2AX levels in crude extracts of tumor cells, CTCs and biopsy tissues and are validating it for applications in irradiation exposure monitoring and in pharmacodynamic evaluation of anti-cancer agents. **Methods:** The ELISA was used to analyze extracts of several NCI60 tumor cell lines that had been exposed to a variety of agents, including ionizing radiation, inhibitors of Top-1 (CPT, SN-38, Topotecan), PARP (ABT-888, AZD-2281, MK-4827) and ATR (VE-821, VE-822, AZD-6738, Compound 45, NU-6027), and their combinations. Combination regimens of CPT-11 with PARP inhibitors (ABT-888, AZD-2281, MK-4827) were further evaluated in vivo in the A375 xenograft mouse model. Patient samples obtained for research purposes were also examined by ELISA for feasibility and utility. **Results:** In vitro, dose-dependent increases in the ratio of γH2AX to H2AX were detected after escalating ionizing radiation exposure and concentration-dependent increases after Top-1 exposure. Treating with inhibitors of PARP or ATR alone did not significantly induce γH2AX. Combinations of Top-1 inhibitors with PARP or ATR inhibitors led to synergistic induction of DNA damage. Among five ATR inhibitors evaluated in combination with Top-1 inhibitors, VE-822 and AZD-6738 were observed to have the highest synergy for γH2AX induction, while NU-6027 showed none. Combinations of CPT-11 with ABT-888, AZD-2281 or MK-4827 showed synergistic induction of γH2AX in A375 xenografts in vivo. Additional testing of human specimens including PBMCs, bone marrow and tumor biopsies proved the assay's clinical suitability and potential advantages. **Conclusions:** A newly developed quantitative ELISA for measuring both γH2AX and H2AX is ready for clinical validation for monitoring DNA damage induced by chemotherapeutic agents or irradiation exposure. Funded by NCI Contract No. HHSN261200800001E.

2560 Poster Session (Board #276), Sat, 8:00 AM-11:30 AM

A phase I study of pazopanib (PAZ) in combination with abexinostat (ABX) in patients (pts) with metastatic solid tumors. *First Author: Rahul Raj Aggarwal, UC San Francisco, San Francisco, CA*

Background: PAZ is a tyrosine kinase inhibitor of VEGFR, PDGFR, and C-KIT approved for use in renal cell carcinoma (RCC) and soft tissue sarcoma (STS). ABX is a potent pan-HDAC inhibitor (HDACi). Pre-clinical models suggest that HDACi-mediated epigenetic modulation of VEGF expression potentiates PAZ's efficacy and may reverse therapeutic resistance. We therefore designed a Phase I clinical trial combining ABX with PAZ in pts with advanced solid tumors. **Methods:** The primary objective was to determine the maximal tolerated dose (MTD) of PAZ plus ABX. Secondary objectives included pharmacokinetics (PK) and efficacy. Altered histone acetylation post treatment denoted HDACi activity and served as a pharmacodynamic (PD) marker in peripheral blood mononuclear cells. PAZ was dosed days 1-28 and ABX days 1-5, 8-12, and 15-19 of 28-day cycle (schedule A) at a starting dose of 400 mg/day and 45 mg/m^{2}orally twice daily respectively. An alternate ABX dosing schedule of days 1-4, 8-11, and 15-18 was also investigated (schedule B). **Results:** 36 patients with advanced solid tumors were enrolled (N = 22 schedule A; N = 14 schedule B). There were six dose-limiting toxicities (DLTs) (5 on schedule A, 1 on schedule B), including fatigue (N = 2), thrombocytopenia (N = 2), and elevated AST/ALT (N = 2). The most common grade ≥ 3 related adverse events observed include thrombocytopenia (8%), fatigue (8%), and diarrhea (6%), the majority of which occurred with schedule A. The MTD was PAZ 800 mg/day + ABX 45 mg/m^2 BID on schedule B. 5 of 29 evaluable pts (17%) (including 2 RCC pts) experienced a partial tumor response (PR). All 6 pts with prior disease progression on PAZ monotherapy had reduction in tumor burden on study. 12 out of 29 evaluable pts (41%) experienced stable disease or better for ≥ 6 months, and two pts with PRs remain on study for > 2 years. PK and PD analyses are ongoing. **Conclusions:** In the first trial to explore the combination of ABX with PAZ in RCC and other solid tumor malignancies, the combination was well tolerated, particularly with schedule B ABX dosing. Preliminary evidence of anti-tumor activity was observed, notably in pts with progression on prior PAZ monotherapy. The promising efficacy in RCC is being further evaluated. Clinical trial information: NCT01543763.

2561 Poster Session (Board #277), Sat, 8:00 AM-11:30 AM

Pharmacokinetics/pharmacodynamics (PKPD) of blinatumomab in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). *First Author: Min Zhu, Amgen Inc., Thousand Oaks, CA*

Background: Blinatumomab is a CD19-directed bispecific T-cell engager antibody construct indicated for treatment of Ph-negative r/r ALL. We evaluated blinatumomab PK/PD and explored their associations with efficacy/safety in 189 r/r ALL patients in a phase 2 study (Topp et al. *Lancet Oncol* 2015;16:57). **Methods:** Blinatumomab was given by continuous IV infusion (4 wk on/2 wk off) for ≤ 5 cycles (Cycle 1: 9 μg/d days 1–7; then 28 μg/d; thereafter: 28 μg/d). Association between exposure and measures of efficacy (complete response [CR]/CR with partial hematologic recovery [CRh] within the first 2 cycles) and safety (cytokine release syndrome [CRS]; neurologic events [NE]) was evaluated by logistic regression. Impact of covariates on exposure-response was assessed in multivariate analyses. **Results:** Blinatumomab PK was linear; mean (SD) serum steady state concentration (C_{ss}) at 28 μg/d was 621 (502) pg/mL in Cycle 1. IL-6, IL-10 and IFNγ were transiently elevated in > 50% of pts on days 1–2 of Cycle 1, much less in later cycles; interpatient variability was high. In Cycle 1, mean peripheral B cells fell from 4660 to ≤ 10 cells/μL. Responders had lower percentages of $CD19^+$ B cells and bone marrow (BM) blasts and higher percentages of $CD3^+$ T cells and granulocytes at screening than nonresponders ($P < .001$); absolute counts were not associated with response. In multivariate analyses, higher C_{ss} (OR, 1.90 [95% CI, 1.12–3.21]; $P = .017$), higher peak IL-10 levels (1.59 [1.13–2.22]; $P = .007$) and lower percentage of BM blasts at screening (0.78 [0.69–0.89]; $P < .001$) were associated with CR/CRh. No association between C_{ss} and time to CR/CRh was found after adjusting for percentage of blasts and B/T cell ratio. Higher platelet counts (0.996 [95% CI, 0.992–1.0]; $P = .03$), $CD19^+$ B cell counts at screening (0.90 [0.84–0.97]; $P = .004$) and C_{ss} (1.40 [1.01–1.94]; $P = .046$) were associated with time to NE. Cytokine peaks were not associated with NE or CRS. C_{ss} was not associated with CRS. **Conclusions:** We found empirical associations of blinatumomab PK, PD and disease-related prognostic factors with CR/CRh and NE. Confounding factors and confirmation of the associations deserve further evaluation. Clinical trial information: NCT01466179.

2562 Poster Session (Board #278), Sat, 8:00 AM-11:30 AM

Pharmacogenetic variants associated with differential sirolimus clearance in pediatric patients. *First Author: Jordan Wright, Cincinnati Childrens Hosp Med Ctr, Cincinnati, OH*

Background: Sirolimus inhibits the mammalian Target of Rapamycin pathway and is widely used in organ transplantation and treatment of malignancy. CYP3A5*3 polymorphisms have been shown to influence sirolimus clearance in solid organ transplant patients, but effects of other drug metabolism enzyme and transporter (DMET) gene polymorphisms have not been investigated thoroughly. We hypothesized that additional variants, alone or in combination, would better predict sirolimus clearance in pediatric and young adult patients with neurofibromatosis type 1 (NF1) associated plexiform neurofibromas and complex vascular malformations (CVM). **Methods:** Patients treated with single agent sirolimus (N = 74) had pharmacokinetic parameters including clearance measured in two studies of NF1 and CVM. Patients were genotyped for 1,931 known polymorphisms using the DMET Microarray (Affymetrix). Initial statistical analysis included univariate linear regression on SNPs with a minor allele frequency of > 0.05 for each of the clinical trials. Subsequently, the datasets were combined and a univariate regression analysis was obtained on the combined data. SNPs for which the association was strengthened in the combined dataset were then placed in a final multivariate regression model. **Results:** The final multiple regression analysis included five SNPs that were significant at $p < 0.05$: rs776746 (CYP3A5*3 6986 A > G), rs909530 (FMO3 855 C > T), rs1339067 (SLC15A1 1347 T > C), rs2276299 (SLC22A8 723 T > A), and rs6774801 (CYP8B1 6468 A > C). The model had an overall F-value of 7.83, p-value < 0.0001, and R-square of 0.38. **Conclusions:** Our analysis identified a multivariate model with five SNPs, of which four are novel and not previously described in the literature. The CYP3A5*3 allele, which has been identified in other studies, was significant in our analysis, offering additional support for the role of this SNP in sirolimus metabolism. Future studies in larger populations are needed to confirm this model, and will lead to potential pharmacogenetically-guided dosing for the safe and effective use of sirolimus.

2563 Poster Session (Board #279), Sat, 8:00 AM-11:30 AM

Mass balance study of TAS-102 using ^{14}C labeling analyzed by accelerator mass spectrometry. *First Author: James J. Lee, University of Pittsburgh, Pittsburgh, PA*

Background: TAS-102 is composed of trifluridine (FTD) and tipiracil hydrochloride (TPI) in a 2:1 ratio. FTD is a thymidine analog, and is degraded to inactive trifluoromethyluracil (FTY) by thymidine phosphorylase (TPase). TPI inhibits degradation of FTD by TPase, increasing systemic exposure to FTD. TAS-102 demonstrated improvement in overall survival in patients with metastatic colorectal cancer refractory to standard therapies. Although the metabolism of FTD has been reported, the metabolic fate and excretion of TAS-102 is unknown. **Methods:** Patients with advanced solid tumors (6 M/2 F; median age 58 years; PS 0-1) enrolled. Group A (N = 4) received 60 mg TAS-102 with 200 nCi [^{14}C]-FTD, and group B (N = 4) received 60 mg TAS-102 with 1000 nCi [^{14}C]-TPI orally. Plasma, blood, urine, feces, and expired air (group A only) were collected up to 168 h, and were analyzed for ^{14}C by accelerator mass spectrometry and for components of TAS-102 by LC-MS/MS. **Results:** FTD: Approximately 10% of plasma ^{14}C AUC is accounted for by FTD (7%) and FTY (3.5%). The long half-life of ^{14}C in plasma (>300 h) is in line with the moderate recovery of FTD-related ^{14}C in the excreta over the 168 h collection period. ^{14}C was mostly excreted in urine, and only very little was in feces and expired air, suggesting good absorption and limited metabolism of the pyrimidine ring. TPI: Approximately 36% of plasma ^{14}C AUC is accounted for by TPI. ^{14}C was mostly excreted in feces likely due to poor absorption of TPI. The majority of absorbed ^{14}C was excreted into urine. **Conclusions:** The mass balance of FTD and TPI as part of TAS-102 was successful. The majority of the ^{14}C-TPI dose was recovered in feces. Approximately 60% of the ^{14}C-FTD dose was recovered, largely in urine. The current data with the ongoing hepatic and renal dysfunction studies will provide a better understanding of the TAS-102 dispositional profile. Clinical trial information: NCT02031055.

	Plasma AUC (h*ng/mL)			^{14}C recovery (%)			
FTD	**^{14}C**	**FTD**	**FTY**	**Urine**	**Feces**	**Expired CO_2**	**Overall**
#1	63000	4640	2870	57.3	3.01	1.75	62.0
#2	64900	4020	2370	54.1	2.65	2.57	58.8
#3	92700	6200	1830	54.3	2.12	2.27	58.5
#4	127000	11600	4930	53.4	2.82	4.34	59.9
TPI	^{14}C	TPI	-	Urine	Feces	Expired CO_2	Overall
#5	901	216		24.5	62.4	-	86.8
#6	437	171		18.8	17.5	-	36.3
#7	509	268		27.0	58.3	-	85.3
#8	965	269		37.9	60.8	-	98.7

2564 Poster Session (Board #280), Sat, 8:00 AM-11:30 AM

First-in-human phase I trial of the PI3Kb-selective inhibitor SAR260301 in patients with advanced solid tumors (NCT01673737). *First Author: Philippe L. Bedard, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: SAR260301 (SAR) is a potent (IC_{50} 52 nM) PI3Kb inhibitor selectively inhibiting the PI3K pathway in PTEN-null models. This phase I Sanofi sponsored study was initiated to evaluate SAR maximum tolerated dose (MTD), overall safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary antitumor activity in patients with advanced solid tumors. **Methods:** Patients (pts) with locally advanced/metastatic solid tumors, ECOG PS ≤ 1, and adequate organ function were eligible. PTEN was evaluated in archival tissue by IHC. SAR was orally administered fasted in 28-day cycles. Dose escalation used an overdose control Bayesian strategy. Serial PK sampling was performed on Days 1 and 28 of Cycle (C) 1, and at C2 for food effect evaluation (n = 6). Platelet phospho-AKT (pAKT) was assessed at pre- and post-SAR for PD by MesoScale Discovery. Physiologically based PK modelling (PBPK) was used for exposure predictions. **Results:** 21 pts were treated at 6 dose levels from 100 mg QD to 800 mg BID. The MTD was not reached. Two DLTs were observed: Gr 3 pneumonitis (400 mg BID) and Gr 3 increase in GGT (600 mg BID). No other Gr ≥ 3 related AE was reported. The most frequent related AEs (≥ 3 pts): nausea (3), vomiting (3), and diarrhea (3). SAR absorption was rapid (t_{max} 0.5-1.5h) and showed a biphasic elimination profile with a rapid decrease in concentration after C_{max}. No significant accumulation or deviation from dose proportionality was observed. C_{max} and AUC_{tau} decreased respectively by 56% and 22% with food. Maximal inhibition of pAKT/tAKT in platelets correlated with exposure at steady state; C_{max} thresholds for 60% & 80% inhibition were respectively ~ 7 & ~11 μM. Concentrations > 7 μM were reached in 3 pts but for no longer than 2h out of 24h. The PBPK model predicted that doses > 1.2g BID would be needed to reach concentrations sufficient to maintain PD effect between doses. No objective response were documented in this study (3 of 21 pts had PTEN-null disease). **Conclusions:** SAR has an acceptable safety profile at pharmacologically active doses. However, the rapid clearance of SAR does not allow for sustained pathway inhibition that is required for anti-tumor activity in preclinical models. Clinical trial information: NCT01673737.

2565 Poster Session (Board #281), Sat, 8:00 AM-11:30 AM

Effect of itraconazole and rifampin on the pharmacokinetics of olaparib tablet formulation in patients with advanced solid tumours: Phase I open-label studies. *First Author: Elizabeth R. Plummer, Northern Centre for Cancer Care, Newcastle-upon-Tyne, United Kingdom*

Background: The metabolism of olaparib (Lynparza) is mediated predominantly by CYP3A4/5 enzymes. Two Phase I studies are reported here investigating pharmacokinetic interactions between olaparib (tablet formulation) and itraconazole, a potent CYP3A4 inhibitor (Study 1, NCT01900028), and rifampin, a potent CYP3A4 inducer (Study 2, NCT01929603). **Methods:** In Study 1, 59 eligible patients (pts) received a single oral dose of olaparib 100 mg on Day 1 and olaparib 100 mg plus itraconazole 200 mg on Day 9; itraconazole 200 mg was administered once daily (qd) on Days 5–11. In Study 2, 22 pts received a single oral dose of olaparib 300 mg on Day 1 and single oral dose olaparib 300 mg plus rifampin 600 mg on Day 14; rifampin 600 mg qd was administered on Days 5–17. **Results:** Co-administration with itraconazole in Study 1 resulted in a significant increase in mean C_{max} (treatment ratio 1.42; 90% CI: 1.33, 1.52) and mean AUC (treatment ratio 2.70; CI: 2.44, 2.97) compared with olaparib alone. Olaparib absorption was slightly slower in the presence of itraconazole (median [range] t_{max}, 1.50 [0.5–12] hours) vs olaparib alone (1.03 [0.5–8.25] hours). In Study 2, a significant decrease in olaparib bioavailability was observed when co-administered with rifampin (decrease of 71% in C_{max} [treatment ratio: 0.29; 90% CI: 0.24, 0.33] and 87% in AUC [0.13; 90% CI: 0.11, 0.16]) vs olaparib alone. Median t_{max}, was reduced in the presence of rifampin (0.78 [0.27–5.95] hours compared with 1.49 [0.57–3.05] hours for olaparib alone). In both studies, the majority of adverse events were of mild or moderate severity; safety data were consistent with the known safety profile of olaparib. **Conclusions:** It is recommended that potent CYP3A enzyme inhibitors (eg. itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritinovir, lopinavir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or inducers (eg. phenytoin, rifampin, carbamazepine, St John's Wort) be avoided during olaparib treatment. Clinical trial information: NCT01900028/NCT01929603.

2566 Poster Session (Board #282), Sat, 8:00 AM-11:30 AM

A first-in-human study of the dual ROCK I/II inhibitor, AT13148, in patients with advanced cancers. *First Author: Dionysios Papadatos-Pastos, The Institute of Cancer Research and The Royal Marsden, London, United Kingdom*

Background: AT13148 is a first-in-class, orally bioavailable, dual ROCK I/II inhibitor, which potently inhibits ROCK I/II (6, 4 nM), PKA (3 nM), AKT (38 nM) and p70S6K (8 nM). Broad anti-cancer activity has been demonstrated in a number of pre-clinical models. **Methods:** Patients (pts) with advanced solid tumors were enrolled into successive dose escalation cohorts of a minimum of three and maximum of six patients. AT13148 was dosed orally on days (D) 1, 3 and 5 of every week. Pharmacokinetic (PK) parameters were assessed and pre- and post-tumor biopsies, platelet-rich plasma (PRP) and hair follicles were analysed to evaluate target inhibition of AKT (p-AKT, p-S6K and p-GSK3B) and PKA (p-VASP). **Results:** 30 pts (16 male, 14 female) were treated with AT13148. Dose escalation started at 5 mg with doubling through 6 cohorts (10, 20, 40, 80 and 160 mg). Following the appearance of grade 2/3 toxicities in pts dosed at 160 mg (hypotension, headache and diarrhea), further dose doubling was not considered and the dose was increased by 50% to 240 mg. Thus far, at this dose there was one DLT of elevated liver enzymes which was reversible on treatment withdrawal. The cohort is currently being expanded to 6 pts. The most common drug-related toxicities in the study so far have been nausea, anorexia, headache and hypotension. PK analysis showed a dose proportional increase in AUC (382-13382 nM.h) and Cmax (21-450 nM) up to 160 mg ($r2 = 0.98$) on the first dose. Preliminary PD analyses in PRP have shown a $\geq$ 88% increase in p-AKT from baseline at cycle 1 D 15-22 ($p \leq 0.01$) in the 160 mg cohort, a 17-21% decrease in pGSK3B from baseline at 6 h and 48 h post-dose ($p \leq 0.03$) in the 160 mg cohort, and a 45% decrease in p-VASP from baseline at 48 h post-dose ($p = 0.004$) in the 80 mg cohort. **Conclusions:** AT13148 was administered orally on D 1, 3 and 5/week in an intermittent schedule and has currently reached a dose of 240 mg. At this dose there have been predictable tolerable 'on target' toxicities and dose escalation is ongoing. **Clinical trial information:** NCT01585701. Clinical trial information: NCT01585701.

2567 Poster Session (Board #283), Sat, 8:00 AM-11:30 AM

Patterns of hepatic impairment in phase I clinical trials. *First Author: Aaron Scott Mansfield, Mayo Clinc, Rochester, MN*

Background: Liver impairment confounds dosing of anti-neoplastic agents. The Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) sponsors standard phase I clinical trials (P1CT) to determine the safety of novel agents and combinations, and hepatic dysfunction phase I clinical trials (HDCT) to determine safe doses for patients with varying degrees of liver dysfunction. We sought to compare patterns of liver injury, number of cycles administered, and reasons for discontinuation between HDCTs and P1CTs in a meta-analysis. **Methods:** The records of participants of 51 NCI-sponsored phase I clinical trials conducted between 1994 and 2014 were reviewed. The NCI's Organ Dysfunction Working Group's definitions of liver impairment were used to classify subjects. Peak liver test results were used to classify patterns of liver impairment using the US Food and Drug Administration's (FDA) R ratio and modified Hy's law (aminotransferase $\geq$ 3xULN, total bilirubin $>$ 2xULN without elevated serum alkaline phosphatase & no other explanation for abnormalities). The Kruskal-Wallis one way analysis of variance was used to compare groups and the Pearson test was used for contingency analyses. **Results:** There were 513 subjects treated on HDCTs and 1328 subjects treated on P1CTs with a median age of 58.6 years [51-66 interquartile range (IQR)] and 59 years (49-67 IQR) respectively. 55.6% and 49.9% were male, on P1CTs and HDCTs respectively. Subjects received a median of 2 cycles of treatment on HDCTs and P1CTs. Cholestatic peak patterns of liver impairment by the FDA R ratio were more frequent in HDCTs than P1CTs ($p < 0.0001$). Criteria for Hy's Law were met in eleven patients on P1CTs. Disease progression was the most common reason for treatment discontinuation, followed by adverse events in HDCTs and P1CTs. Subjects with severe liver function abnormalities on HDCTs typically received one cycle of treatment, and 9.9% died on study compared to those with less severe hepatic dysfunction (range of 3.0-3.7% $p < 0.0001$). **Conclusions:** Subjects on HDCTs are more likely to experience cholestatic peak patterns of liver function abnormalities, but receive a similar number of cycles of therapy, and discontinue from trial participation for similar reasons as those on P1CTs.

2568 Poster Session (Board #284), Sat, 8:00 AM-11:30 AM

Predictive PK/PD models for hematological toxicities to inform MTD determination and regimen selection for ADCs. *First Author: Santhosh Palani, Clinical Pharmacology, Biotechnology Clinical Development, Pfizer Inc., La Jolla, CA*

Background: Off-target hematological toxicities have primarily been dose-limiting for ADCs. Here, we present a PK/PD model framework where the incidences of hematological toxicities can be predicted across ADCs if they share the same linker/payload (LP), and can be predicted across regimens within an ADC. Having prior knowledge of the MTD can provide a safe and efficient dose-escalation design, reduce the number of patients receiving sub-efficacious doses and aid in regimen selection. **Methods:** A semi-mechanistic PK/PD model of neutropenia (NP) for SGN-35 was constructed using a previously established structural model. Published ADC thrombocytopenia (TCP) PK/PD models were also utilized. **Results:** *Predicting across regimens*:Due to the availability of the clinical data in multiple regimens for T-DM1 and SGN-35, models developed using data from Q3W regimen were utilized to predict the toxicity incidences of QW regimen. T-DM1 Q3W model predicted 10% grade 3+4 TCP in patients at QW MTD, matching with the clinically observed incidence of 11%. SGN-35 Q3W model predicted 19% grade 3+4 NP at QW MTD, which is consistent with the clinically observed incidence of 10%. *Predicting across ADCs*: Since SGN-35, CDX-011 and PSMA-ADCs share the same LP (vcMMAE), we utilized the SGN-35 model to predict incidences for CDX-011 and PSMA-ADC. SGN-35 Q3W model predicted 18% and 50% grade 3+4 NP incidences for the 1.9 mg/kg CDX-011 and 2.8 mg/kg PSMA-ADC, respectively, again in concordance with the observed incidences of 26% and 55%. *Predicting across ADCs, regimens and populations*: As CMC-544 and GO share the same LP (abCali), we predicted TCP incidences for GO in AML patients from the Q4W CMC-544 model developed with data from NHL patients. The model predicted grade 3+4 TCP incidence of 98% for GO regimen of 9 mg/m^2 (2 doses, 14-days apart), which agrees with the observed incidence of 99%. **Conclusions:** Robust predictability of hematological toxicity is demonstrated across 5 ADC, 2 toxicities and 3 regimens. With prospective validation, the approach presented here can help construct a safe and efficient dose-escalation scheme, provide a projected MTD, and assist in optimal regimen selection for ADCs entering clinical development.

2569 Poster Session (Board #285), Sat, 8:00 AM-11:30 AM

Regulatory considerations for clinical pharmacology during development of antibody-drug conjugates. *First Author: Stacy Shifflett Shord, US Food and Drug Administration, Silver Spring, MD*

Background: Antibody-drug conjugates (ADCs) provide unique challenges during clinical development, as these products are a heterogeneous mixture of a monoclonal antibody and a small molecule payload. As such, the current paradigm has been to conduct studies that characterize the clinical pharmacology of both the antibody and small molecule components of the ADC. We have compiled a database of ADCs approved and under development to assess the study designs and outcomes to guide future FDA regulatory recommendations on evaluation of the clinical pharmacology for ADCs. **Methods:** Investigational New Drug (IND) applications, Biologics License Applications (BLA), product labeling and published literature were reviewed to develop the database. A description of the indication, antibody target, payload, linker, clinical pharmacology studies and available study results were compiled and analyzed. **Results:** Approximately 50 ADCs are currently under development and two ADCs are approved (Adcetris, Kadcyla). The most common payloads are auristatins (~60%) and maytansinoids (~20%), and the most common linkers are cleavable (~90%). Three components (i.e., conjugate, total antibody, and payload) were characterized to describe the pharmacokinetics of Adcetris and Kadcyla. While both the Adcetris and Kadcyla labeling describes the potential for drug interactions, dedicated drug interaction studies were only conducted for Adcetris. Organ impairment studies for both Adcetris and Kadcyla suggest decreased tolerability in patients with varying degrees of hepatic or renal impairment. **Conclusions:** As most ADCs are in early clinical development, FDA recommendations for clinical pharmacology studies are still evolving. Currently available data suggest that the pharmacokinetics of at least two components (e.g., conjugate and payload) should be described and incorporated into population and exposure-response analyses. The potential for drug interactions should be addressed. Organ impairment studies should be conducted with a specific focus on the assessment of safety, as well as on pharmacokinetics.

2570 Poster Session (Board #286), Sat, 8:00 AM-11:30 AM

A phase I, first-in-human study to evaluate the tolerability, pharmacokinetics and preliminary efficacy of HuMax-tissue factor-ADC (TF-ADC) in patients with solid tumors. *First Author: Ulrik Niels Lassen, Rigshospitalet, Copenhagen, Denmark*

Background: TF-ADC is an antibody drug conjugate composed of a TF-specific human IgG1 monoclonal antibody conjugated to a microtubule disrupting agent Monomethyl Auristatin E (MMAE). TF-ADC is presently being tested in an ongoing Phase I dose-escalation study (NCT02001623) in patients (pts) with locally advanced and/or metastatic solid tumors known to express TF. **Methods:** The primary study objective is to assess the tolerability of TF-ADC. In addition, maximum tolerated dose (MTD), pharmacokinetics and preliminary efficacy will be evaluated. Pts with cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophageal, SCCHN and lung (NSCLC) will be included. This is a classical 3+3 dose escalation study followed by cohort expansion. Responses are evaluated according to RECIST 1.1. **Results:** Eighteen pts have been enrolled across the first 6 dose cohorts (0.3-1.8 mg/kg). Mean number of prior lines of therapy is 3.7 (range 1-14). The most common AEs seen in $\geq$ 4 pts are fatigue, anemia, epistaxis, nasal congestion, pyrexia, and diarrhea. Elevation in liver enzymes was seen in 9 pts mainly grade (Gr) 1 including 2 pts with Gr 3 single events. One event of fatal pharyngeal hemorrhage in the 0.6 mg/kg cohort has been reported in a SCCHN pt with normal coagulation values previously treated with 3 lines of therapy including radical radiotherapy. Relationship with trial drug could not be excluded. Five pts experienced related AEs Gr $\geq$ 3. Seven SAEs were observed in 5 pts (transaminitis Gr 3, pharyngeal hemorrhage Gr 5, fever Gr 1, myalgia pain Gr 2, dyspnea Gr 2, hyponatremia Gr 3, gastritis Gr 3). No significant changes in coagulation parameters and no DLTs have been observed. Preliminary evidence of activity includes prolonged disease stabilization in 1 ovarian cancer pt (23 weeks), 2 CRPC pts (18 and 36 weeks) and a confirmed PR in an ongoing pt with cervical cancer. **Conclusions:** Preliminary data demonstrated manageable toxicity, with no DLTs observed and no changes in coagulation values up to 1.8 mg/kg. Preliminary evidence of anti-tumor efficacy is encouraging and study design allows for increased exposure to establish therapeutic window. Clinical trial information: NCT02001623.

2571 Poster Session (Board #287), Sat, 8:00 AM-11:30 AM

Exhaustive single nucleotide polymorphism (SNP) analysis of *DPYD* exome in breast cancer patients (pts) receiving capecitabine. *First Author: Marie-Christine Etienne-Grimaldi, Centre Antoine Lacassagne, Nice, France*

Background: Consensual *DPYD* variants *2A, D949V and I560S are associated with fluoropyrimidine toxicity (*Caudle, CPT 2013*). Full sequencing of *DPYD* exome was conducted in a prospective cohort of advanced breast cancer pts receiving capecitabine (88.5% monotherapy) to examine relationships between *DPYD*SNPs and toxicity. **Methods:** 243 over 303 pts included in 12 French institutions were analyzed. Digestive, neurologic and hematotoxicity over cycles 1-2 showed 10.3% G3 (25 pts) and 2.1% G4 (5 pts), including one toxic death. *DPYD* exome along with flanking intronic regions (20 bp), 3'UTR and part of 5'UTR (500 bp upstream transcription initiation) were sequenced on MiSeq Illumina (Integragen, PCR multiplex, 97% coverage on average, HWE checked). **Results:** In addition to consensual variants *2A, D949V and I560S carried by 7 pts (all heterozygous), 45 SNPs were identified: 7 in 3'UTR, 17 in coding regions (4 synonymous including E412E; 13 missenses including V732I, R592W, I543V, S534N, S492L, M406I, D342G, M166V, T65M, C29R), 18 in flanking intronic regions, 3 in 5'UTR. The number of variant alleles per pt varied from 0 (8 pts) to 16. In total, 11 SNPs have not been previously described (dbsnp 141 database), including 3 missense variations each heterozygous in 3 separate pts: R696H (exon 17), F100L (exon 4) and A26T (exon 2). The patient with toxic death carried one D949V allele and 3 variant alleles in 3'UTR (rs291592, rs291593). First analysis of consensual variants showed that they were associated with G3-4 toxicity (RR = 6.69, $p < 0.001$, sensitivity 16.7%) but not with G4 toxicity. Adding the variants previously shown to possibly decrease DPD activity (*Offer, Cancer Res 2014*), i.e. R592W, S492L and D342N/G, increased sensitivity on G3-4 (23.3%, RR = 7.03, $p < 0.001$) and was predictive of G4 toxicity (sensitivity 40%, RR = 15.4, $p = 0.015$). Of note, adding the new F100L variant further improved predictivity of genotyping on both G3-4 (sensitivity 26.7%, RR = 7.60, $p < 0.001$) and G4 toxicity (sensitivity 60%, RR = 31.36, $p = 0.001$). **Conclusions**: Present data confirm the impact of consensual variants on capecitabine toxicity and reveal the existence of a novel *DPYD* variant, F100L, associated with G4 toxicity. Clinical trial information: 2008-004136-20.

2572 Poster Session (Board #288), Sat, 8:00 AM-11:30 AM

Identification of candidates for sorafenib dose-escalation using sorafenib plasmatic concentration monitoring: Proof of concept. *First Author: Jennifer Arrondeau, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France*

Background: Sorafenib is approved in various advanced cancers, including hepatocellular carcinoma (HCC), differentiated iodo-resistant thyroid cancer (DTC), and renal cell carcinoma (RCC). We previously described that sorafenib plasmatic concentrations may decrease over months. We examined the inter-individual variability of sorafenib exposure at the time of disease progression to identify a subset of patients likely to benefit from dose increase. **Methods:** Patients treated with sorafenib from October 2008 to December 2014 were included in the analysis. Adverse events were prospectively collected and graded using the National Cancer Institute Common Terminology Criteria. The sorafenib plasma concentrations were prospectively determined by liquid chromatography, 30 days after treatment initiation (Cm1) and at disease progression (Cp). Variations of sorafenib concentrations were analyzed using the Wilcoxon test. **Results:** A total of 124 patients (85 males and 39 females) were studied, 68 having a sorafenib concentration measurement at the time of disease progression. The primary tumor was HCC (n = 46), melanoma (n = 32), DTC (n = 20), RCC (n = 16) or others (n = 9). In the 37 patients without change in dose between treatment initiation and disease progression, the sorafenib dose-normalized concentration decreased significantly over time : median sorafenib Cm1 was 5.54 mg/L while the median sorafenib Cp was 5 mg/L ($p = 0.018$). When considering all patients at disease progression, 53 patients (43%) had no limiting toxicity, and the inter-individual variation in sorafenib Cp was very large: median Cp 3.82 mg/L; range 2.08-132.9 mg/L. Among the 34 patients with sorafenib Cp $<$ 3.82 mg/L, 22 (65%) had no limiting toxicity, allowing to increase sorafenib dose for treatment optimization, which resulted in clinical benefit in 45% of patients, the more dramatic being 1 complete response in a choroidal melanoma patient, and a 36.9 months disease control in a DTC patient. **Conclusions:** A subset of patients with disease progression due to sorafenib underexposure and who may respond after dose increase can be identified using sorafenib plasmatic concentration monitoring.

2573 Poster Session (Board #289), Sat, 8:00 AM-11:30 AM

Population pharmacokinetics and dosing implications for cobimetinib in patients with solid tumors. *First Author: Kelong Han, Genentech, Inc., South San Francisco, CA*

Background: Cobimetinib (COBI), an inhibitor of mitogen-activated protein kinases, when combined with vemurafenib (VEM) has been shown to significantly improve PFS ($p < 0.001$) over VEM alone in patients with BRAF V600 mutated melanoma in the Phase 3 study, coBRIM. This analysis aimed to characterize COBI PK and evaluate impact of clinically relevant covariates on COBI PK and exposure to inform dosing. **Methods:** Plasma samples (n = 4886) were collected from 487 patients with various solid tumors (mainly melanoma) in 3 clinical studies (MEK4592g, NO25395, GO28141). COBI was administered orally, once daily on a 21-day-on/7-day-off, 14-day-on/14-day-off or 28-day-on schedule in a 28-day dosing cycle as a single agent or in combination with VEM. COBI doses ranged from 2.1 to 125 mg. Nonlinear mixed effect modeling was used for PK analysis. **Results:** A linear two-compartment model with first-order absorption, lag time and first-order elimination described COBI PK. The typical estimates (inter-individual variability) of apparent clearance (CL/F), central volume of distribution (V/F) and terminal half-life were 322 L/day (58%), 511 L (49%) and 2.2 days, respectively. Inter-occasion variability on relative bioavailability (F) significantly improved the fitting and was estimated at 46%. CL/F decreased with age. V/F increased with body weight (BWT). However, the impact of age and BWT on COBI steady-state exposure (peak and trough concentrations and AUC following 60 mg 21-day-on/7-day-off) was limited (< 25% changes across the distribution of age and BWT in the population studied). No significant difference in COBI PK parameters or steady-state exposure was observed between patient subgroups by gender, renal function, ECOG score, hepatic function tests, race, region, cancer types, V600 mutation subtype and co-administration of moderate and weak CYP3A inducers or inhibitors and VEM. **Conclusions:** A population PK model was developed for COBI in cancer patients. Age and BWT were the only statistically significant variables influencing COBI PK, but showed minimal impact on steady-state exposure, suggesting no need for dose adjustment and supporting the recommended daily dose of 60 mg 21-day-on/7-day-off for all patients.

2574 Poster Session (Board #290), Sat, 8:00 AM-11:30 AM

Recommendations in a new drug application review for dose optimization to potentially improve gastrointestinal tolerability of a tyrosine kinase inhibitor. *First Author: Ruby Leong, US Food and Drug Administration, Silver Spring, MD*

Background: On April 29 2014, the U.S. FDA approved ceritinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. At the approved dosing regimen of ceritinib 750 mg once daily taken on an empty stomach, diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients with dose modification in 38% of patients. Anecdotal reports from patients and investigators suggest that gastrointestinal (GI) tolerability may improve when ceritinib is taken with food; however, administration of ceritinib with food increases exposure and may also increase the occurrence of non-GI related toxicities. **Methods:** Data were obtained from the multicenter, single-arm registration trial in 255 patients with ALK-positive tumors who received ceritinib 750 mg daily under fasted conditions and from a food effect study in healthy subjects. Exposure-response relationships for safety endpoints were evaluated by logistic regression analyses and Kaplan-Meier analyses using average exposure quartiles. **Results:** Compared to fasting conditions, a high-fat meal and a low fat meal increased ceritinib AUC_{inf} by more than 50%. Higher systemic exposure appeared to be associated with more frequent and earlier safety events including overall Grade 3-4 adverse reactions (ARs), and individual ARs such as ≥ Grade 3 AST/ALT elevation and ≥ Grade 2 hyperglycemia. Higher systemic exposure also appeared to be associated with earlier and more frequent dose reductions or interruptions. A pharmacokinetic / pharmacodynamic analysis showed concentration-dependent QTc interval prolongation. **Conclusions:** The analyses along with the observed safety data led to an FDA requirement to conduct a postmarketing clinical trial to evaluate a lower dose of ceritinib taken with a meal (providing similar systemic exposure to that of the 750 mg dose taken under a fasted state) that potentially improves GI tolerability.

2575 Poster Session (Board #291), Sat, 8:00 AM-11:30 AM

When investigating predictive biomarkers, beware of the qualitative interaction. *First Author: Howard M Mackey, Genentech, Inc., South San Francisco, CA*

Background: The investigation of predictive biomarkers in clinical trials often involves estimation of the biomarker by treatment interaction effect (Royston and Sauerbrei, *Journal of Clinical Oncology* 2008). A so-called *qualitative interaction* (Gail and Simon, *Biometrics* 1985) occurs when a subgroup of patients appear to benefit from treatment while another subgroup is harmed. Spurious, statistically significant interactions are more likely to be observed as *qualitative interactions* than so called *quantitative interactions, i.e.* interactions where no subgroup is harmed. Thisissueisexemplifiedbyrecentstudyresults(*e.g.*,http://www.cancernetwork.com/gastrointestinal-cancer/amgen-halts-rilotumumab-development-due-increased-death-signal), highlighting the challenges to developing personalized therapies. **Methods:** We graphically and statistically illustrate how, under the null hypothesis of no treatment or biomarker effects, spurious qualitative interactions occur much more frequently than quantitative interactions, potentially leading to erroneous conclusions regarding a biomarker's clinical utility. Following the approach of Mackey and Bengtsson (*Contemporary Clinical Trials* 2013), we propose a strategy for investigating potential predictive biomarkers that focuses on detecting clinically meaningful treatment effects, as opposed to focusing on interactions which have greater variability. We provide sample size formulae and an inference approach for use in proof-of-concept oncology clinical trials with time-to-event data. **Results:** By targeting inference on the *maximal* and *minimal* biomarker effects (*i.e.* the largest- and smallest levels of clinical benefit), the proposed method yields lower false positive rates and higher power for detecting the presence of biomarker subgroups than standard approaches. For fixed false positive rates and power, sample size savings were found to be as large as 40%. **Conclusions:** This new inferential method improves on existing approaches of identifying predictive biomarkers by minimizing false positive risks associated with qualitative, biomarker by treatment interactions.

2576 Poster Session (Board #292), Sat, 8:00 AM-11:30 AM

Carboplatin dosing based on estimated Glomerular Filtration Rate (GFR) using IDMS creatinine: A comparison of estimated GFR based on IDMS creatinine in the Cockroft-Gault (CG) formula (IDMS-GFR), with measured GFR using ^{51}Cr-EDTA (^{51}Cr-GFR). *First Author: James R. Whittle, Royal Melbourne Hospital, Melbourne, Australia*

Background: ^{51}Cr-GFR is considered a gold standard of GFR assessment, but the CG formula is routinely used to estimate GFR for dosing of Carboplatin. Gynaecological cancer trials adopted the convention that Carboplatin be dosed at AUC5 in patients using ^{51}Cr-GFR, and AUC6 in patients using IDMS-GFR. IDMS-GFR is routinely capped at 125ml/min for Carboplatin dosing, as low IDMS levels in patients with normal renal function can generate spuriously high GFR estimates. **Methods:** We performed a multicenter retrospective study of patients who had a ^{51}Cr-GFR assessment, with a matched serum IDMS creatinine. IDMS-GFR and ^{51}Cr-GFR were compared in each patient. Carboplatin dose based on ^{51}Cr-GFR in the Calvert formula at AUC 5 was used as the reference. **Results:** 551 patients were available for analysis. Median age 62 (19 – 90), 64% female. Indication for GFR evaluation: malignancy (85%), assessment for live kidney donation (12%), other (3%). Median ratio of IDMS-GFR : ^{51}Cr-GFR 1.04 (0.43 – 3.38); < 0.8 in 72 patients (13%), > 1.2 in 180 patients (33%). Median (IDMS-GFR - ^{51}Cr-GFR) +3.95ml/min (-81 – +176). Mean percentage error (MPE) was 12%. Despite capping of IDMS-GFR at 125ml/min, its use in the Calvert formula at AUC6 would have underdosed 99 patients (18%) by > 100mg Carboplatin compared to ^{51}Cr-GFR at AUC6, and overdosed 128 patients (23%) by the same amount. 104 patients (19%) would be overdosed by > 20%. The convention of the use of AUC5 in patients who have ^{51}Cr-GFR, and AUC6 in patients who have IDMS-GFR (capped), would lead to differences in planned dose between the 2 methods of > 100mg in 326 patients (59%), and by > 20% in 264 (48%). Univariate analysis identified BMI (> 35, MPE 39%), gender (female MPE 15%), GFR indication (malignancy MPE 11%) as risk factors for overestimate of GFR by IDMS-GFR, and BMI < 20 for underestimate (MPE -3.5%). **Conclusions:** IDMS-GFR is an unreliable surrogate for ^{51}Cr-GFR. The convention of considering AUC5 carboplatin based on ^{51}Cr-GFR, and AUC6 carboplatin based on calculated GFR, as equivalent is invalid, and should be abandoned.

2577 Poster Session (Board #293), Sat, 8:00 AM-11:30 AM

Results of OAK: A phase 1, open-label, multicentre study to compare two dosage forms of AZD5363 and to explore the effect of food on the pharmacokinetic (PK) exposure, safety, and tolerability of AZD5363 in patients with advanced solid malignancies. *First Author: Emma Jane Dean, The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: AZD5363 is a potent pan-Akt inhibitor and acts on cancers by blocking a cell survival pathway. AZD5363, administered to patients in the fasted state, was originally formulated as a capsule (C). For patient convenience and ease of manufacture a tablet (T) formulation has been developed. *In vitro* work has indicated that T and C perform similarly; PK comparability needed to be verified to introduce T to the clinical programme. The effect of food on PK, safety and tolerability was unknown. **Methods:** Part A assessed whether PK of T was comparable to C when both were given as a 480 mg bd dose in a 4 days on / 3 days off schedule; patients received T (Week 1) followed by C (Week 2). Part B examined the effect of a standardised meal on PK of T; patients received T in the fasted state (Week 1) and 30 minutes after a meal (Week 2). PK was assessed on the last day of weekly dosing in each of the cross-overs. **Results:** Part A data are available in 13 evaluable patients. AUC_{ss} and $C_{ss,max}$ observations for T and C were comparable with GLS mean ratios (90% CIs) of 0.9 (0.79 to 1.03) and 1.01 (0.88 to 1.16) respectively. CIs of the ratios lay within the 0.75 to 1.33 pre-specified limits. Median $t_{ss,max}$ was shorter for T than C (1.03 vs 2.03 h respectively), consistent with the *in vitro* dissolution data. T and C safety data were comparable and consistent with the known safety profile for AZD5363. Part B data are available from 10 patients. PK profiles for T(fasted) versus T(fed) indicated a later t_{max} and lower exposure in the fed state. GLS mean ratios of $C_{ss,max}$ and AUC_{ss}were 0.86 (0.74 to 1.01) and 0.68 (0.57 to 0.81) respectively. No significant differences in safety profiles were noted between the fasted and fed states. **Conclusions:** PK, safety and tolerability of the tablet and capsule formulations of AZD5363 are comparable. Tablets are being introduced across the ongoing clinical trials. Food has been shown to reduce the rate and extent of absorption of AZD5363 without a discernible effect on safety and tolerability; the existing food restrictions in ongoing clinical trials will be maintained. Clinical trial information: NCT01895946.

2578 Poster Session (Board #294), Sat, 8:00 AM-11:30 AM

Exposure-response (E-R) and case-control analyses of ramucirumab leading to recommendation for dosing optimization in patients with gastric cancer. *First Author: Runyan Jin, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Ramucirumab was approved for the treatment of advanced gastric or gastro-esophageal junction adenocarcinoma in combination with paclitaxel based on an efficacy and safety trial that demonstrated 2.2 months (median) of overall survival (OS) benefit with a hazard ratio of 0.81 ($p = 0.02$) for patients treated with ramucirumab plus paclitaxel as compared to patients treated with placebo plus paclitaxel. In exploratory Kaplan-Meier survival analyses stratified by model predicted ramucirumab minimum concentration after first dose ($C_{min,1}$), the OS effect was only shown for the patients with $C_{min,1}$ greater than the median value. Further exploratory E-R analyses were conducted. **Methods:** Data for E-R analyses were obtained from a randomized (1:1), double-blind, placebo-controlled, efficacy and safety trial that randomized 665 patients. Case-control analysis was conducted to match patients in the placebo arm to patients in each $C_{min,1}$ quartile subgroup (Q1-Q4) based on key baseline prognostic factors, which could potentially confound assessment of therapeutic benefit from ramucirumab. The relationship between $C_{min,1}$ and OS based on exposure subgroups and matched placebo controls was re-evaluated by Kaplan-Meier analyses. **Results:** Four baseline prognostic factors were identified: ECOG performance status (0 vs. 1), tumor differentiation (well, moderately, poorly or unknown), Asian (yes or no), and the total number of target and non-target tumor lesions (≤ 4, 4-8 or ≥ 9). These were used for selection of case-controls. Kaplan-Meier curves showed no apparent difference in OS throughout the treatment period for the Q1 and Q2 subgroups and $>$ 4-month difference in estimated median OS for the Q3 and Q4 subgroups as compared to their corresponding controls. **Conclusions:** An incremental OS benefit was observed with increasing exposure of ramucirumab after case control, suggesting that patients with higher ramucirumab exposure may derive more benefit from the addition of ramucirumab to paclitaxel. These analyses led FDA to recommend a post-marketing clinical trial to explore the benefits and safety of a higher dosing regimen of ramucirumab.

2579 Poster Session (Board #295), Sat, 8:00 AM-11:30 AM

Population pharmacokinetic (PK) analysis of TAS-102 in patients (pts) with metastatic colorectal cancer (mCRC): Results from 3 phase 1 trials and the phase 3 RECOURSE trial. *First Author: James M. Cleary, Dana Farber Cancer Institute, Boston, MA*

Background: TAS-102 is comprised of an antineoplastic thymidine-based nucleoside analog, trifluridine (FTD), and the thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI), at a molar ratio of 1:0.5 (weight ratio, 1:0.471). The efficacy and safety of TAS-102 in pts with mCRC refractory to standard therapies were evaluated in the RECOURSE trial. The major elimination pathways of FTD and TPI are by thymidine phosphorylase metabolism and renal excretion, respectively. Objectives of the current analysis were to establish population PK models for FTD and TPI, and to identify significant intrinsic and extrinsic factors that influence drug exposure. **Methods:** The population PK approach used the nonlinear mixed-effect modeling program. The analysis consisted of sparse sampling data in RECOURSE (n = 139 of 800 pts, 3 time points) and extensive sampling data in 3 TAS-102 phase 1 trials (n = 102) [Japanese dose-finding study (*Br J Cancer.* 2012;107:429-434), PK contribution study (NCT01867866), and QTc study (NCT01867879)]. **Results:** Actual doses based on body surface area (BSA) were similar among studies except for the Japanese dose-finding study. The 1- and 2-compartment models with transit and first-order absorptions were adopted for FTD and TPI, respectively. BSA clearly related to the central volume of distribution (Vd/F) and creatinine clearance (CLCR) was a significant covariate for apparent oral clearance (CL/F) in the final models of FTD and TPI. Serum albumin (ALB) was a significant negative covariate for CL/F of FTD. The fixed effect for individual CL/F and Vd/F were modeled as follows: FTD: Vd/F (L) = $10.0 \times (BSA/1.81)^{0.94}$, CL/F (L/h) = $2.93 \times (CLCR/103)^{0.507} \times (ALB/3.90)^{-0.633}$; TPI: Vd/F (L) = $192 \times (BSA/1.81)^{1.46}$, CL/F (L/h) = $88.7 \times (CLCR/103)^{0.592}$. **Conclusions:** Renal function and body size were the primary determinants of the PK of TAS-102, highlighting the importance of monitoring renal function in pts treated with TAS-102. Dosing of TAS-102 by BSA is adequate to reduce the variability of exposure to FTD and TPI. Significantly, the PK parameters did not vary with race, age, gender, or hepatic function. Clinical trial information: NCT01607957.

2580 Poster Session (Board #296), Sat, 8:00 AM-11:30 AM

A phase I, first-in-human study of argx-111, a monoclonal antibody targeting c-met in patients with solid tumors. *First Author: Philippe G. Aftimos, Institut Jules Bordet – Université Libre de Bruxelles, Brussels, Belgium*

Background: Dysregulation of the tyrosine kinase receptor c-Met, is associated with tumorigenesis, metastasis and progression via hepatocyte growth factor (HGF)-dependent or-independent mechanisms. **Methods:** ARGX-111, a monoclonal IgG1 SIMPLE Antibody glyco-engineered for enhanced ADCC properties (POTELLIGENT), is currently being investigated in a Phase 1 clinical trial (accelerated titration design) in patients with advanced solid tumors (NCT 02055066). **Results:** As of January 2015, 16 patients (median age: 59 years; prior chemotherapy/targeted therapies/biological therapies: 81%/44%/31%;) with tumors staining positive ($>$ 50% of tumor cells) for c-Met by immunohistochemistry have been treated at 4 dose levels (0.3, 1, 3, and 10 mg/kg IV q3 weeks; n = 2, 2, 9, and 3, respectively) and received a total of 41 cycles (median = 2; range 1-9). Patients with different histologies were enrolled (5 upper GI, 3 RCC, 2 pancreas, 2 NSCLC, 2 cervix and 2 others). The most common drug-related adverse events (AE) were: infusion-related reaction (IRR) (56%), fatigue (38%) and diarrhea (25%). Drug-related Grade 3 AEs (IRRs) were observed in 2 patients. The MTD was 3 mg/kg IV q3 weeks. Pharmacokinetics were dose-linear, with a half-life of 3-4 days. Serum HGF levels remained stable during treatment. *Ex vivo*ADCC and depletion of circulating c-Met+ cells were observed in all patients and NK cell counts remained stable during treatment across all dose levels. One patient with metastatic, c-Met amplified gastric cancer refractory to platinum and taxane-based chemotherapy regimens, was treated at 0.3 mg/kg (escalated to 1.0 mg/kg) and maintained stable disease by RECIST for 6 months, associated with mixed metabolic response on PET scan, and a more than 50% reduction in CTCs. **Conclusions:** Recruitment of the safety expansion cohort is ongoing. Full results will be presented at the meeting. Clinical trial information: NCT 02055066.

Dose	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
C_{max}(mean) (μg/ml)	5.6	11.4	43.4	113.2
ADA	No	No	No	No
HGF levels	Stable	Stable	Stable	ND
ADCC	Yes	Yes	Yes	Yes
NK-cell count	Stable	Stable	Stable	Stable

2581 Poster Session (Board #297), Sat, 8:00 AM-11:30 AM

Comparison of adult oncology phase 1 trials to pediatric oncology phase 1 trials of targeted therapies. *First Author: Vivek Subbiah, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Intractable aggressive cancers continue to take the lives of children, adolescents and young adults at the prime of their lives. The prior era of drug development wherein pediatric cancer becomes the last cancer to be tested with novel agents, 'if' the agent seems promising in adult cancers may need to be re-visited. Phase 1 trials are the first critical step in drug development. Data based on cytotoxic chemotherapy phase 1 trials demonstrated a strong correlation between adult and pediatric maximum tolerated dose (MTD)s. We sought to compare pharmacokinetic (PK) parameters and dosing of small molecule inhibitors and monoclonal antibodies (MAbs) studied in adult vs. pediatric phase 1 trials. **Methods:** We conducted an extensive review of all published pediatric phase 1 trials of small molecule inhibitors and MAbs, and their corresponding adult phase 1 trials. Multiple data elements including MTD, recommended phase 2 dose (RP2D), and dose-limiting toxicity (DLT) were collected from pediatric and adult phase 1 trials. PK parameters for the small molecules including drug clearance (CL), area under the concentration curve (AUC), and half-life were analyzed. **Results:** We identified 25 targeted agents (21 small molecules, 4 MAbs) and compared data from the pediatric and adult trials. The MTD was not reached for 14 of the 25 (56%) agents in adults (3/25), pediatric patients (7/25), or both (4/25). Excluding the agents for which the MTD was not reached, the median ratio of pediatric to adult MTD was 1. PK data was available for 13 small molecules and 2 MAbs. The median ratio of pediatric to adult PK parameters for small molecules was: 0.9 for drug CL, 1 for AUC, and 0.8 for half-life. There was substantial heterogeneity in the PK parameters investigated across the studies. **Conclusions:** The PK and MTD of small molecule targeted agents in pediatric and adults patients are comparable. Initial pediatric dosing close to the adult MTD or RP2D and extrapolation of PK data from adults may help expedite drug development of these agents in children. Standardized strategies to study and report PKs are needed.

2582 Poster Session (Board #298), Sat, 8:00 AM-11:30 AM

The association of relative survival benefit and approval of oncological drugs: An analysis of oncology drug advisory committee reviews. *First Author: Idoroenyi Usua Amanam, St. Mary Medical Center, Long Beach, CA*

Background: To evaluate the association of relative survival benefit (additional benefit / historic control) as a modality to predict for oncology drug approval. **Methods:** Data was extracted from transcripts of drug license application sessions of the FDA's Oncology Drug Advisory Committee (ODAC). Relative survival benefit (RB) is defined as the percent survival improvement associated with new therapy over standard therapy. SAS was used to conduct statistical analysis. **Results:** The FDA approved 13 of 29 oncological drug license applications from 2001 to 2014. 5 breast, 3 pancreatic, 3 renal, 3 ovarian, 2 hematologic, 2 prostate, 2 soft tissue sarcoma, 2 lung, 2 bone metastasis, 2 brain, and 2 skin drug applications were reviewed by the FDA. 11 (38%) drug license applications used overall survival (OS) as an endpoint, 8 (28%) used PFS, and 10 (34%) used both OS and PFS as endpoints. The median relative benefit (RB) of all reviewed end points (n = 39) was 15.1% (range: 0% to 190%). Of the studies that used PFS (n = 18) vs. OS (n = 21) as an endpoint, the average relative benefit was 70% (range: 7% to 190%) and 11% (range: 0% to 50%) ($p < 0.01$), respectively. Using the median RB of 15%, drugs with a greater RB had an approval rate of 68%, while drugs with a lower RB had an approval rate of 6% ($p = 0.24$). Subset analyses of studies using OS or PFS as the primary endpoint showed no difference in approval of drugs with RBs higher or lower than the median ($p = 0.47$, $p = 0.066$, respectively). Analysis of the years 2001-6, 2007-10, and 2011-14 showed significant increases in RB ($p < 0.01$) and drug approval ($p = 0.032$) as well as greater use of PFS rather than OS as an endpoint in studies ($p = 0.017$). **Conclusions:** The use of relative survival benefit may assist as a predictive indicator for prediction of FDA approval of novel anti-cancer agents. Researchers may need to consider using relative survival benefit to improve the success of FDA approval of novel drug agents.

2583 Poster Session (Board #299), Sat, 8:00 AM-11:30 AM

A phase I dose escalation study of the tolerability of the oral VEGFR and EGFR inhibitor vandetanib (V) in combination with the oral MEK inhibitor selumetinib (S) in solid tumors. *First Author: Wasiru Olugbenga Saka, Oxford University Hospitals NHS Trust, Oxford, United Kingdom*

Background: The clinical utility of agents that target EGFR and VEGFR signaling in Non-Small Cell Lung Cancer (NSCLC) is limited by resistance due to emergent alternative growth stimulatory pathways, particularly that of MEK. Thus, there is a strong rationale for developing a strategy to combine EGFR, VEGFR and MEK inhibitors. **Methods:** Patients (Pts) aged > 18y, life expectancy > 12w and cytologically proven solid tumors for which no conventional therapy exists were eligible to participate. Six dose levels have been explored. PK samples were obtained on D4, 15 and 29. Pts remained on treatment until progressive disease or unacceptable toxicity. **Results:** 41 pts of median age 62y (36 – 80y); M-20, F-21; lung-23, CRC-9, Mesothelioma-3, pancreas-2, Other-4 were enrolled. 40 pts were eligible for safety assessment. Median treatment time was 10 w (range 2-44 w). GI and skin toxicities were the most prevalent related AEs (GI: 124 AEs in 88% pts; Skin: 74 AEs in 95% pts). Sixteen related eye disorders were seen in 12 pts to include retinal detachments-6 (G1-2) and retinopathies-2 (G2 and 3). Evidence of dose dependent skin and eye toxicity was observed. Six DLTs were identified; Cohort (Coh) 1 - G3 hypertension, Coh 3 & 5a - G2-3 eye events (3 AEs), Coh 4 - G3 bradycardia and Coh 5b - G3 raised ALP. The PK data for V alone and in combination with S were similar to those previously reported for either drug alone. **Conclusions:** V and S have overlapping toxicities, yet the combination has been manageable, with the AE profile consistent with the known monotherapy profiles. A higher incidence of reversible eye events was observed in combination than with single agent S. PK has shown no drug interaction. S dose of 100mg once daily or 50mg twice daily is the MTD in combination with V. V combination MTD to be confirmed. Stable disease was confirmed in four NSCLC patients who received 6-10 cycles. An expansion cohort in NSCLC with known EGFR, VEGFR and MEK activation status will open with anti-tumor efficacy endpoint. Clinical trial information: NCT01586624.

Cohort	V Lead in (po) Days 1-4	V Steady state (po) Days 5-14	S (po), from Day 15, in combination with steady state V
1	300mg od	100mg od	25 mg bd
2			50 mg bd
3			75 mg bd
4			100mg od
5a			125mg od
5b		200mg od	50 mg bd

2584 Poster Session (Board #300), Sat, 8:00 AM-11:30 AM

Phase I study of the mTOR inhibitor sirolimus and the HDAC inhibitor vorinostat in patients with advanced malignancies. *First Author: Haeseong Park, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Preclinical models suggest synergistic anticancer activity of histone deacetylase (HDAC) and mTOR inhibitors by reducing activity of AKT/mTOR and HDAC. **Methods:** This is a phase I study (NCT01087554) to determine the safety, maximum tolerated dose (MTD)/recommended phase II dose (RP2D) and dose limiting toxicities (DLT) of the mTOR inhibitor sirolimus (1mg-5mg PO daily q 28 days) and HDAC inhibitor vorinostat (100mg-400mg PO daily q 28 days) in patients with advanced cancers. The expansion cohorts at RP2D, which included optional pre- and post-treatment tumor biopsies and other pharmacodynamic (PD) and pharmacokinetic (PK) endpoints, enrolled patients with classical Hodgkin lymphoma (cHL), hepatocellular carcinoma (HCC), perivascular epithelioid cell tumor (PEComa) and other cancers. **Results:** From March 2010 to August 2014, 102 patients were treated (dose escalation, n = 69, expansions, n = 33). cHL (n = 22) and HCC (n = 12) were most common diseases. Patients (n = 66), who either had DLT or completed the first cycle without dose modifications were evaluable for DLT asessment, which included grade (G) 4 thrombocytopenia (n = 10) and G3 mucositis (n = 1). Sirolimus 5mg and vorinostat 300mg was declared as MTD. Because of significant non-DLT hematological toxicities, sirolimus 4mg and vorinostat 300mg was established as RP2D. All G 3/4 drug related toxicities (including DLT) were thrombocytopenia (37%), neutropenia (13%), anemia (8%), mucositis (3%), diarrhea (3%), fatigue (2%), febrile neutropenia (1%), peripheral neuropathy (1%). 57 (56%) patients required dose modifications. Of 102 patients, 78 had at least one restaging imaging;7 (7%; cHL, n = 6; peripheral T-cell lymphoma, n = 1) had a complete response, 7 (7%; cHL, n = 6; PEComa, n = 1) had a partial response and 3 (3%, HCC, n = 2, fibromyxoid sarcoma, n = 1) had stable disease for 12 months or longer. Among the responders, two had known aberrations in the PI3K pathway (TSC2 and PIK3CA). PD studies and PK analysis are pending. **Conclusions:** The combination of sirolimus and vorinostat is well-tolerated at RP2D and demonstrates promising activity in lymphoma, PEComa and HCC. Further investigation is warranted in these disease types. Clinical trial information: NCT01087554.

2585 Poster Session (Board #301), Sat, 8:00 AM-11:30 AM

Dose-escalation of the first-in human phase I/Ib study of ABTL0812, a novel antitumor drug inhibiting the Akt/mTOR pathway in patients with advanced solid tumors. *First Author: Laura Vidal Boixader, Hospital Clinic Barcelona, Barcelona, Spain*

Background: ABTL0812 is a novel drug with reported preclinical activity in several tumor types. *In vitro* and *in vivo* assays have shown that ABTL0812 is an inhibitor of the Akt/mTOR pathway by a novel mechanism of action. **Methods:** A Phase I/Ib First in Human (FiH) clinical trial started on February 2014 (NCT02201823) in which patients with solid tumors and no standard treatment were enrolled. ABTL0812 was administered daily, by the oral route in 28-day cycles. The primary objective of the trial was to obtain a maximum tolerated dose and a recommended phase II dose (RP2D). The secondary objectives of the trial were assessment of dose-limiting toxicity (DLT), response rate, progression-free survival and overall survival. Pharmacokinetic (days 1 and 29) and pharmacodynamic (inhibition of the phosphorylation of Akt in platelets at day 29 vs. predose, as biomarker) end-points were also introduced. The study design consisted in a 3+3 dose escalation with up to five cohorts. An expansion phase with 12 patients is planned. **Results:** The dose-escalation, in which 15 patients were recruited, started at 500 mg/day and was completed in December 2014 at 4,000 mg/day. ABTL0812 showed overall a good safety profile. Grade 1-2 adverse events included swallowing disturbance, asthenia, increase of hepatic enzymes, hyperglycemia and nausea; grade >2 adverse events were rare and included anemia and asthenia. No DLTs were observed and therefore, RP2D has been determined as 1,300 mg tid by pharmacokinetic-pharmacodynamic modeling of drug plasma concentrations at steady state vs. platelet pAkt inhibition. One patient with endometrial cancer and one patient with sigmoid colon cancer currently show stable disease (SD) after 10 and 5 months of treatment, respectively. **Conclusions:** RP2D of ABTL0812 has been determined. ABTL0812 has demonstrated a good safety profile, with only mild adverse events. Additionally, ABTL0812 has shown activity on biomarkers, and hints of activity in two patients presenting prolonged SD. Clinical trial information: NCT02201823.

2586 Poster Session (Board #302), Sat, 8:00 AM-11:30 AM

Phase I study of pemetrexed and sorafenib in advanced solid tumors. *First Author: Andrew Stewart Poklepovic, Virginia Commonwealth Univ Health Sys, Richmond, VA*

Background: Pemetrexed (Pem) blocks thymidylate synthase, activates AMPK, and inactivates mTOR, increasing autophagy. Sorafenib (Sor) also stimulates autophagy through down-regulation of GRP78/BiP and ER stress signaling. Preclinical data demonstrated the combination of Pem and Sor caused synergistic cell death through a form of toxic autophagy. A phase I trial evaluating the combination of Pem and Sor in advanced solid tumors was initiated. **Methods:** An open-label, dose escalation study was conducted in patients (pts) with advanced malignancies. Standard 3+3 dose escalation design was used, with escalating doses of Pem (500 mg/m^2-1000 mg/m^2 IV) every 2 weeks with Sor (200-400 mg PO BID) continuously (cohort A). The initial 4-week period (Cycle 1) was used for dose-limiting toxicity (DLT) assessment. After treatment of 24 pts on cohort A, it was determined that continuous dosing of Sor with any dose of Pem was associated with unacceptable cumulative constitutional symptoms beyond Cycle 1. The protocol was amended to evaluate intermittent Sor (BID dosing days 1-5 of each Pem dose) (cohort B). Radiographic assessments were conducted every 8 weeks using RECIST 1.1. **Results:** Thirty-seven pts were enrolled and 36 treated, 24 on cohort A and 12 on cohort B. The MTD in cohort A was defined as Pem 500 mg/m^2 and Sor 200 mg PO BID on a continuous schedule. Dose reductions for cumulative toxicity became necessary in the majority of patients in cohort A. Intermittent dosing was more tolerable, with 0/12 cohort B pts experiencing DLTs, treated at both 500 mg/m^2 and 750 mg/m^2 of Pem every 2 weeks with intermittent Sor at 200-400 mg. Of the 36 treated pts, best responses to date are 1 CR, 4 PR, 10 SD, 15 PD, 2 NE, and 4 TETE. Five pts with progressive breast cancer were identified as responders. One PR and the CR had durations of response approximating 1 year. All responding pts were heavily pretreated, with a median of 6 prior lines of therapy. Cutaneous, nodal, and visceral metastases were all observed to respond to treatment. **Conclusions:** The RP2D for the combination is Pem 750 mg/m^2 IV every 2 weeks with Sor 400 mg PO BID days 1-5 with each dose of Pem. A phase II study in breast cancer is planned. Clinical trial information: NCT01450384. Clinical trial information: NCT01450384.

2587 Poster Session (Board #303), Sat, 8:00 AM-11:30 AM

Phase I study of INC280 plus erlotinib in patients with MET expressing adenocarcinoma of the lung. *First Author: Caroline Elizabeth McCoach, University of Colorado School of Medcn, Aurora, CO*

Background: MET dysregulation is one mechanism of EGFR-TKI (epidermal growth factor receptor-tyrosine kinase inhibitor) resistance in patients (pts) with EGFR mutated lung cancer. INC280 is a potent oral small molecular inhibitor of the MET kinase. Inhibiting both pathways may circumvent EGFR-TKI resistance. A phase I study of INC280 plus erlotinib (E) to determine the maximum tolerated dose, dose limiting toxicity (DLT), pharmacokinetics (PK) and preliminary antitumor activity of this combination was conducted. **Methods:** Using a 3 + 3, dose escalation design, INC280 was increased over 5 dose levels (DL) from 100 - 600 mg po bid. Daily E was given at 100 mg in DL1 and 150 mg in DL2- 5. Both agents were given for 28 days (1 cycle). Key eligibility included: lung adenocarcinoma with MET expression by a CLIA certified lab, age $\geq$ 18 years old, ECOG PS of ≤ 2, acceptable organ function, and >1 systemic therapy for advanced disease. **Results:** 18 pts have been treated on 5 dose levels. Pt characteristics: median age 59, M/F (7/11), ECOG 0-1/2 (16/2), MET expression by IHC/FISH/RT-PCR/NGS (6/2/9/1), EGFR mutated tumors (8) and prior E treatment (12). 14 patients have completed at least 1 cycle. One DLT (grade (Gr) 3 neutropenia) occurred in DL 5 (INC280 600mg bid, E 150mg daily). Common drug-related adverse events (AE) of any Gr were diarrhea and rash (47% each), fatigue (40%), increased AST and ALT (27% each), nausea, anorexia and paronychia (27% each). Drug-related Gr 3/ 4 AE were anorexia, increased amylase or lipase and neutropenia (all 7%). PK analysis revealed that INC280 exhibited a linear PK and no interaction with E. Of the 12 evaluable pts, 6 had stable disease (3 EGFR mutated) and 2 with EGFR mutated tumors had a minor response (10-29% decrease in target lesion size). Seven pts received treatment for $\geq$ 3 months (5 EGFR mutated). **Conclusions:** In patients with MET-expressing lung adenocarcinoma, INC280 plus erlotinib is feasible, tolerable and demonstrates anti-tumor activity. Expansion cohorts will enroll pts with EGFR mutated tumors refractory to an EGFR-TKI or EGFR-TKI naïve in the first-line setting and in wild type EGFR pts who are EGFR-TKI naïve as second or third-line therapy. The recommended phase II dose and updated results will be presented. Clinical trial information: NCT01911507.

2588 Poster Session (Board #304), Sat, 8:00 AM-11:30 AM

Phase I combination of pazopanib and everolimus in *PIK3CA* mutation positive/PTEN loss patients with advanced solid tumors refractory to standard therapy. *First Author: Heloisa Veasey Rodrigues, Centro de Oncologia e Hematologia - Hospital Israelita Albert Einstein, Sao Paulo, Brazil*

Background: Combining agents that block both the VEGF and PI3K/AKT/mTOR pathways may be synergistic. We explored a novel dosing schedule to assess safety, toxicity and activity in patients with advanced solid tumors. **Methods:** Patients with refractory solid tumors were enrolled in a modified 3+3 Phase I dose escalation study to determine dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of a combination of everolimus (mTOR inhibitor) and pazopanib (tyrosine kinase inhibitor with anti-VEGF activity). An expansion cohort selected for patients with molecular alterations in the PI3K/AKT/mTOR pathway. **Results:** Sixty-two patients were enrolled; median age was 60 years; 29 were women. The MTD was pazopanib 600mg every other day (QOD) alternating with everolimus 10mg PO QOD. DLTs were grade 3 thrombocytopenia and creatinine elevation. Most common toxicities of any grade were thrombocytopenia, transaminitis, leukopenia/neutropenia and lipid abnormalities. Among 52 patients evaluable for response, the clinical benefit rate (CBR) was 27% (14/52) including four partial responses (PR), and 10 stable disease (SD) $\geq$ 6 months. 26 of 45 patients evaluated for molecular alterations had at least one alteration in the PI3K/AKT/mTOR pathway. CBR in patients with a matched alteration was 27% (7/26) versus 26% (5/19) for patients without an alteration ($p = 0.764$). However, 64% of those with CBR and molecular testing done for alteration in the PI3K/AKT/mTOR pathway were positive. **Conclusions:** Combination treatment with pazopanib and everolimus was well tolerated and demonstrated activity in solid tumors. Further exploration of this combination and molecular correlation with treatment outcomes is warranted. Clinical trial information: NCT01430572.

2589 Poster Session (Board #305), Sat, 8:00 AM-11:30 AM

Phase I study of receptor tyrosine kinase (RTK) inhibitor, MGCD265, in patients (pts) with advanced solid tumors. *First Author: Christian K. Kollmannsberger, BC Cancer Agency, Vancouver Cancer Centre, Vancouver, BC, Canada*

Background: MGCD265 is a spectrum-selective and ATP-competitive inhibitor with MET and Axl as clinically relevant RTK targets. In nonclinical studies, MGCD265 demonstrated anti-tumor activity in cancer models exhibiting dysregulation of MET or Axl RTKs. **Methods:** Phase I objectives were to evaluate the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), pharmacodynamics (PD) and clinical activity of MGCD265. Eligible pts with advanced solid tumors received MGCD265 on Cycle 1 Day 1, then continuous dosing starting on Cycle 1 Day 3 for 21-day cycles. PK/PD were evaluated after single dose and repeated administration. **Results:** 12 pts (6 males; median age 57 years; range 48-75) with advanced malignancies were treated with 600, 1200 or 1050 mg BID of MGCD265 in non-aqueous suspension capsules. At 1200 mg BID, 2 out of 6 evaluable pts experienced DLT (G3 fatigue; G3 diarrhea). 1050 mg BID was defined as the MTD with no DLTs in 3 pts. Treatment-related AEs ($>$ 20% all grades) included diarrhea, nausea, vomiting, fatigue, AST increase, ALT increase and lipase increase. Stable disease of at least 6 weeks was observed (n = 2). At MTD, preliminary data show that steady state average and maximum concentrations were 501 and 562 ng/mL, respectively; the area under the concentration-time curve for the dosing interval was 6010 ng●h/mL. Preliminary data show that plasma concentrations exceeded levels projected for near complete inhibition of both MET and Axl for the full dosing interval. Maximal increase of plasma soluble MET ectodomain (sMET) was observed at each dose level including those associated with sustained steady state plasma concentrations (C_{min}) as low as 200 ng/mL, suggesting that the MET pathway was inhibited at all 3 dose levels and concentrations achieved in this study. **Conclusions:** MGCD265 is well tolerated at the MTD of 1050 mg BID. Based on safety, PK data and PD data suggesting robust inhibition of MET and Axl, the expansion phase of the study began recruitment in December 2014. Patients with NSCLC and other solid tumors with specific genetic alterations for *MET* and *AXL* will be enrolled. Clinical trial information: NCT00697632.

2590 Poster Session (Board #306), Sat, 8:00 AM-11:30 AM

Phase I study of the PI3K/mTOR inhibitor PF-05212384 in combination with other antitumor agents. *First Author: Zev A. Wainberg, UCLA Medical Center, Los Angeles, CA*

Background: Inhibition of phosphatidylinositol-3-kinase (PI3K)-mediated signaling may overcome resistance to different classes of chemotherapies as well as epidermal growth factor receptor (EGFR) inhibitors. PF-05212384 (PF384) is an intravenous (IV) inhibitor of PI3K/mammalian target of rapamycin (mTOR) in development for metastatic colorectal cancer and other solid tumors in combination with other agents. **Methods:** An ongoing phase I dose escalation study is enrolling cohorts of 3–6 patients (pts) to determine maximum tolerated dose (MTD) and safety of PF384 plus docetaxel (arm A), cisplatin (arm B), or the EGFR tyrosine kinase inhibitor dacomitinib (arm C). Eligible pts have castrate resistant prostate cancer, advanced breast cancer, or non-small cell lung cancer (NSCLC; arm A); urothelial transitional cell cancer, triple negative breast cancer, or NSCLC (arm B); or refractory Her2+ breast cancer, Her2+ esophagogastric cancer, head and neck squamous cell cancer, or EGFR-mutated NSCLC (arm C). Dose assignment is guided by a modified toxicity probability interval method (arms A,B) or zone-based design (arm C). Pts receive a lead-in PF384dose 7 (arms A,B) or 14 days (arm C) prior to cycle 1 day 1. Then, pts receive weekly PF384plus standard chemotherapy (docetaxel or cisplatin 75 mg IV every 3 wk) or dacomitinib (30–45 mg/d orally; started 7 days prior to cycle 1 day 1). Primary endpoint is cycle 1 dose-limiting toxicities (DLTs), including lead-in dose. Secondary endpoints include pharmacokinetics, tumor response, and PI3K pathway protein biomarkers. **Results:** 52 pts received escalating doses (90–150 mg) of PF384: 14, 12, and 26 pts in arms A, B, and C. Drug-related adverse events in $>$ 30% pts were neutropenia, mucositis, and nausea in arm A; nausea, decreased appetite, fatigue, vomiting, anemia, and hypomagnesaemia in arm B; and mucositis, diarrhea, nausea, dermatitis acneiform, and decreased appetite in arm C. There were no DLTs in arms A or B; in arm C, DLTs were grade 3 mucositis, pneumonitis, and rash, and grade 2 fatigue ($<$ 75% of planned dose received). **Conclusions:** PF384can be combined with docetaxel, cisplatin, or dacomitinib with a manageable toxicity profile. Dose escalation to determine MTD is ongoing. Clinical trial information: NCT01920061.

2591 Poster Session (Board #307), Sat, 8:00 AM-11:30 AM

Efficacy, safety, biomarkers, and phase II dose modeling in a phase I trial of the oral selective c-Met inhibitor tepotinib (MSC2156119J). *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute At HealthONE, Denver, CO*

Background: Tumor c-Met overexpression is associated with tumor aggression and poor prognosis, making it a target for therapy. This phase I study (NCT01014936) in patients (pts) with advanced solid tumors provided data that allowed determination of a recommended phase II dose (RP2D) for the selective oral c-Met inhibitor tepotinib (MSC2156119J). **Methods:** Primary objectives were to determine the MTD and RP2D. Secondary endpoints included antitumor activity, safety, pharmacokinetics (PK), and pharmacodynamics. Pts received tepotinib according to one of three 3-weekly regimens (R): 30–230 mg/d d1–14 followed by 7-d rest (R1); 30–115 mg/d 3x/week (R2); or 300–1400mg/d d1–21 (R3). Interim PK and biomarker data were analyzed using a population modeling approach. Using these data and the exposure/target inhibition relationship established in mice, a human population PK model was developed to simulate c-Met inhibition profiles in humans and determine the biologically active dose of tepotinib. **Results:** As of 9/30/2014,143 pts had been enrolled (R1 = 42; R2 = 45; R3 = 56). The MTD was not reached at $\leq$ 1400 mg/day d1–21 (R3). Among the 56 pts treated with R3 (c-Met overexpressing 12; amplified 4; overexpressing and amplified 3), treatment-related adverse events (trAEs) were observed in 61%. Of these, $>$ 75% experienced trAEs of worst grade 1/2. Seven pts (13%) experienced trAEs of worst grade $\geq$ 3: fatigue (2), peripheral edema (2), ALT increase (1), AST increase (1), hyponatremia (1), edema (1), and thrombocytopenia (1). Of the 56pts treated with R3, 2 had a PR and 7 had SD as their best overall response. Patients with PRs had tumors with c-Met overexpression or amplification, as did 2/7 pts with SD. A biologically active dose of 500 mg/d was selected as the RP2D based on a translational modeling approach, with simulations indicating that $\geq$ 95% pMET inhibition was required for tumor regression. Human population PK simulations suggested that tepotinib 500 mg daily could achieve continuous pMET inhibition of $\geq$ 95% in 90% of the population. **Conclusions:** Tepotinib is well tolerated and shows antitumor activity, particularly in pts with c-Met overexpressing/amplified tumors. Clinical trial information: NCT01014936.

2592 Poster Session (Board #308), Sat, 8:00 AM-11:30 AM

A phase 1 first-in-human (FIH) dose-escalation (DE) study of the oral dual PI3K/mTOR inhibitor PQR309 in patients (pts) with advanced solid tumors: Final DE results. *First Author: Rebecca Sophie Kristeleit, University College London Cancer Institute, London, United Kingdom*

Background: PQR309 is a novel, orally bioavailable, balanced pan-PI3K, mTORC1 and mTORC2 inhibitor. **Methods:** An accelerated 3+3 DE, open label Phase 1 trial of continuous once daily (OD) PQR309 to evaluate safety, pharmacokinetics (PK) and pharmacodynamics (PD) in pts with advanced solid tumours was performed. Pts had no standard therapeutic options. An expansion cohort at maximum tolerated dose (MTD) is planned. The starting dose of PQR309 was 10mg OD. The dose limiting toxicity (DLT) period was the first cycle of treatment, 21 days (d). Paired tumour biopsies (PTB) were collected. **Results:** 25 pts (18F:7M) were enrolled as of January 2015 and treated at 11 doses ranging from 10-150mg. Common adverse events (AE) ($\geq$ 30% pts) included fatigue, hyperglycaemia, nausea, diarrhea, constipation, rash, anorexia and vomiting. Grade (G) 3/4 drug-related AE were seen in 11 and 3 pts respectively. The most common drug-related AE $\geq$ G3 was hyperglycaemia observed in 7 pts. DLT occurred in 2/6 pts at 100mg OD associated with sequential AE G2-4; one patient (pt) with $>$ 14d interruption in PQR309 due to G2-4 rash, hyperbilirubinaemia, suicide attempt and one pt with dose reduction to 80 mg due to G2-3 fatigue, diarrhea, transaminitis, both during cycle 1. Preliminary PK shows fast absorption (T_{max} 1-2h), dose proportionality for C_{max} and AUC and an estimated $T_{1/2}$ of around 20 hours, consistent with PQR309 *in vivo* models. Preliminary PD analysis of 16 phosphoproteins (PP) involved in PI3K/mTOR/MAPK signalling in PTB shows marked decrease of p-Akt, pS6 and p4EPB from 40mg OD with moderate inhibition of p-Erk. A partial response (PR) in a pt with metastatic thymus cancer (ca) and *RICTOR* gene amplification, 24% disease volume reduction in a pt with sinonasal ca and PIK3CA E545K mutation and stable disease for over 16 weeks in a pt with clear cell Bartholin's gland ca have been observed. **Conclusions:** The MTD and recommended phase-2 dose of PQR309 is 80mg OD. PD shows PI3K pathway PP downregulation in PTB and PK is dose-proportional. Clinical activity including a PR has been observed in pts with known PI3K pathway dysregulation. Recruitment in the 80mg and planned expansion cohort is ongoing. Clinical trial information: NCT01940133.

2593 Poster Session (Board #309), Sat, 8:00 AM-11:30 AM

A phase Ib dose-escalation study of GSK2256098 (FAKi) plus trametinib (MEKi) in patients with selected advanced solid tumors. *First Author: Hendrik-Tobias Arkenau, Sarah Cannon Research United Kingdom, London, United Kingdom*

Background: The focal adhesion kinase (FAK) and MAPK pathways share common upstream activators and contribute to cell proliferation, differentiation, migration and survival. Dual inhibition of both pathways with GSK2256098 and trametinib, respectively, are synergistic in cellular growth and survival assays, especially in mesothelioma cell lines. **Methods:** This phase Ib study (NCT01938443, funded by GSK) evaluated GSK2256098 twice daily combined with trametinib once daily in pts with advanced solid malignancies enriching for mesothelioma. The objectives were to determine the maximum-tolerated dose (MTD), safety, pharmacokinetics (PK), and pharmacodynamics (PD). **Results:** As of 25 Nov 2014, 24 pts were enrolled (14 M, 10 F; median age 66 yr (range 30 to 78)). GSK2256098 at 250 or 500 mg twice-daily (BID) was orally co-administered with trametinib at 0.25, 0.375, 0.5 or 1 mg once-daily (QD) in 28-day cycles. Systemic exposure to trametinib was 2-4 X > than predicted for monotherapy causing DLTs (skin rash) and dose de-escalation. GSK2256098 PK was unchanged in the presence of trametinib. The MTD was determined to be GSK2256098 250 mg BID plus trametinib 0.5 mg QD and exposure for both agents are at concentrations that achieve antitumor activities *in vitro*. DLTs were observed in 6 pts (25%) at dose levels 0.5 or 1.0 mg trametinib + 500 mg GSK2256098. Median exposure was 52 days (range 17 - 181). Common adverse events (AEs), regardless of study drug relationship, were nausea (58%), diarrhea (38%), rash (33%), pruritus (33%), and vomiting (29%). Grade 3 AEs occurred in 9 individual pts (38%), and 1 (4%) Grade 4 AE occurred. One Grade 3 AE of increased CPK occurred at the MTD. Tumor biopsy PD data indicate FAK target engagement. Of 12 mesothelioma pts, 8 (67%) had stable disease lasting > 6 weeks reported as best response. **Conclusions:** The MTD for combined GSK2256098 and trametinib was reached, and the preliminary safety and PK/PD profile justifies further exploration. Clinical trial information: NCT01938443.

2594 Poster Session (Board #310), Sat, 8:00 AM-11:30 AM

NCIC CTG IND.206: A phase II umbrella trial of sunitinib (S) or temsirolimus (T) in advanced rare cancers. *First Author: Janet Dancey, NCIC Clinical Trials Group at Queen's University, Kingston, ON, Canada*

Background: Patients (Pts) with rare cancers have few treatment options due to the challenges of conducting clinical trials when projected accrual is low. However, rare cancers may have driver mutations that can be targeted with potentially dramatic therapeutic effects. **Methods:** IND.206 is a multi-center, non-randomized phase II study of S or T in 11 rare tumor cohorts (< 100 eligible patients/year in Canada). Cohorts: 8 histologic, 2 genetic, 1 exploratory unspecified. Pts received S (50 mg PO daily x 28 days, q 6 weeks) or T (25 mg IV weekly, q 6 weeks). Each cohort and drug was evaluated separately using a 2 stage design targeting 5 versus 25% RECIST response rate. Blood and tumor were collected for genomic analyses. For trial efficiency, 1) pts could be re-entered to the alternate drug at progression; 2) data collection and SAE reporting were streamlined; 3) cohorts could be stopped early for activity, inactivity or failure to accrue. Central pathology review was performed. **Results:** The trial was activated in 7/2011. To date, 134 patients were enrolled, 156 registered (22 pts crossed over). 132 are evaluable for response, 134 are evaluable for toxicity. 4 cohorts failed meet the minimum accrual. Only the medullary thyroid cohort treated with S met the protocol defined activity level. Responses were seen in the following: medullary thyroid carcinoma (7/16 on S), clear cell carcinomas of ovary/endometrium (3/22 S; 3/22 T), pheochromocytomas and paragangliomas (1/4 S), 1 extraskeletal myxoid chondrosarcoma (ESMCS) on S, 1 perivascular epithelioid cell tumor on T. Responses were not seen in vascular sarcomas (n = 16 10 S, 6 T) Ewing's sarcoma family tumours (n = 10, T), adrenocortical (n = 12 S, 10 T) or thymic carcinomas (n = 5 S, 2 T) despite case reports in the literature. Toxicity was consistent with previously studies although quantity of grade 1-2 and expedited reports were reduced as per protocol. Genomic studies are underway. **Conclusions:** S and T induce responses in clear cell carcinomas of ovary and endometrium, medullary carcinoma of thyroid, paraganglioma and ESMCS. Case reports in the literature may overestimate activity. Our umbrella design is efficient for evaluating drug activity in rare cancers. Clinical trial information: NCT01396408.

2595 Poster Session (Board #311), Sat, 8:00 AM-11:30 AM

Activity of crizotinib in relapsed MET amplified malignancies: Results of the French AcSé Program. *First Author: Gilles Vassal, Institut Gustave Roussy, Paris, France*

Background: Crizotinib (crz) is registered only for the treatment of patients (pts) with ALK-translocated lung cancer. Crz is also a MET inhibitor. MET is amplified in several malignancies. Activity of crz in MET amplified (+) tumors was explored as part of the French National Cancer Institute (INCa) AcSé program, including both access to tumor molecular diagnosis and an exploratory multi-tumor 2-stage design phase II trial. We report here results in pts with MET + tumors. **Methods:** MET analysis on formalin-fixed, paraffin-embedded tumor samples was proposed in 170 investigating centers and performed in 28 regional INCa molecular genetic centers. MET+ was explored by FISH in tumor samples showing an IHC score of ≥2+. Pts with a tumor showing > 6 MET copies, whatever the MET/CEN7 ratio, were eligible, providing they were not eligible for any other academic or industry trial evaluating another MET inhibitor. Study treatment consisted in crz 250 mg BID. The objective response rate (ORR) and disease control rate (DCR) were assessed every 8 weeks, using RECIST v1.1. **Results:** From Aug. 2013 to Dec. 2014, MET was prospectively analyzed in the tumors of 3,044 pts, and amplification (median copy number=7) was found in 100/1,358 lung, 19/591 colon, 5/275 ovary, 13/218 glioblastoma, 10/180 gastric, 1/63 hepatocarcinoma, 1/50 kidney and 0/11 thyroid. 46 pts were enrolled in the trial. Median age: 59 yrs (range 30–92), 65% males and 95% metastatic disease at study entry. 23 pts were still on treatment at the cut-off date, 23 have stopped crz (18 PD, 2 adverse events, 1 death, 2 others reasons). Among the 30 pts evaluable for response at 8 weeks, we observed 4 PR and 8 SD, leading to DCR=40% [95% CI: 23-59]. At 6 months, DCR=15% achieved in 4/26 evaluable pts (3 lung, 1 gastric). Crz was well tolerated with only 8 grade ≥3 adverse events (AEs) or SAE. Most common AEs, mainly grade 1, were fatigue (64 % pts), anemia (53%), ALAT and ASAT increased (both 53%) and visual disorders (50%). **Conclusions:** Nationwide biomarker-driven access to crz for pts with MET+ malignancy is feasible. Crz showed responses in MET+ lung. No response was observed in MET+ colon cancer. Clinical trial information: NCT02034981.

	Lung N=14	Colon N=10	Gastric N=2	Ovary N=2	Cholangiocarcinoma N=1	Other (urachus) N=1
PR	4					
SD	4	2	1			1
PD	6	8	1	2	1	

2596 Poster Session (Board #312), Sat, 8:00 AM-11:30 AM

STARTRK-1: Phase 1/2a study of entrectinib, an oral Pan-Trk, ROS1, and ALK inhibitor, in patients with advanced solid tumors with relevant molecular alterations. *First Author: Manish R. Patel, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL*

Background: Entrectinib (formerly RXDX-101), a potent and selective small molecule inhibitor of TrkA/B/C, ROS1, and ALK kinases, has demonstrated early clinical activity when orally administered intermittently under fasting conditions (ASCO 2014). In this abstract, we report a companion Phase 1/2a trial of entrectinib administered daily in the fed state. **Methods:** Pts with advanced solid tumors with molecular alterations in *NTRK1/2/3, ROS1* or *ALK* were treated daily with entrectinib in the fed state. Pts with asymptomatic untreated brain metastases were allowed; pts may have received prior TKI therapy. Endpoints include safety, RP2D, PK, and tumor response **Results:** Entrectinib was well tolerated across all dose levels. No DLTs or significant safety issues were reported from any cohort. Of 15 pts treated, the majority reported only G1 or G2 AEs. 3 pts reported > G3 AEs (each unrelated to entrectinib). 1 SAE (unrelated) has been reported. Entrectinib was readily absorbed with median T_{max} of 4 hr at steady state. Steady state was reached within 7 days of dosing and the estimated $t_{1/2}$ was approximately 17 hrs. There were dose proportional exposure increases with moderate accumulation (~2x or less) at steady state. 15 pts with various molecular alterations identified by local lab testing were treated in the following dose cohorts (mg/m^2): 100 (N = 5), 200 (N = 5), 400 (N = 5). Summary of alterations of enrolled pts: *NTRK* (point mutation = 5; amplification = 1; rearrangement = 1); *ROS1* (SNP = 1); *ALK* (SNP = 2; ampl = 1; rearr = 4). 3 pts with *ALK*-rearranged NSCLC failed at least 2 prior ALK inhibitors. No pts with *ROS1* rearrangements have been treated. No objective responses observed to date. **Conclusions:** Entrectinib, administered daily in fed condition, is well tolerated. In STARTRK-1, there have been no responses at doses ≤ 200 mg/m^2 (400 mg/m^2 cohort recently opened). Doses ≥ 400 mg/m^2 were associated with responses in the ALKA-372-001 Phase 1 study. Dose escalation will continue until the RP2D is identified. Thereafter, Phase 2a cohort expansion will begin enrolling pts with *NTRK1/2/3, ROS1*, or *ALK* molecular alterations to assess antitumor activity. Clinical trial information: NCT02097810.

2597 Poster Session (Board #313), Sat, 8:00 AM-11:30 AM

Phase I study of combination of crizotinib (C) and dasatinib (D) in patients (pts) with advanced cancer. *First Author: Shumei Kato, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Although C and D both demonstrate activity resistance can develop. Preclinical studies demonstrated that activation of MET requires c-SRC. We hypothesized that a c-SRC inhibitor (D), in combination with a MET inhibitor (C), may overcome resistance and demonstrate activity. This study is the first in-human attempt to combine C and D. **Methods:** This is a 2 arm concurrent phase I study (3+3) to determine the safety of oral C and D (Table). Arm A: C fixed at 250mg BID with escalation of D. Arm B: D was fixed at 140mg QD with escalation of C. Endpoints included MTD, DLT, RP2D at least 10 evaluable pts at MTD of each arm and response (RECIST 1.1). **Results:** 47 pts were enrolled. Median age was 59 yrs (16- 76), 3 median prior therapies (1 - 11). Most common cancers were prostate (21%) and sarcoma (19%). 27 pts in Arm A were enrolled. 10 pts were not evaluable: consent withdrawal (n=3) primarily for G2 AEs, missed doses <15% (n=7) primarily for early progression. Among 17 pts evaluable for DLT/AE (dose level [DL] 1 [n=13], DL2 [n=4]), 7 pts (41%) had at least one G3 drug-related AE with diarrhea (n=3) the most common AE. 2/4 pts had DLTs at DL2 (all G3; dehydration, infection, nausea, vomiting [n=1 each]). We expanded Arm A DL1 to determine the MTD with 1/13 pts with DLT (G3 esophageal pain). Arm B, 20 pts were enrolled. 6 pts were not evaluable: consent withdrawal (n=1), missed doses (n=5). Among 14 pts evaluable for DLT/AE (DL1 [n=10], DL2 [n=4]), 5 pts (36%) had at least one G3 drug-related AE with fatigue (n=3) being the most common. 2/4 pts had DLT at DL2 (G3 renal failure, G3 fatigue, G3 anorexia [n=1 each]). We expanded Arm B DL1 to determine the MTD with 2/10 pts with DLT (G3 fatigue [n=2]). Based on number of DLTs in the MTDs of each arm, our preliminary RP2D is DL1 on Arm A. 2 pts had PR (prostate [-34%] and uterine carcinosarcoma [-27%]) and 2 pts had SD ≥ 6 months (NSCLC [10.1] and melanoma [(+)14.4]). **Conclusions:** Preliminary RP2D for the combination is C (250mg PO BID) + D (50 mg QD). Responses have been observed and specific tumor and molecular expansions are ongoing. Clinical trial information: NCT01744652.

Arm A Crizotinib 250 mg BID	Dasatinib (mg)
DL 1	50 QD
DL 2	70 QD
DL 3	100 QD
DL 4	120 QD
DL 5	140 QD
Clinical trial information: NCT01744652.	
Arm B Dasatinib 140 mg QD	**Crizotinib (mg)**
DL 1	250 QOD
DL 2	200 QD
DL 3	250 QD
DL 4	200 BID
DL 5	250 BID

2598 Poster Session (Board #314), Sat, 8:00 AM-11:30 AM

A phase 1, open-label study to evaluate the safety and pharmacokinetics of the anti ErbB3 antibody, KTN3379, alone or in combination with targeted therapies in patients with advanced tumors. *First Author: Todd Michael Bauer, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: KTN3379 is a human monoclonal antibody against a unique epitope of human epidermal growth factor receptor-3 (ErbB3) blocking ligand (neuregulin (NRG)) dependent and independent activation. This trial assessed safety and pharmacokinetics (PK) of KTN3379 alone or with each of four targeted agents in advanced cancers and evaluated potential biomarkers of KTN3379 activity. **Methods:** Part I evaluated KTN3379 in a single agent dose escalation design. Part II evaluated KTN3379 with each of cetuximab, erlotinib, vemurafenib and trastuzumab in patients with refractory SCCHN, CRC, NSCLC, melanoma and HER2+ breast cancer (n = 6 each). Dose limiting toxicities (DLT) were evaluated in the first treatment cycle, RECIST tumor measurements every 3rd treatment cycle and PK and blood pharmacodynamic (PD) assessments each treatment cycle. Archival tumor tissue was evaluated for biomarkers and correlated with KTN3379 activity. **Results:** In Part I, no DLTs were observed in the 16 patients treated with KTN3379 at doses of 5 up to its maximally administered dose of 20 mg/kg IV every 3 weeks. PK parameters were linear, supported every 3-week dosing, and trough blood levels following dosing of KTN3379 at 10-20 mg/kg were consistent with maximum antitumor activity in preclinical models. Grade 3 or higher treatment related AE was reported in 1 patient (diarrhea). Other treatment related AEs were low grade diarrhea (n = 5), mucositis (n = 3), rash (n = 3), anemia (n = 2), and fatigue (n = 2). Patients in Part II to date had a similar profile, with low grade diarrhea, mucositis and rash being the most common AEs. In both Parts, elevations of soluble ErbB3 were noted after treatment. Other blood biomarkers and NRG expression are being evaluated. The best tumor response to date has been stable disease. **Conclusions:** Doses of 10-20 mg/kg exceed target blood concentrations. KTN3379 doses of 20 mg/kg with other targeted agents are safe and PK supports 3-week dosing. KTN3379 has the potential to benefit patients in combination with other targeted agents against ErbB family members, and NRG may be a predictive biomarker of response to KTN3379 in future studies. Clinical trial information: NCT02014909.

2599 Poster Session (Board #315), Sat, 8:00 AM-11:30 AM

Phase I study of temsirolimus in combination with cetuximab in patients with advanced solid tumors. *First Author: Antoine Hollebecque, Drug Development Department, Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France*

Background: Preclinical studies suggest that temsirolimus (T), an inhibitor of mammalian target of rapamycin (mTOR) combined with cetuximab (C), an anti-EGFR monoclonal antibody, may have synergistic antitumor effects. **Methods:** A dose escalation study was conducted to define the MTD and to characterize the pharmacokinetics and safety profile of T (30 min infusion) given 1 hour later after C (1 hour infusion) on a weekly schedule of a 28-day cycle. Five dose-levels were evaluated with dose range of T from 15 to 25 mg weekly and C from 150 to 250 mg/m^{2}weekly. Sequential biopsies were mandatory during the expansion cohort. **Results:** 39 patients (15M/24F), median age 57 years (range 38-76), previous number of lines 3 (range: 2-15) received the combination of T + C. The most common tumor types were colorectal (N = 6), breast (N = 5), uterine cervix SCC (N = 4) and NSCLC (N = 4). Three patients experienced dose limiting toxicities: grade 3 pulmonary embolism (at C 200 + T 20 level), grade 3 stomatitis (at C 250 + T 20 level) and grade 3 acneiform rash (at C 250 + T 25 level). The C 250 mg/m^{2}and T 25mg/week dose level was selected as the recommended dose. The most common treatment-related adverse events were (All grade/grade 3-4): rash acneiform (97%/15%), mucositis oral (82%/23%), fatigue (59%/13%), nausea (41%/0%) diarrhea (36%/0%), hypomagnesaemia (79%/5%), , and hyperglycemia (66%/10%). The median progression-free survival and overall survival were respectively 2.0 months 95%CI [1.8-3.5] and 7.5 months 95%CI [5.5-11.9]. Among all patients partial responses (PR) and stable diseases were observed in 2 (5.1%) and 18 pts (46.2%). Fifteen pts (38.5%) were treated because of a molecular aberration involving the EGFR and/or PIK3 pathways. Among molecularly selected patients (N = 16), 2 PR (12.5%) were observed (cervix scc with an EGFR amplification and head and neck cancer with a PIK3CA amplification) and 7 pts (44%) had a PFS upper 5.5 months. **Conclusions:** Tolerance of T + C was acceptable. Clinical activity was modest among all patients. Molecular selection increased the objective response rate. Pre and post-exposure biopsies are available in 20 patients and are currently been analyzed for pathway modulation and DNA structural changes. Clinical trial information: NCT02215720.

2600 Poster Session (Board #316), Sat, 8:00 AM-11:30 AM

A phase I study of temsirolimus plus erlotinib in patients with refractory solid tumors. *First Author: Andrea Wang-Gillam, Division of Oncology, Washington University in St. Louis, St. Louis, MO*

Background: Resistance to treatment with inhibitors of mammalian Target of Rapamycin (mTOR) is partially mediated by activation of epidermal growth factor receptor (EGFR). Based on pre-clinical evidence of synergy, we conducted a phase I study to determine the recommended phase II dose (RP2D) and dose-limiting toxicities (DLT) of temsirolimus (mTOR inhibitor) combined with erlotinib (EGFR inhibitor) in patients with refractory solid tumors. **Methods:** A classic 3+3 design was used for the dose escalation portion of the study. An expansion cohort at RP2D included only those with mutations that may contribute to PI3K or EGFR pathway activation or squamous histology. A cycle was defined as 28 days. Patients started daily erlotinib 7 days prior to starting temsirolimus on cycle 1. Intravenous temsirolimus was administered weekly. Starting dose levels were 15 mg temsirolimus and 100 mg erlotinib. **Results:** Forty-six patients were enrolled in this study (29 in dose escalation and 17 in the expansion cohort). Two patients experienced (DLTs) (grade 3 dehydration and grade 4 renal failure). The most common drug-related adverse events of all grades were rash, mucositis/stomatitis, diarrhea, nausea and fatigue. The RP2D is temsirolimus at a 25 mg weekly dose and 100 mg of daily erlotinib. No complete or partial responses were observed in the study. The median duration on this study was 77 days (range 15-770 days). Among 12 evaluable patients in the expansion cohort, 9 (75%) had stable disease and 3(25%) had progressive disease. The median duration on the study was 98 days (range 25- 243 days) for the expansion cohort. Clinical benefits were seen in patients with squamous cell histology; for example, a patient with refractory squamous cell cancer of the head and neck had durable disease control lasting 770 days. Stable disease was also observed in patients with specific genetic alternations; for example, a patient with refractory sarcoma with PTEN loss achieved stable disease of 194 days. **Conclusions:** The combination of temsirolimus and erlotinib at the RP2D is well tolerated, and the regimen resulted in prolonged disease stabilization in selected patients. Clinical trial information: NCT00770263.

TPS2601 **Poster Session (Board #317a), Sat, 8:00 AM-11:30 AM**

Pharmacodynamic study using FLT PET/CT in advanced solid malignancies treated with a sequential combination of X-82 and docetaxel. *First Author: Murtuza M. Rampurwala, University of Wisconsin, Madison, WI*

Background: Clinical experience has shown that despite resolution of tumor pain while on vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKI), pain not only returns, but increases during treatment break. We believe this is due to a *withdrawal flare* i.e. increased tumor proliferation after VEGFR TKI cessation driven by VEGF. We have previously demonstrated this *flare* using 18-Fluorothymidine (FLT) PET/CT. (Liu G et.al. Clin Cancer Res 2011;17:7634-44) A sequential approach synchronizing cell-cycle specific chemotherapy with this *withdrawal flare* may maximize therapeutic index of chemotherapy. Here we propose a novel sequential study using X-82, a VEGFR TKI with docetaxel using FLT PET/CT to measure change in vascular parameters and proliferation. We plan comparing low and high doses of X-82 to explore if low dose is preferable with chemotherapy. **Methods:** A phase 1 pharmacodynamic study in advanced solid malignancies is planned. Inclusion criteria include at least one lesion amenable to FLT PET/CT, ECOG performance status of $\leq$ 1 with normal organ and marrow function. 30 patients will be randomized 1:1 to low dose X-82 (200 mg) or high dose X-82 (400 mg) arm. In Cycle 1, X-82 is administered daily on days 2-15. FLT PET/CT (FLT 1) is obtained on day 1, once on day 12-15 (FLT 2) and day 19-21 (FLT 3). Comparison between FLT 1 and 2 will characterize response to X-82 and FLT 2 and 3 will characterize *withdrawal flare*. In Cycle 2, docetaxel (75 mg/m2) is administered on day 1, followed by X-82 on days 2-15. FLT PET/CT (FLT 4) once on day 12-15 will characterize response to X-82 and docetaxel. Sequential treatment is continued until progression or unacceptable toxicity. Correlative studies include VEGF levels and X-82 pharmacokinetics. Primary objectives are to evaluate safety, tolerability and FLT PET/CT changes with X-82 alone and with docetaxel. Secondary objectives include evaluating objective response rate to the combination. Toxicities will be monitored based on Pocock stopping boundaries with overall type I error of 0.10. At this time, 2 patients are enrolled on study. After establishing safety, we plan dose expansion cohorts in multiple disease sub-types. Clinical trial information: NCT02146222.

TPS2602 **Poster Session (Board #317b), Sat, 8:00 AM-11:30 AM**

A phase I study of a novel inhibitor of protein phosphatase 2A alone and with docetaxel. *First Author: Aaron Scott Mansfield, Mayo Clinc, Rochester, MN*

Background: Protein phosphatase (PP2A) is a multifunctional protein involved in regulation of cell cycle, DNA-damage response, and apoptosis. In pre-clinical studies, LB-100, a novel small molecule inhibitor of PP2A, inhibits the growth of a broad spectrum of leukemic and solid tumor cell lines. In cancer xenografts, LB100 potentiates the effectiveness of cytotoxic drugs (temozolomide, docetaxel, doxorubicin, cisplatin) and radiation without significant increases in toxicity. The predominant mechanisms responsible for potentiation are inhibition of mitotic exit and homologous recombination repair. PP2A inhibition also results in synthetic lethality of cancer cells overexpressing Mad2 (mitotic arrest deficiency protein 2) as a result of mutations in Rb and/or p53 pathways, suggesting that Mad2-overexpression may be a biomarker for LB100 responsiveness. In addition, cancers deficient in PP2A by somatic mutation such as (del)5q MDS are vulnerable to further PP2A inhibition, raising the possibility that other cancers with decreased PP2A resulting from increased endogenous PP2A inhibitors, CIP2A and SET, which include blast crisis CML, NSCLC (40%) and prostate cancers (60%), may also be vulnerable. PP2A has not been considered a practical target for anti-cancer therapy for concern of off-target effects. This trial seeks to determine appropriate doses of LB100 alone and LB100 plus docetaxel for phase II studies in (del)5q MDS and in cancers for which docetaxel is appropriate 2nd line treatment. **Methods:** This two-part phase I study aims to determine the MTD of LB100 alone given intravenously over 15 minutes daily for 3 days q3w and when given on the same schedule with docetaxel on day 2. In part 2, the starting dose of LB-100 is two levels lower than its single agent MTD combined with docetaxel at 60mg/m^2. LB100 is escalated to its MTD, and if tolerated, docetaxel is increased to 75mg/m^2 and LB-100 re-escalated. Eligible patients are $\geq$ 18 y with progressive or metastatic tumors having failed standard treatment. In part 2, patients are also docetaxel-naive. Enrollment through the 5th dose level of LB100 alone was completed in January 2015. Clinical trial: NCT01837667. Clinical trial information: NCT01837667.

TPS2603 **Poster Session (Board #318a), Sat, 8:00 AM-11:30 AM**

First-in-human, dose-escalation, safety, and PK study of a novel 5T4-ADC in patients with advanced solid tumors. *First Author: Geoffrey Shapiro, Dana-Farber Cancer Institute, Boston, MA*

Background: PF-06263507 is an anti-5T4 antibody drug conjugate (ADC) comprised of a humanized anti-5T4 IgG1antibody conjugated via cysteine residue to the microtuble disrupting agent monomethylauristatin F (MMAF) with a maleimidocaproyl (mc) linker. 5T4, also known as trophoblast glycoprotein (TPBG) is a cell surface protein, with over-expression observed in a variety of cancers as compared to normal adult tissue. PF-06263507 has demonstrated potent activity in human tumor xenograft models. **Methods:** PF-06263507 is being evaluated in an open-label study in patients with advanced solid tumors at increasing dose levels in cohorts of 2 to 4 patients. PF-06263507 is given intravenously once every 21 days. A modified continual reassessment method (mCRM) with a target dose limiting toxicity (DLT) rate of 25% is being utilized. Primary objectives include assessing the safety and tolerability of PF-06263507 in order to determine the maximum tolerated dose (MTD). Secondary objectives include evaluating the overall safety profile, characterization of pharmacokinetic (PK), evaluating the immunogenicity, and documenting any preliminary evidence of anti-tumor activity. Standard definitions are being used to classify hematological and non-hematological DLTs. Serum concentrations of ADC, total antibody, and unconjugated payload are measured with validated bioanalytical methods. Immunogenicity evaluation is performed with anti-drug antibody (ADA) assessment. Radiologic assessment of tumor burden is conducted every 6 weeks according to RECIST. Once the MTD is determined, expansion cohorts for patients with 5T4-expressing non-small cell lung cancer, breast cancer and ovarian cancer are planned. Accrual has completed in Cohort 1 (0.05 mg/kg) through Cohort 8 (5.4 mg/kg). The study is continuing to enroll patients at increasing dose levels. Clinical trial information: NCT01891669.

TPS2604 **Poster Session (Board #318b), Sat, 8:00 AM-11:30 AM**

A multicenter phase II basket clinical trial of lurbinectedin (PM01183) in selected advanced solid tumors. *First Author: Mariano Provencio Pulla, Hospital Puerta de Hierro, Madrid, Spain*

Background: PM01183 (lurbinectedin) is a new anticancer drug that binds to the DNA minor groove and blocks trans-activated transcription, inducing formation of double-strand DNA breaks leading to cell apoptosis. COMPARE analysis revealed that lurbinectedin's mechanism of action differs from the other 98 chemotherapy agents tested Advanced small cell lung cancer (SLCL), neuroendocrine tumors (NET), head and neck (H&N), biliary tract and endometrial carcinoma, BRCA1/2-associated metastatic breast cancer, carcinoma of unknown primary site, germinal cell tumors and Ewing family of tumors represent unmet medical needs. Cytotoxic chemotherapy remains a major component of their therapeutic armamentarium but new anticancer agents are needed to broaden clinical benefit. PM01183 has already shown clinical activity in BRCA1/2 breast cancer, SCLC, endometrial carcinoma, NET, H&N and in tumors with high proliferation index. This exploratory phase 2 trial has been designed to confirm the PM01183 anticancer activity, as a single agent, in several difficult-to-treat tumors. **Methods:** Primary objective: antitumor activity of PM01183 in terms of response rate by RECIST v.1.1, in the aforementioned indications. Secondary objectives: duration of response, clinical benefit, progression-free survival and 1-year overall survival in each tumor type. Pharmacokinetics, pharmacogenomic analyses of potential prognostic/predictive factors. Safety profile. Patients with each tumor type will be enrolled in nine cohorts. Up to 25 evaluable patients are planned to be recruited in each of them. To consider PM01183 active in the tumors analyzed, at least two confirmed responses in the 25 patients of each cohort are expected. If no responses are observed in the first 15 evaluable patients of each cohort, the accrual of this cohort will be stopped. If one confirmed response is observed in the first 15 evaluable patients, recruitment of this cohort will continue to 25 patients. Patients will receive PM01183 i.v. as a 1 hour infusion, every three weeks at a dose of 4 mg/m^2. In patients with ECOG PS = 2 or $>$ 70-years-old, dose will be 3 mg/m^2. Twenty six centers in 8 countries participate in this trial.

TPS2605 Poster Session (Board #319a), Sat, 8:00 AM-11:30 AM

A phase I study of RX-3117, an oral agent activated by uridine cytidine kinase 2, to treat subjects with advanced solid tumors. *First Author: Drew Warren Rasco, START Center for Cancer Care, San Antonio, TX*

Background: RX-3117 is an oral small-molecule antimetabolite, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117's efficacy in xenograft models (Colo-205, H460, H69 and CaSki), which are moderately sensitive or resistant to gemcitabine, indicates that RX-3117 may have the potential to treat tumors that do not respond to gemcitabine or have become gemcitabine resistant. **Methods:** This phase I, open-label, multicenter study evaluates the efficacy and safety of RX-3117 in subjects with solid tumors). RX-3117 is administered 3 times a week for 3 weeks with 1 week off during each 4 week cycle. Dose escalation starts with an accelerated design treating 1 subject per dose followed by a standard 3 + 3 design using a modified Fibonacci sequence after the occurrence of a single related Grade 2 or greater adverse event. The primary endpoint is the overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapy of any adverse events, or abnormalities of laboratory tests or electrocardiograms, any dose limiting toxicities that occur during Cycle 1, serious adverse events, or adverse events leading to study treatment discontinuation. Secondary endpoints include pharmacokinetic parameters (e.g., time to maximum observed concentration [T_{max}], maximum observed plasma concentration [C_{max}], trough concentration [C_{trough}], area under the concentration-time curve [AUC]) and Indices of anti-tumor activity (e.g., overall response rate , time to response, duration of response, and progression-free survival). Exploratory endpoints are baseline biomarker expression/concentration, including (but not limited to) concentrative nucleoside transporter 2; equilibrative nucleoside transporter 1; uridine-cytidine kinase 1 and 2; DNA methyltransferase 1, 3a and 3b; and ribonucleotide reductases 1 and 2. Target recruitment is approximately 30 subjects. Eligible subjects must have confirmed histologic or cytologic evidence of metastatic or locally advanced solid neoplasm that has failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. Clinical trial information: NCT02030067.

TPS2606 Poster Session (Board #319b), Sat, 8:00 AM-11:30 AM

A phase I, dose-escalation, multi-center study of PFK-158 in patients with advanced solid malignancies explores a first-in-man inhbibitor of glycolysis. *First Author: Rebecca A. Redman, James Graham Brown Cancer Center, University of Louisville, Louisville, KY*

Background: In human cancers, activation of the MAP kinase and PI3K/PTEN/AKT pathways converge to increase the expression and activity of a potent regulator of glycolysis, 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase (PFKFB3). This enzyme synthesizes fructose-2,6-bisphosphate (F2,6BP), which is an activator of PFK-1, a key enzyme of glycolysis that is tightly controlled by multiple metabolic feedback mechanisms and dictates the overall rate of glycolytic flux to lactate and the TCA cycle. PFK158 is a potent small molecule inhibitor of PFKFB3 that is selectively cytotoxic to cancer cells and displays broad anti-tumor activity causing significant growth inhibition in preclinical models of breast, lung, glioblastoma, ovarian, pancreatic, melanoma and colon cancer. In addition, because resistance mechanisms frequently activate pathways that result in up-regulation of glycolysis, combination treatments with cytotoxic and targeted agents result in increased efficacy and tumor regressions. Importantly, IND-enabling safety and toxicity studies have demonstrated that PFK158 is well tolerated in rats and dogs resulting in an acceptable pre-clinical therapeutic index. **Methods:** The primary objective of this phase I clinical trial is to describe the dose limiting toxicity of PFK158 and to determine either the maximum tolerated dose or biological effective dose of PFK-158 in a "3+3" cohort-based dose escalation design that follows a modified Fibonacci scheme. Multiple secondary endpoints have been incorporated to assess the effects of PFK-158 on peripheral blood mononuclear cell F2,6BP activity, and on glucose uptake using FDG-PET imaging. This trial is currently enrolling at four US sites; Cohort 3 (96 mg/m^2) has been completed without dose-limiting toxicity and Cohort 4 (168 mg/m^2) has been enrolled as of February 2015. In conclusion, PFK158 is a first-in-human and first-in-class PFKFB3 inhibitor that is currently under evaluation in a phase I trial and is expected to have significant clinical utility either as a monotherapy or when combined with other targeted agents. Clinical trial information: NCT02044861.

TPS2607 Poster Session (Board #320a), Sat, 8:00 AM-11:30 AM

Phase I study of procaspase activating compound-1 (PAC-1) in the treatment of advanced malignancies. *First Author: Oana C. Danciu, University of Illinois at Chicago, Chicago, IL*

Background: Members of the caspase family of cysteine proteases are key players in both the initiation and execution of apoptosis; the activation of procaspase-3 to caspase-3 is a critical event in the apoptotic cascade. Procaspase-3 levels are elevated in: glioblastoma, breast cancer, colon cancer, lung cancer, lymphoma, neuroblastoma, melanoma, and liver cancer. As a consequence, caspase-3 levels are abnormally low in these tumors, allowing the tumors to avoid apoptosis. PAC-1 is a small molecule that activates procaspase-3 and induces apoptosis of cancer cells in culture. PAC-1 showed efficacy across a wide range of cancer cell lines, as well as in animal models of cancer, including brain cancer. This novel compound potently synergizes with chemotherapy agents (e.g.doxorubicin, temozolomide, etoposide, carboplatin). **Methods**: This is a Phase I dose escalation study with a modified- Fibonacci 3+3 design, consisting of two parts: to determine the maximum tolerated dose (MTD) of PAC-1 in advanced malignancies, and to determine the MTD of PAC-1 when combined with temozolomide in patients with primary brain tumors. For both parts the MTD dose level will expand to a total of 9 patients to ensure safety. Primary objectives: establish MTD, tolerability and toxicity. Secondary and correlative objectives: pharmacokinetics, pharmacodynamics, preliminary antitumor activity correlation with procaspase-3 expression in tumor, clinical response and adverse effects. Neurological symptoms of CNS toxicity will be assessed throughout the trial. Inclusion criteria: diagnoses of advanced malignancies (for part 1) and high grade glioma (for part 2), ECOG PS 0-2, adequate organ function. Exclusion criteria: received prior cytotoxic therapy in the last 3-6 weeks (duration based on prior therapy) or uncontrolled chronic illness. Administration and design: Part 1, PAC-1 (PO) will be dosed at 75-450 mg daily (up to 5 dose levels) on days 1-21 on 28 days cycle. In Part 2, the first PAC-1 dose will be 1 dose lower than the PAC-1 MTD established in Part 1 (up to 3 dose levels).Temozolomide (PO) will be dosed at 150 mg/m2 daily for 5 days starting on day 8 of each cycle. The study is open to enrollment. Clinical trial information: NCT02355535.

TPS2608 Poster Session (Board #320b), Sat, 8:00 AM-11:30 AM

A phase 1 study of RX-5902, an oral agent targeting phosphorylated p68, to treat subjects with advanced solid tumors. *First Author: S. Gail Eckhardt, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO*

Background: RX-5902 is a novel compound that targets phosphorylated p68 RNA helicase (also known as DDX5), a member of the DEAD box family of RNA helicases. Phosphorylated p68 may play a vital role in cell proliferation and tumor/cancer progression. As a single agent, RX-5902 inhibits tumor growth and enhances survival in a variety of in vivo animal xenograft tumor models (e.g., renal, ovarian, pancreatic, melanoma). **Methods:** This Phase 1, open-label, multicenter study evaluates the efficacy and safety of RX-5902 in subjects with solid tumors. RX-5902 is administered orally once weekly for 3 weeks with 1 week of rest in each 4 week cycle. Dose escalation starts with an accelerated design treating 1 subject per dose followed by a standard 3 + 3 design using a modified Fibonacci sequence after the occurrence of a single Grade 2 or greater adverse event that is considered at related to RX-5902. The primary endpoint is the overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapy of any adverse events, or abnormalities of laboratory tests or electrocardiograms as well as the description of any dose limiting toxicities that occur during Cycle 1, serious adverse events, or adverse events leading to discontinuation of study treatment. Secondary endpoints include pharmacokinetic parameters (e.g., time to maximum observed concentration [T_{max}], maximum observed plasma concentration [C_{max}], trough concentration [C_{trough}], area under the concentration-time curve [AUC]) and Indices of anti-tumor activity (e.g., overall response rate , time to response, duration of response, and progression-free surviva during treatment. Exploratory endpoints are biochemical levels of drug targets in blood and tumor samples. Eligible subjects must have confirmed histologic or cytologic evidence of metastatic or locally advanced solid neoplasm that has failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens. Clinical trial information: NCT02003092.

TPS2609 **Poster Session (Board #321a), Sat, 8:00 AM-11:30 AM**

A phase Ib study of investigational pan-RAF kinase inhibitor MLN2480 plus investigational TORC1/2 inhibitor MLN0128, investigational Aurora A kinase inhibitor alisertib (MLN8237), or paclitaxel in patients (pts) with advanced solid tumors. *First Author: Anthony J. Olszanski, Fox Chase Cancer Center, Philadelphia, PA*

Background: Signaling hyperactivation secondary to MAPK pathway aberrations are common. RAF kinases play key roles in the RAS/RAF/MEK/ERK signaling cascade, representing potentially valid therapeutic targets**.** In a phase 1 study, single-agent MLN2480 had an acceptable safety profile, expected pharmacodynamic effects and preliminary antitumor activity (Middleton et al, ENA 2014, Abstract 364). Preclinically, MLN2480 has shown synergistic/additive effects in xenograft models and cell lines when combined with MLN0128, alisertib or the taxane, docetaxel. Potential overlapping toxicities of each combination are expected to be manageable, with no apparent risks for clinically meaningful pharmacokinetic (PK) drug–drug interactions based on *in vitro* ADME data and exposures achieved clinically. **Methods:** This three-arm, open-label study (NCT02327169) is the first-in-human study for MLN2480 + MLN0128/alisertib/paclitaxel. Primary objective is to evaluate the safety, tolerability, and MTD of each combination. Secondary objectives are to characterize PK profiles and preliminary antitumor activity. An exploratory objective is to assess tumor samples and circulating tumor DNA for biomarkers of response/resistance. Pts aged ≥ 18 yrs with radiographically/clinically evaluable advanced solid tumors who failed standard therapies are eligible. Pts in the expansion phase require tumors measurable by RECIST v1.1. MAPK pathway aberrations are not required. Pts will receive MLN2480 100–200 mg (d 1, 3, 5 per week) in 28-d cycles plus: (A) MLN0128 2–9 mg (d 2, 3, 4 per week), (B) alisertib 30–50 mg twice daily (d 1–3, 8–10, 15–17) or (C) paclitaxel 80 mg/m^2 (d 1, 8, 15) for up to 12 cycles. Serial blood samples will be taken in cycle 1 for PK evaluation. A 3+3 dose escalation algorithm, based on cycle 1 DLTs, will be used, with up to 20/20/15 pts in groups A/B/C. Enrollment is ongoing. Once MTDs are established, ≥ 1 combination regimens will be selected for the expansion phase (~16 pts per group) based on safety, exposure and preliminary antitumor activity data. Clinical trial information: NCT02327169.

TPS2610 **Poster Session (Board #321b), Sat, 8:00 AM-11:30 AM**

STM-01: Phase I EFFTox study of aurora A kinase inhibitor alisertib (MLN8237) given in combination with selective VEGFR inhibitor pazopanib for therapy of solid tumors. *First Author: Arkadiusz Z. Dudek, University of Illinois at Chicago, Chicago, IL*

Background: Pazopanib is a potent and selective multi-targeted tyrosine kinase inhibitor targeting VEGF, PDGF and C-KIT and inhibits angiogenesis and tumor growth. Alisertib is a highly selective small molecule inhibitor of Aurora A kinase which may result in disruption of the assembly of the mitotic spindle apparatus and cell proliferation inhibition. At highest non-toxic concentrations, mitosis targeting agents may reduce endothelial activity and consequently, exhibit antiangiogenic activity. By this way they can enhance the antiangiogenic effects of VEGF inhibitors as well as complement anti-tumor activity, making combination therapy clinically useful to treat advanced refractory malignancies. **Methods:** This is a Phase I dose escalation study with a modified toxicity probability interval design to evaluate activity and safety of alisertib when given in combination with pazopanib to patient with advanced, previously treated solid tumors and hematologic malignancies. The primary objectives of this study are to determine the optimal tolerated dose, safety and toxicity. Secondary objectives are to establish PK/PD and preliminary antitumor activity. **Inclusion Criteria:** ECOG PS 0-2, good organ function and a rest period of 2-6 weeks fromprior systemic chemotherapy, immunotherapy, or biological therapy. **Administration and Design:** Alisertib is taken orally, twice a day for the first 7 days of a 21-day cycle. Pazopanib is taken orally, once a day, continuously. Since study opened in July 2013, 26 patients have been enrolled, so far 16 of them have been on treatment. Study is continuing accrual at dose of alisertib 30 mg twice a day for 7 days and pazopanib 600 mg daily for 21 days. Clinical trial information: NCT01639911.

TPS2611 **Poster Session (Board #322a), Sat, 8:00 AM-11:30 AM**

A randomized Phase 2a study to assess pharmacodynamics, antitumor activity and safety of intravenous BAL101553, a novel microtubule inhibitor, at two dose levels in adult patients with selected advanced solid tumors. *First Author: Rebecca Sophie Kristeleit, University College London, London, United Kingdom*

Background: BAL101553 is the pro-drug of BAL27862, a novel small-molecule microtubule-targeting agent with potent activity in drug-refractory tumor models. It exerts antiproliferative effects and dose-dependent vascular disruption, acting as a tumor checkpoint controller by modulating the spindle assembly checkpoint (SAC). In a Phase 1 dose escalation study pharmacodynamic (PD) effects were observed in post-treatment tumor biopsies[1]. The maximum tolerated dose (MTD) was determined at 60 mg/m^2 IV (intravenous), however clinical activity was observed at dose levels of 15-30 mg/m^2. A non small cell lung cancer (NSCLC) xenograft mouse model showed similar BAL27862 tumor exposure (AUC) at the MTD and a sub-MTD dose, with 11-fold higher peak intratumoral levels at the lower dose. Thus, enhanced vascular disruption at high BAL101553 doses may be associated with lower intratumoral drug disposition. The goal of this Phase 2a study is to assess the pattern of antivascular and antiproliferative effects and antitumor activity at two BAL101553 dose levels. **Methods:** This is an ongoing multicenter randomized, open-label Phase 2a study (NCT01397929) to assess PD, antitumor activity and safety of BAL101553. Eligible patients (pts) with advanced colorectal, gastric, pancreatic, ovarian, NSCLC or triple negative breast cancers are randomized to either 60 (MTD) or 30 mg/m^2 BAL101553 as a 2-h IV infusion on day(d) 1, 8 and 15 q28d. PD evaluations include serial collection of circulating tumor cells (CTCs), circulating endothelial cells and circulating endothelial progenitor cells. Pts with lesions amenable to biopsy will be asked to undergo pre- and post-dose biopsies. Biomarkers analyzed in CTCs and tumor biopsies include BubR1, a protein kinase involved in the SAC and a potential biomarker for BAL101553 activity. Antivascular effects will be quantified by dynamic-contrast enhanced MRI in a subset of pts. Tumor response will be assessed every 2 cycles using RECIST 1.1. Forty pts will be enrolled into this Phase 2a study, which started in June 2014. [1]Molife LR et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 2562) Clinical trial information: NCT01397929.

TPS2612 **Poster Session (Board #322b), Sat, 8:00 AM-11:30 AM**

Phase I study of ADI-PEG 20 in combination with pemetrexed and cisplatin (TRAP) in patients with ASS1-deficient mesothelioma and non-squamous lung cancer. *First Author: Peter Wojciech Szlosarek, St Bartholomew's Hospital, London, United Kingdom*

Background: Loss of the metabolic tumor suppressor, argininosuccinate synthetase (ASS1), a rate-limiting enzyme in arginine biosynthesis, sensitizes mesothelioma and lung carcinoma cells to apoptosis following arginine withdrawal. Recently, we showed potentiation of the cytotoxic effect of pemetrexed by the arginine depletor pegylated arginine deiminase (ADI-PEG 20) in ASS1-negative tumor cells, which was accompanied by suppression of *de novo* pyrimidine synthesis and the pyrimidine salvage pathway (Allen et al, Cancer Res 2014). Consequently, we have initiated a phase I study (NCT02029690) to assess the maximum tolerated dose (MTD), safety and toxicity, and preliminary efficacy of ADI-PEG 20 combined with first-line pemetrexed and cisplatin chemotherapy in patients with ASS1-deficient mesothelioma or non-squamous non-small cell lung cancer (NSCLC). **Methods:** Up to 47 good performance (ECOG 0-1) patients are being enrolled in a 3+3+3 phase 1 design using tumoral ASS1 loss as a selection biomarker. Weekly ADI-PEG 20 is being dose escalated (18, 27 and 36 mg/m^2 IM), with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 both given every 3 weeks, for a maximum of 18 weeks of treatment. Cohorts 1 and 2 have been completed without dose-limiting toxicity and enrollment to cohort 3 began in January 2015 at the maximum ADI-PEG 20 dose of 36mg/m^2. A further 10 patients with mesothelioma and 10 patients with non-squamous NSCLC will be recruited at the MTD with pharmacodynamic monitoring of response using plasma arginine and citrulline, and assessment of tumor proliferation with [(18)F]-fluoro-L-thymidine (FLT)-positron emission tomography (PET). In summary, TRAP is the first triplet chemotherapy combination study to assess the role of arginine deprivation with ADI-PEG 20 in solid cancers using ASS1 as a selection biomarker. Patient accrual at the MTD cohort is nearing completion and ADI-PEG 20 in combination with cisplatin and pemetrexed will be evaluated further in the planned expansion cohorts. Clinical trial information: NCT02029690.

TPS2613 Poster Session (Board #323a), Sat, 8:00 AM-11:30 AM

A phase 1, dose-escalation, safety, pharmacokinetic, pharmacodynamic study of thioureidobutyronitrile, a novel p53 targeted therapy, in patients with advanced solid tumors. *First Author: Geoffrey Shapiro, Dana-Farber Cancer Institute, Boston, MA*

Background: Thioureidobutyronitrile, Kevetrin, induced apoptosis in wild type p53, mutant p53 and p53 null cell lines. In A549 lung carcinoma cells, wild type p53 was stabilized by Kevetrin. Kevetrin induced nongenotoxic activation of the p53 signaling pathway. Kevetrin also induced p21 and PUMA, known transcriptional targets of p53. Kevetrin caused accumulation of monoubiquitinated p53 and induced transcriptional independent apoptosis. In p53 mutant breast carcinoma cells (MDA-MB-231), Kevetrin induced degradation of hyperstable oncogenic mutant p53 and induced apoptotic cell death. Apoptotic cell death was also induced in K-562, a p53 null CML cell line. Consistent with *in vitro* data, Kevetrin showed potent antitumor activity in wild type p53 (A549), mutant p53 (MDA-MB-231), and p53 null (K-562) human tumor xenograft models. Kevetrin has the unique ability to target both wild type and mutant p53 tumors controlling tumor growth in various preclinical tumor models (ASCO 2013). Based on the pre-clinical data, a Phase I study was initiated at Dana-Farber/Harvard Cancer Center in 2012. **Methods:** Adults with refractory locally advanced or metastatic solid tumors, acceptable liver, kidney function, and hematologic status were eligible. Objectives include determination of DLT, MTD, pharmacokinetics, pharmacodynamics, and evaluating preliminary evidence of antitumor activity. Kevetrin is given as an intravenous infusion once weekly for 3 weeks in 28-day cycles. The starting dose was 10 mg/m^2. In a 3+3 design, groups of 3-6 patients are evaluated for toxicity at each dose level. Dose escalation is based upon the number and intensity of adverse events in cycle 1. Kevetrin PK is characterized for the first and last doses given in cycle 1. Kevetrin induced p21 in lymphocytes preclinically; therefore p21 expression in peripheral blood mononuclear cells is measured as a PD biomarker. Antitumor activity by RECIST 1.1 criteria and serum tumor markers is assessed. The p53 status of tumors of selected patients will be determined. The first nine cohorts were completed in December 2014. Enrollment in the tenth cohort at 450 mg/m^2 began January 2015. Clinical trial information: NCT01664000.

TPS2614 Poster Session (Board #323b), Sat, 8:00 AM-11:30 AM

Phase I trial of the combination of bortezomib and clofarabine in adults with refractory solid tumors. *First Author: Geraldine Helen O'Sullivan Coyne, Early Clinical Trials Development Program,, Bethesda, MD*

Background: We conducted a systematic combination drug screen across the NCI-60 cell line panel encompassing nearly all pairwise combinations of FDA-approved small-molecule cancer drugs ($>$ 5000) using multiple, clinically-achievable drug concentrations to discover efficacious combinations that could be advanced rapidly into clinical trials (Eur J. Cancer 2012 Nov;48, Suppl 6:11). The proteasome inhibitor bortezomib combined with the nucleoside inhibitor clofarabine was found to be supra-additive in multiple cell lines. Several solid tumor xenograft models were used to confirm enhanced responses to this combination than to the individual single agents at their Maximum Tolerated Doses (MTDs), with the combination displaying either prolonged tumor stasis or regression. Because both bortezomib and clofarabine have individually demonstrated to enhance tumor cell apoptosis *in vitro*, we investigated the role of alterations in the apoptotic pathway in producing the observed supra-additive efficacy for the bortezomib/clofarabine combination *in vivo*. We found that the combination significantly enhanced caspase-3 activation and decreased survivin levels in xenografts using our recently-validated 15-plex apoptosis ELISA. **Methods**: We are conducting an open label phase I trial (NCT02211755) of the bortezomib/clofarabine combination, following a 3+3 trial design, with Dose Limiting Toxicities (DLT) defined during cycle 1. Estimated enrollment: 35 patients. Bortezomib is administered subcutaneously on days 1 and 4 of a 21-day cycle. Clofarabine is administered intravenously over 1 hour on days 1-5 of a 21-day cycle. Patients must have histologically confirmed solid tumors that have progressed on standard of care therapy known to prolong survival or for which no standard treatment exists, an ECOG $\leq$ 2 and life expectancy $\geq$ 3 months. Exclusion criteria include a prolonged QTc interval (Fridericia formula) at study entry. Patients with treated brain metastasis whose disease is stable for $\geq$ 4 weeks without requiring steroids or anti-seizure medication are eligible. At this time, cohort 1 has enrolled 1 of 3 planned patients; accrual is ongoing with measurement of apoptosis biomarkers at the MTD. Clinical trial information: NCT02211755.

TPS2615 Poster Session (Board #324a), Sat, 8:00 AM-11:30 AM

First-in-human investigation of the oral first-in-class fatty acid synthase (FASN) inhibitor, TVB-2640. *First Author: Andrew Jacob Brenner, The University of Texas Health Science Center at San Antonio, Boerne, TX*

Background: FASN is a central mediator of neoplastic lipogenesis. It catalyzes the production of palmitate, the building block of long chain fatty acids needed to support cancer cell signaling and proliferation. Tumor cells have more dependence on *de novo* lipogenesis than normal cells, and express higher levels of FASN. Several studies have shown a correlation between high levels of FASN expression and both advanced disease stage and poorer prognosis in patients. The combination of these observations provides the rationale for FASN inhibition as an antitumor therapy. TVB-2640 is a potent, reversible and selective fatty acid synthase (FASN) inhibitor currently in its first Phase 1 study (3V2640-CLIN-002) in patients with refractory solid tumors (NCT02223247), EORTC 2014 Abstract number: 3 LBA. **Methods:** TVB-2640 is administered in monotherapy orally once daily continuously on a 21 day cycle to assess dose-limiting toxicities (DLT). An accelerated dose-escalation method was used initially with single-patient cohorts and 100% dose escalations planned until NCI-CTCAE toxicity $\geq$ Grade 2 was encountered. Thereafter, the classical "3 + 3" design was used. Additionally, exploration of combination therapy using TVB-2640 co-administered with a taxane has begun. Eligibility includes adult patients with adequate bone marrow, hepatic and renal function and other standard Phase I characteristics. Patients with significant cardiovascular, ophthalmological disease, or any conditions that might interfere with oral absorption are excluded. In addition to standard safety assessments and pharmacokinetic (PK) sampling (over 24 hours on Days 1 and 8), specialist ophthalmological examinations and 24-hour Holter monitoring for QTc assessments are required. Tumor tissue (archival and/or fresh) is being obtained to assess the consequences of FASN inhibition on neoplastic lipogenesis and a pharmacodynamic effect has been evaluated by measuring metabolite changes in patient sera. Clinical trial information: NCT02223247.

TPS2616 Poster Session (Board #324b), Sat, 8:00 AM-11:30 AM

Phase 1 dose-escalation study of EBC-46 given by intratumoral injection to patients with refractory cutaneous and subcutaneous tumors. *First Author: Jason D. Lickliter, Nucleus Network, Melbourne, Australia*

Background: EBC-46 is a novel protein kinase C (PKC) activator being developed for intratumoral treatment of cutaneous and subcutaneous tumors. Studies in syngeneic and xenograft mouse models showed that intratumoral injection of EBC-46 into subcutaneous tumors resulted in PKC-dependent hemorrhagic necrosis within 24 hours and complete loss of viable tumor cells. Immunostaining of tumor tissue for the endothelial marker CD31 showed marked vascular disruption at 24 hours after treatment (Boyle GM, et al. PLoS ONE 2014; 9: e108887). EBC-46 is also being studied in veterinary clinical trials in companion animals as an intratumoral treatment for spontaneous skin tumors. Notably, EBC-46 therapy leads to rapid healing at treated sites in animals and the mechanism of this is currently under investigation (Campbell J, et al. Proc ETRS 2014). **Methods:** This is a phase 1 first-in-human dose-escalation trial of intratumoral injection of EBC-46 in patients with cutaneous and subcutaneous tumors refractory to standard therapies. Other key eligibility criteria include an ECOG score of 0-2, adequate organ function, no involvement of major blood vessels by the tumor and no therapeutic anticoagulation or major abnormality of hemostasis. The starting dose of EBC-46 is 0.06 mg/m^2, which is prepared as a 0.25 mg/mL solution and infiltrated into a tumour volume 2-fold greater than the EBC-46 volume. Initial dose escalations are based on increasing the concentration of the EBC-46 solution until a maximum concentration is reached. Subsequent dose levels will inject higher volumes of EBC-46 solution into a correspondingly greater target tumour volume. Patients who tolerate the first dose, and who are deemed to be benefiting from treatment, will continue intratumoral injections in an extension protocol. Study endpoints include safety and tolerability parameters (local and systemic), pharmacokinetics of EBC-46 and preliminary efficacy assessments. Blood samples will be evaluated for biomarkers of vascular disruption and inflammation, and optional tumor biopsies will be performed pre- and post-treatment. Enrolment into the first dose level commenced in January 2015. Clinical trial information: ACTRN12614000685617.

TPS2617 **Poster Session (Board #325a), Sat, 8:00 AM-11:30 AM**

Phase II study of the PARP inhibitor talazoparib (BMN-673) in advanced cancer patients with somatic alterations in BRCA1/2, mutations/deletions in PTEN or PTEN loss, a homologous recombination defect, mutations/deletions in other BRCA pathway genes and germline mutation S in BRCA1/2 (not breast or ovarian cancer). *First Author: Sarina Anne Piha-Paul, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cancer cells deficient in BRCA1/2 and other components of the homologous recombination repair pathway are selectively sensitive to the double stranded DNA breaks whose repairs are inhibited by poly (ADP-ribose) polymerase (PARP) inhibitors, and in particular PARP inhibitors with "trapping" properties. Talazoparib tosylate, a potent oral "trapping" PARP1/2 inhibitor, exhibits selective anti-tumor cytotoxicity at far lower concentrations than other PARP inhibitors. Multiple ongoing trials are evaluating PARP inhibitor efficacy in patients with germline BRCA mutations. There is, however, a great need to define the spectrum of patients who may benefit. **Methods:** This is an investigator-initiated, single-center, non-randomized, multi-cohort trial of subjects >18 years old with measurable advanced solid tumors with no curative therapeutic options. Up to 180 patients will be treated with talazoparib at 1 mg PO daily following a two stage design with futility assessment at ten patients in each cohort with a maximum enrollment of thirty patients in each cohort. Patients will be enrolled in one of 6 cohorts: 1) Somatic mutations of BRCA1/ 2, 2) Somatic deletions of BRCA1/2, 3) Mutations or homozygous deletions in other BRCA pathway genes (e.g. ATM, PALB2, NBS1, Fanconi Anemia genes), 4) Mutations or homozygous deletions in PTEN and/or PTEN loss by IHC, 5) HR defects (Myriad HRD assay LOH >40), 6) Germline BRCA1/2 mutations (not breast or ovarian cancer). Primary endpoint is clinical benefit rate (CR, PR or SD>24 weeks). Secondary endpoints include baseline molecular and pharmacodynamics markers, concordance of BRCA1/2 alterations and HRD status, concordance of genomic alterations in tumor and circulating free DNA, progression free survival, duration of response, and overall survival. Statistical plan includes descriptive statistics, Kaplan Meier techniques and Cox proportional hazard modeling. Enrollment has already commenced. Clinical trial information: NCT 02286687.

TPS2618 **Poster Session (Board #325b), Sat, 8:00 AM-11:30 AM**

A phase I trial of veliparib, an inhibitor of poly(ADP-ribose) polymerase (PARP), and topotecan (TPT) in patients with solid tumors. *First Author: Andrea Elisabeth Wahner Hendrickson, Mayo Clinic, Rochester, MN*

Background: PARPs are a highly conserved family of enzymes whose predominant function is to preserve genomic integrity following DNA damage. Preclinical studies demonstrated that PARP inhibitors enhance the cytotoxicity of DNA damaging agents. Specifically, PARP inhibition sensitizes tumor cells to topotecan in vitro and in vivo by trapping PARP1 on damaged DNA and preventing repair of topo I-induced DNA damage (Patel *et al.*, J. Biol. Chem. 287:4198, 2012). Veliparib has been combined with daily topotecan but found to be quite myelosuppressive, requiring reduction in doses of both agents (Kummar *et al.*, Cancer Res. 71:5626, 2011). Based on these data, we sought to determine the maximum tolerated dose (MTD) of veliparib in combination with the less myelosuppressive weekly administration of topotecan in patients with solid tumors. Correlative studies were included to assess the impact of topotecan and veliparib on poly(ADP-ribose) levels in peripheral blood mononuclear cells as well as the pharmacokinetics of both agents. **Methods:** Eligible patients include any histologically confirmed solid tumor malignancy that is metastatic or unresectable with measurable disease (longest diameter > 2 cm with conventional CT) in patients 18 or older who have received < 2 chemotherapy regimens, ECOG PS < 2 and adequate bone marrow, renal and hepatic function. Using a standard 3+3 design, patients have been treated with veliparib PO twice daily on days 1-3, 8-10 and 15-17 and topotecan IV on days 2, 9 and 16 every 28 days. The trial is currently enrolling at veliparib 300 mg PO twice daily and topotecan 3 mg/m^2/dose. Once MTD is established, a phase II clinical trial in platinum resistant ovarian, peritoneal and fallopian tube malignancies is planned. Supported in part by UM1 CA186686 and P50 CA136393. Clinical trial information: NCT01012817 Clinical trial information: NCT01012817.

TPS2619 **Poster Session (Board #326a), Sat, 8:00 AM-11:30 AM**

A phase I trial of oral 5-azacitidine in combination with romidepsin in advanced solid tumors with an expansion cohort in virally mediated cancers and liposarcoma. *First Author: Kim Anna Reiss, Johns Hopkins Univ, Batimore, MD*

Background: Epigenetic alterations leading to silencing of tumor-suppressor genes play a key role in carcinogenesis and are reversible, therefore representing an appealing anti-cancer target. Hypermethylation of promoter regions by DNA methyltransferases (DNMTs) and deacetylation of histones by histone deacetylases (HDACs) are two mechanisms by which tumor suppressors are silenced. DNMT and HDAC inhibitors have been shown to reverse this process in multiple tumor types. Preclinically, combination DNMT and HDAC inhibition can synergistically re-express tumor suppressor genes and inhibit tumor growth in xenograft models. Emerging work shows that epigenetic agents modulate genes involved in viral response. We designed a phase I dose-escalation trial of oral 5-azacitidine (CC-486) and romidepsin in advanced solid tumors with an expansion cohort in virally mediated cancers and liposarcoma. **Methods:** We have enrolled 11 patients to date. Patients must have a metastatic or unresectable solid tumor or, for the expansion cohort, a known virally mediated cancer (e.g. EBV+ nasopharyngeal cancer, HPV+ head and neck, cervical, or anal cancer) or liposarcoma and must have failed at least one prior line of chemotherapy. Patients are enrolled in a standard 3+3 design. Toxicity is followed using the NCI CTCAE version 4.0 and disease response is followed using RECIST 1.1 criteria with serial imaging q8weeks. In the expansion cohort, patients will have paired biopsies as well as blood work for PK and PD analysis. Correlative work includes global and candidate gene methylation analysis of plasma samples and biopsy specimens. Potential candidate genes include: p16, SFRP1, TFP1, IGFBP3, EVL, CD109 and SOX17. Clinical trial information: NCT01537744.

TPS2620 **Poster Session (Board #326b), Sat, 8:00 AM-11:30 AM**

Phase I/II study of PF-06463922, an ALK/ROS1 tyrosine kinase inhibitor, in patients with advanced non-small-cell lung cancer harboring specific molecular alterations. *First Author: Todd Michael Bauer, Tennessee Oncology and Sarah Cannon Research Institute, Nashville, TN*

Background: Lung cancer is the most common cancer worldwide, with non-small cell lung cancer (NSCLC) occurring in 85% of cases. Oncogenic fusions of anaplastic lymphoma kinase (ALK) or c-ros oncogene 1 (ROS1)–receptor tyrosine kinase inhibitors (TKIs) define 2 distinct subsets of NSCLC patients (pts) and play essential roles in tumor cell survival, growth, and metastasis. While most biomarker-selected pts derive some clinical benefit from initial treatment with a TKI, most will eventually develop resistance. PF-06463922 is a selective TKI of ALK and ROS1 that preclinically demonstrated dose-dependent inhibition of mutations that confer resistance to treatment with other TKIs. As the central nervous system (CNS) is a common site of metastases in these pts and PF-06463922 is a brain-penetrant compound, it is hypothesized that PF-06463922 will also be active in pts with CNS metastases. **Methods:** This ongoing, single-arm, phase I/II trial (NCT01970865) is evaluating the safety, pharmacokinetics, and efficacy of PF-06463922 in pts with advanced ALK+ or ROS1+ NSCLC with or without CNS metastases. In all, 22 pts have been enrolled in Phase I and, thus far, PF-06463922 has demonstrated clinical activity in ALK+ and ROS1+ NSCLC pts, most of whom had CNS metastases and had received at least 1 prior TKI. Phase II was designed to assess efficacy across 4 distinct populations: ALK+ pts who are treatment-naïve, ALK+ pts with progression after crizotinib, ALK+ pts with progression after 1 or 2 prior TKI, and ROS1+ pts in any line of treatment. All pts must have at least 1 measurable extracranial lesion by RECIST v1.1. Pts with asymptomatic CNS metastases, leptomeningeal disease, or carcinomatous meningitis are eligible. The starting dose for phase II will be identified in phase I. Correlative biomarker studies on blood and tumor tissue (archival tissue and de novo biopsies) will be performed. Five of the 75 planned sites are open and recruiting. For more information, visit ClinicalTrials.gov or contact Pfizer Oncology at 1-800-718-1021. Clinical trial information: NCT01970865.

TPS2621 Poster Session (Board #327a), Sat, 8:00 AM-11:30 AM

A first-in-human phase I/Ib study of receptor tyrosine kinase (RTK) inhibitor, MGCD516, in patients with advanced solid tumors. *First Author: Gary K. Schwartz, Columbia University Medical Center, New York, NY*

Background: MGCD516, is an orally-available, potent small molecule inhibitor of a closely related family of RTKs including RET, TRK family, DDR2, MET, Axl family, KIT, as well as VEGFR and PDGFR family members. RTKs inhibited by MGCD516 are genetically altered in a variety of cancers, including non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC), functioning as oncogenic drivers promoting cancer development and progression. Alterations in these RTKs have also been implicated in tumor resistance mechanisms. MGCD516 has demonstrated broad antitumor activity including demonstration of tumor regression in preclinical models harboring genetic dysregulation of MGCD516 targets including MET amplification, METex14del, RET rearrangement and CHR4q12 amplification. **Methods:** This first-in-human, open label Phase 1/1b study is designed to evaluate the safety, pharmacokinetics, metabolism, pharmacodynamics and clinical activity of MGCD516 in patients with advanced solid tumors. Phase 1 is the dose escalation phase and uses the modified toxicity probability interval (mTPI) method to determine the MTD /Recommended Phase 1b Dose. Phase 1b is the expansion phase in which MGCD516 will be evaluated in patients with NSCLC, HNSCC, or any other solid tumor type harboring specific MGCD516 RTK target mutations of interest. Phase 1 and 1b are each anticipated to enroll 60 patients. Phase 1 enrollment started in September 2014, with patients receiving continuous daily dosing (QD) of 10mg MGCD516 in cycles of 21 days. Cohort 1 and Cohort 2 (QD 20mg) have been completed without DLTs and enrollment to Cohort 3 (QD 40mg) started in January 2015. Pharmacokinetics is evaluated after single and repeated administration. Pharmacodynamic biomarkers, including soluble (s)MET, sVEGFR2 and VEGFA will be explored in plasma samples for prognostic potential and possible relationship with clinical outcome. Clinical trial information: NCT02219711.

TPS2622 Poster Session (Board #327b), Sat, 8:00 AM-11:30 AM

A randomized, open-label, Phase II trial evaluating the clinical benefit of a maintenance treatment targeting tumor molecular alterations in patients with advanced solid tumors. *First Author: Maud Toulmonde, Institut Bergonié, Department of Medical Oncology, Bordeaux, France*

Background: Therapeutic decision for most cancers is mainly based on primary disease site, histological type and/or tumor burden. However, genotype-driven clinical trials where treatments are adapted to the molecular alteration supposed to drive tumor progression have recently emerged with promising early results (e.g. BATTLE, SAPHIR01/02, SHIVA, ...). **Methods:** MOST (My Own Specific Therapy) is a multicenter, randomized, open-label, adaptive phase II trial conducted in patients (pts) with progressive solid tumors (any subtype) after at least one prior therapy in the advanced setting. This trial aims to evaluate the clinical benefit of maintenance therapy targeting molecular alterations identified in the patient's tumor. Primary endpoint is progression-free survival. Secondary endpoints include toxicity, objective response rate (RECIST1.1) and overall survival. Based on the presence of molecular alterations detected by a previous tumor molecular profiling, pts are treated with one of the following targeted therapies: nilotinib (400 mg BID for ABL1, KIT, PDGFRA/B, DDR1/2, CSF1R mut/amp/transloc.); everolimus (10 mg QD for PIK3CA, PIK3R1, AKT1/2, mTOR mut/amp or TSC1/2 or PTEN loss); sorafenib (400 mg BID for VEGFR1-3, PDGFRB, FLT3, BRAF, CRAF, KRAS or RET mut/amp/transloc); lapatinib (1500 mg QD for HER2 mut/amp) or pazopanib (800 mg QD for VEGFR1-3, PDGFRA/B or KIT mut/amp). After 12 weeks of treatment, pts with objective response are proposed to continue the targeted therapy, while pts with stable disease are randomly assigned (1:1) to continuation (arm A) or interruption of treatment (arm B; reintroduction is allowed at disease progression). Statistical analysis will be carried out in each of the 5 treatment groups using a sequential Bayesian approach. Three interim analyses are planned after randomization of 10, 15 and 20 pts per arm. The trial will continue until the maintenance arm is shown with high posterior probability to be superior to the interruption arm according to a pre-defined stopping rule, or until the maximum sample size (i.e. 50 pts) is reached. To date, 66 of 400 planned patients have been enrolled. Clinical trial information: NCT02029001.

TPS2623 Poster Session (Board #328a), Sat, 8:00 AM-11:30 AM

First-in-human dose escalation study of oral ONC201 in advanced solid tumors. *First Author: Mark N. Stein, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: ONC201 is an orally active first-in-class small molecule with strong antitumor activity in preclinical models of advanced cancers. In cancer cell lines and patient samples ONC201 induces an integrated stress response (Ishizawa et al, 2014), late-stage inactivation of Akt and ERK, and downstream activation of the apoptotic TRAIL pathway as part of innate immune surveillance (Allen J et al, Sci Trans Med, 2013). Activity is independent of p53 status. ONC201 is well tolerated at efficacious doses in animal models, crosses the blood brain barrier, is particularly effective in refractory tumors, depletes cancer stem cells (Ishizawa et al, ASH 2014; Prabhu et al, Blood 2014; Zhao et al, ASCO 2014), and is effective with infrequent dosing preclinically. Based on the compelling efficacy and safety profile of ONC201 as well as the engagement of signaling pathways critical for many cancers, the clinical introduction ONC201 in advanced cancer patients is warranted. **Methods:** The first-in-human study of ONC201 (NCT02250781) began in January 2015 as an open-label single-site phase I trial enrolling adult patients with refractory advanced solid tumors and glioblastoma (GBM). Patients with symptomatic brain metastases or prior bevacizumab for treatment of GBM are excluded. The primary endpoint is determination of the recommended phase II dose (RP2D) of single agent ONC201 given orally once every 3 weeks (1 cycle). Secondary endpoints include assessment of pharmacodynamics using select biomarkers for ONC201 (Allen et al, 2015), pharmacokinetics, toxicity, and efficacy. The study employs an accelerated, single patient per cohort, dose escalation design with expansion to a standard 3+3 design if a subject has grade $>/=$ grade 2 toxicity or dose limiting toxicity within cycle 1. The maximum tolerated dose is the highest dose level in which 6 patients have been treated with $</=1$ instance of DLT. A subject in Cohort 1 (125mg) has completed the first cycle of treatment without any $>/=$ grade 2 toxicity. Cohort 2 (250mg) is currently enrolling. This phase I study will identify the RP2D to enable evaluation of the antitumor efficacy of ONC201 in select advanced cancer indications. Clinical trial information: NCT02250781.

TPS2624 Poster Session (Board #328b), Sat, 8:00 AM-11:30 AM

A first-in-human study of LOXO-101, a highly selective inhibitor of the tropomyosin receptor kinase (TRK) family. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: TheTRK family of neurotrophin receptors, TRKA, TRKB, and TRKC (encoded by *NTRK1, NTRK2,* and *NTRK3* genes, respectively) and their neurotrophin ligands regulate growth, differentiation and survival of neurons. Translocations involving the *NTRK1/2/3* kinase domain, mutations involving the TRK ligand-binding site, amplifications of *NTRK*, TRK splice variants, and autocrine/paracrine signaling have been described in a diverse number of tumor types and may contribute to tumorigenesis. Recently *NTRK1* fusions were described in a subset of adenocarcinoma lung cancer patients (Vaishnavi, 2013) and *NTRK2 and NTRK3* fusions have been described in multiple tumor types (Skalova, 2014; Ricarte-Filho, 2013; Vaishnavi, 2014). LOXO-101 is a potent, oral, ATP-competitive pan-TRK inhibitor with IC_{50} values in the low nanomolar range for inhibition of TRK family members in binding and cellular assays, with 100x selectivity over other kinases. LOXO-101 has demonstrated tumor inhibition in preclinical models. **Methods:** This study (NCT02122913) is an ongoing phase Ia/Ib dose escalation plus expansion trial in adults with advanced solid tumors. The phase Ia component is an open-label, multicenter, dose escalation trial. Patients with solid tumors refractory to standard therapy, with normal hematopoietic and major organ function are eligible for study. LOXO-101 is administered orally QD or BID for continuous 28-day cycles. This component of the trial will determine the MTD for LOXO-101. The phase Ib component is an open-label, multicenter, global, dose expansion study. In addition to the Phase Ia eligibility criteria, patients must have a demonstrated alteration in one of the three *NTRK* genes or three TRK proteins. The number of expansion cohorts will be determined by the molecular characteristics of the tumors in the patients enrolled. Data will provide initial evidence of tumor activity of LOXO-101, stratified by the type of *NTRK* or TRK alteration or tumor type, as well as further elucidation of the safety profile of LOXO-101 in cancer patients. Archival tissue is required for further characterization of molecular abnormalities. Clinical trial information: NCT02122913.

3000 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Atypical patterns of response in patients (pts) with metastatic melanoma treated with pembrolizumab (MK-3475) in KEYNOTE-001. *First Author: Jedd D. Wolchok, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immune-related response criteria (irRC) were developed to better characterize the atypical response patterns observed with ipilimumab. Previously, we showed that 7.2% of melanoma pts treated with the anti–PD-1 monoclonal antibody pembrolizumab also demonstrate atypical response patterns and that irRC may better represent the clinical benefit of pembrolizumab than conventional RECIST. This updated analysis includes all 655 melanoma pts enrolled in KEYNOTE-001 (NCT01295827). **Methods:** Pts received pembrolizumab 2 mg/kg every 3 wk (Q3W), 10 mg/kg Q3W, or 10 mg/kg Q2W. Imaging was performed every 12 wk. Response was assessed centrally by irRC and RECIST v1.1. Investigator-assessed irRC was used for pt management. Early pseudoprogression was defined as ≥25% increase in tumor burden at first assessment that was not confirmed as progressive disease (PD) per irRC at the next assessment performed ~4 wk later. Delayed pseudoprogression was defined as ≥25% increase in tumor burden at any time point after the first assessment, followed by non-PD at the next assessment. **Results:** Of the 655 pts enrolled, 327 had ≥28 wk of follow-up by imaging at the time of analysis and were assessed for atypical responses. Overall, 29 pts (8.9%) experienced atypical response. Early pseudoprogression was observed in 15 (4.6%) pts. Late pseudoprogression was observed in 14 (4.3%) pts. In the 592 pts who survived ≥12 wk, 331 (56%) had best overall response of non-PD per RECIST and irRC, 177 (30%) had PD per both criteria, and 84 (14%) had PD per RECIST v1.1 but non-PD per irRC. OS was longer in pts with PD per RECIST but non-PD per irRC compared with those who had PD by both criteria (Table). **Conclusions:** Results of this expanded analysis are consistent with previous reports suggesting that pembrolizumab may result in atypical response patterns and that conventional response criteria may underestimate the therapeutic benefit of pembrolizumab in advanced melanoma. New standards such as irRC or irRECIST should be considered for assessing response to immunotherapy. Clinical trial information: NCT01295827.

	OS	
	12-mo Rate, %	24-mo Rate, %
Non-PD by RECIST and irRC (n = 331)	92.1	77.6
PD by RECIST, non-PD irRC (n = 84)	74.4	37.5
PD by RECIST and irRC (n = 177)	33.5	17.3

3001 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. *First Author: Antoni Ribas, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA*

Background: Immunotherapy with anti–PD-1 monoclonal antibodies such as pembrolizumab shows robust, durable antitumor activity in patients with advanced melanoma. Examining gene expression related to the immune response within the tumor may provide new insights into the molecular features associated with clinical response to these agents. We evaluated immune-related gene expression patterns in patients with melanoma enrolled in the phase Ib KEYNOTE-001 study. **Methods:** Baseline tumor biopsy samples from 19 patients with melanoma enrolled in KEYNOTE-001 were used as a discovery set. Results were validated using samples from 62 additional patients from KEYNOTE-001, of whom 51 were evaluable for response per RECIST v1.1 by central review. RNA was extracted from formalin-fixed paraffin-embedded tissue sections and analyzed using the NanoString nCounter. Two signatures, the "Interferon-gamma [IFNγ] 10-gene" and the "Expanded-immune 28-gene," were pre-specified prior to linking NanoString data to clinical outcomes. **Results:** The overall response rate (ORR) was 47% in the validation cohort. Both the IFNγ and the expanded-immune signatures showed statistically significant associations with ORR ($P = 0.047$ and 0.027, respectively) and progression-free survival ($P = 0.016$ and 0.015). Analysis of top-ranked genes on the platform led to the discovery of two new signatures, "TCR-signaling" and "Denovo" that were enriched in T-cell markers and MHC Class I and II genes. **Conclusions:** Measuring immune-related biomarkers, including T-cell specific, antigen presentation–related, and IFNγ signaling–related genes, may allow for improved selection of patients likely to respond to anti–PD-1 therapy with pembrolizumab. Results are consistent with the hypothesis that clinical responses to PD-1 blockade occur in patients with a preexisting interferon-mediated adaptive immune response. Further confirmation of these new signatures in melanoma is required. Clinical trial information: NCT01295827.

3002 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Density of immunogenic antigens and presence or absence of the T cell-inflamed tumor microenvironment in metastatic melanoma. *First Author: Thomas Gajewski, The University of Chicago, Chicago, IL*

Background: Patients with melanoma can be categorized based on the presence or absence of a T cell-inflamed tumor microenvironment. The presence of baseline $CD8^+$T cells is associated with clinical benefit to immunotherapies, including anti-PD1 and anti-CTLA4. The molecular mechanism explaining lack of a T-cell infiltrate in a major subset are poorly understood, but differential expression of immunogenic antigens has been proposed as one explanation. **Methods:** Using the TCGA data set for malignant melanoma, the T cell-inflamed gene expression signature was used to segregate patients by immune phenotype. Three categories of antigens were examined: cancer-testis (CT) antigens, differentiation antigens, and somatic mutational antigens. **Results:** By transcriptional profiling, no difference was observed in levels of CT antigens or differentiation antigens. Using exome sequencing of tumor versus germline, a range of 18 to 3001 of non-synonymous mutations was observed in both cohorts. Using the syfpeithi algorithm for HLA-A*0201 patients, a median of 123 mutations having a high immunogenicity score were found in the T cell-inflamed cohort versus 176 in the non-T cell inflamed. To confirm actual immunogenicity, several synthesized peptides show positive HLA-A*0201 binding and can be recognized by human $CD8^+$T cells in vitro. **Conclusions:** Both the T cell-inflamed and non-T cell-inflamed subsets of melanoma show comparable expression of CT, differentiation, and mutational antigens. Lack of spontaneous immune infiltration in a major subset of tumors is unlikely to be due to lack of antigens. Strategies that improve spontaneous T-cell infiltration into tumors therefore could, in principle, render these patients response to immunotherapies once these antigens become recognized.

3003 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Phase I study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma. *First Author: Antoni Ribas, UCLA, Los Angeles, CA*

Background: Inhibition of the MAPK pathway with dabrafenib (D) and trametinib (T) is efficacious in BRAF-mutant melanoma. MEK inhibitors have also shown activity in BRAF WT melanoma, particularly in NRAS-mutant tumors. However, most patients (pts) develop resistance to D and T. MEDI4736 (M), a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity, has shown clinical activity with durable responses and an acceptable safety profile in multiple tumor types. Combined therapy with these agents may lead to enhanced durable tumor responses. **Methods:** A phase I, multicenter, open-label study (NCT02027961) evaluating the safety and efficacy of M at 3 or 10 mg/kg IV every 2 weeks (q2w) in combination with D 150 mg twice daily + T 2 mg daily, or T alone in pts with stage IIIc/IV melanoma. Pts enroll by BRAF status into dose escalation cohorts (3+3 design), followed by dose expansion: BRAF mutant in Cohort A (M+D+T); BRAF WT in Cohort B (M+T) or Cohort C (sequential T→M). Prior BRAF/MEK inhibitors were prohibited; prior immunotherapy was allowed, including anti-PD-1/anti-PD-L1 therapy. **Results:** As of December 5, 2014, 50 pts were treated. DLTs were observed in 1 pt in Cohort A1 (reversible grade [G] 3 thrombocytopenia) and 1 pt in Cohort B (reversible G3 choroidal effusion). No MTD was identified; M 10 mg/kg q2w was selected for expansion in all cohorts. The most frequent drug-related adverse events (AEs) by cohort were: pyrexia (63%) and fatigue (54%) (Cohort A); diarrhea (30%) and rash (25%) (Cohort B); and vomiting (67%) (Cohort C). 2 pts discontinued due to drug-related AEs (DLTs above). Clinical activity to date is shown below. Most responses are ongoing (range of duration: 0.1+ - 32+ wk). **Conclusions:** M can be combined with T ± D at full doses with a manageable safety profile, and evidence of clinical activity in BRAF-mutant and WT melanoma. Clinical trial information: NCT02027961.

Cohort	n	Any AE (%)	Related AE (%)	Related G ≥ 3 AE (%)	CR/PR (n/n)[a]	SD (n/n)[a]
A1 (3 mg/kg M + D + T)	6	100	100	17	6/6	0/6
A2 (10 mg/kg M + D + T)	18	94	94	39	10/15	5/15
B (10 mg/kg M + T)	20	90	85	40	3/14	6/14
C (sequential T + 10 mg/kg M)	6	100	100	17	3/6	1/6

[a]Includes pts with ≥ 1 follow up scan or discontinuation due to PD or death prior to first scan (confirmed and unconfirmed CR/PR).

3004 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

A phase I study of PF-05082566 (anti-4-1BB) + rituximab in patients with CD20+ NHL. *First Author: Ajay K. Gopal, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: 4-1BB agonists enhance cytotoxic T-cell and NK cell responses, including antibody-dependent cellular cytotoxicity, resulting in anti-tumor activity in preclinical models. PF-05082566 (PF-566), a fully humanized IgG2 monoclonal antibody, activates 4-1BB while blocking binding to endogenous 4-1BBL. **Methods:** This Phase I study evaluated PF-566 in doses ranging from 0.03-10 mg/kg in combination with 375 mg/m^2 rituximab (R) in patients (pts) with relapsed or refractory CD20+ NHL. Patients were treated using a Time-To-Event Continuous-Reassessment-Method design. Pts received PF-566 from D1 Q4 weeks up to 24 mo. and R from D-7 Q1W X4. The 1° endpoint was first 2-cycle DLT with PK/PD, safety, and anti-tumor activity as 2° endpoints. **Results:** 35 pts with CD20 + NHL were treated with PF-566 combined with R: Follicular (FL) (n = 22), mantle cell (MCL) (n = 5), diffuse large B cell (n = 3), marginal zone (n = 2), small lymphocytic (n = 2) and nodular lymphocyte predominant Hodgkin's (n = 1), 34 (97%) with prior R, and 20 (57%) with R-refractory disease. The median number of prior regimens was 3 (range of 1 - 9). No DLTs were observed and no pts discontinued treatment due to treatment-related AEs. The MTD was estimated as ≥ 10 mg/kg. No severe immune-related AEs were observed. PK data show a dose proportional increase in exposure and a half-life of ~10 days. Increases in soluble 4-1BB, memory T cells, and activated NK cells were observed. For pts up to 2.4 mg/kg (higher doses under evaluation for efficacy), the ORR was 21% (6/28), and in R-refractory pts the ORR was 29% (4/14), with 2 CR (0.03 and 0.12 mg/kg, both FL) with a duration of response > 2 years and 2 PR (FL and MCL). Enrollment into an expansion cohort is ongoing. The PFS for all of the R-refractory responders was > 6 mo and for all R-refractory pts the 6 mo PFS rate was 66% by Kaplan-Meier. **Conclusions:** PF-05082566 in combination with rituximab was well tolerated, with anti-tumor activity in R-refractory NHL patients, along with biomarker modulation consistent with 4-1BB agonist activity. In these R-refractory patients, the durability of anti-tumor activity appeared greater than their previous therapy. Further clinical studies of this combination in R-refractory indolent NHL patients are warranted. Clinical trial information: NCT01307267.

3005 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Phase I study of RG7155, a novel anti-CSF1R antibody, in patients with advanced/metastatic solid tumors. *First Author: Carlos Alberto Gomez-Roca, Institut Claudius Regaud, Department of Medicine, Toulouse, France*

Background: Tumor associated macrophages (TAM) suppress anti-tumor immunity and have been associated with poor prognosis in several types of cancer. CSF-1 is a critical survival and differentiation factor for TAM. Preclinically, TAM depletion has been shown to enhance/restore the activity of several clinically established treatment modalities and also novel immunotherapies. Here, we report on the phase I study of a monoclonal antibody (RG7155) that blocks the dimerization interface of the CSF1 receptor (CSF1R). **Methods:** In this dose-escalation and extension study, patients with advanced solid tumors or locally advanced pigmented villonodular synovitis (PVNS, a CSF1-driven "model disease" for clinical investigation of CSF1R targeting approaches) received RG7155 IV at dose levels between 100 – 3000mg Q2W. Primary objectives were to assess safety, tolerability, pharmaco-kinetics and –dynamics. Clinical activity was evaluated using FDG-PET (at 4 weeks after treatment start; EORTC criteria) and CT/MRI (every 6 weeks; RECIST 1.1). PD markers in pre- and on-treatment biopsies of tumor and surrogate skin tissue as well as peripheral blood were analyzed. **Results:** To date, data is available for 44 patients with solid tumors and 29 patients with PVNS. RG7155 treatment led to significant reduction of CSF1R$^+$ and CD68/CD163$^+$ macrophages in tumor and surrogate skin tissue and rapid elimination of CD14^{Dim}CD16^{Bright} peripheral monocytes. In solid tumors, partial metabolic responses (FDG-PET) and disease stabilization were observed in 5/44 and 6/40 patients, respectively. 24/28 patients with PVNS experienced an objective response (best time point response). RG7155 was well tolerated. The MTD was not reached. Grade 3/4 AEs assessed as related to RG7155 were reported in 18% of patients (21/114). Most frequent AEs (any grade) were asthenia (70% of patients), peripheral edema (44%) and pyrexia (27%). **Conclusions:** RG7155 was well tolerated and biologically highly active. RG7155 is now being tested as a promising combination partner with immunotherapies (e.g. Phase Ib study (NCT02323191) in combination with Mab-PDL1 (MPDL3280A) is ongoing). Clinical trial information: NCT01494688.

3006 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Immunotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells of defined subset composition. *First Author: Cameron John Turtle, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Genetically modified T cells derived from distinct T cell subsets differ in the capacity to persist after adoptive transfer. We are conducting the first phase I/II clinical trial in which patients (pts) with CD19$^+$ B cell malignancies receive T cells comprised of a defined composition of CD8$^+$ T$_{CM}$ and CD4$^+$ T cells engineered to express a CD19 CAR. **Methods:** CD8$^+$ T$_{CM}$ and CD4$^+$ T cells were separately enriched from each patient, transduced with a CD19 CAR lentivirus and expanded in vitro. The cell product for infusion was formulated in a 1:1 ratio of CD8$^+$:CD4$^+$ CAR$^+$ T cells and infused at one of three dose levels ($2x10^5$ – $2x10^7$ CAR-T cells/kg) after lymphodepleting chemotherapy. **Results:** Thirty-seven pts with ALL (n = 20), NHL (n = 14) or CLL (n = 3) have been treated and 33/37 received a product that conformed to a prescribed CD8$^+$:CD4$^+$ composition. There was no serious acute infusional toxicity. Severe cytokine release syndrome (sCRS) consisting of fever, hypotension, coagulopathy and neurotoxicity associated with elevated serum IFN-γ and IL-6 was only observed in ALL pts with high tumor burden. One ALL patient treated at the highest cell dose died of complications associated with sCRS. No NHL or CLL pts had sCRS. Eighteen of 20 ALL pts were evaluated for response, with 15 (83%) achieving complete marrow remission by high resolution flow cytometry. Clinical responses in NHL included complete (n = 1) or partial (n = 6) remission in 7/13 pts. Two of 3 CLL pts achieved marrow remission by flow cytometry. The peak level and duration of persistence of both CD4$^+$ and CD8$^+$ CAR-T cells were associated with clinical response. We are investigating the impact of distinct lymphodepletion regimens on CAR-T cell proliferation and persistence in vivo. A T cell immune response to the murine CD19-specific scFv component of the CAR transgene was detected in a subset of pts with limited CAR-T cell persistence. **Conclusions:** Adoptive immunotherapy with CD19 CAR-T cells of defined subset composition is feasible and safe in a majority of heavily pretreated pts with refractory B cell malignancies and has potent anti-tumor activity at low cell doses. CAR-T cell doses for phase II studies in ALL and NHL cohorts have been determined. Clinical trial information: NCT01865617.

3007 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Safety and antitumor activity of chimeric antigen receptor modified T cells in patients with chemotherapy refractory metastatic pancreatic cancer. *First Author: Gregory Lawrence Beatty, Hosp of the Univ of Pennsylvania, Philadelphia, PA*

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterized by an immunosuppressive microenvironment with a scarcity of effector T cells. Adoptive T cell therapy to restore anti-tumor immunity has demonstrated promise in several advanced malignancies. However, its role in PDAC remains to be established. This Phase I study was performed to determine the safety and feasibility of administering autologous T cells genetically modified with a chimeric antigen receptor (CAR) that recognizes mesothelin overexpressed on PDAC. **Methods**: Patients (ECOG 0-1; adequate organ function) with chemotherapy refractory metastatic PDAC (> 1 prior chemotherapy) were treated with autologous T cells engineered using *in vitro* transcribed mRNA to transiently express a mesothelin-specific CAR that includes both CD3-zeta and 4-1BB co-stimulatory domains. CAR T cells were infused 3 times per week for 3 weeks. The primary endpoint was to determine safety and manufacturing feasibility. Secondary endpoints were to measure clinical and immune responses. **Results**: 10 patients were enrolled (6 treated, 2 withdrew due to progressive disease prior to treatment, 1 manufacturing failure, 1 did not complete apheresis necessary for manufacturing). 53 of 54 (98%) planned CAR T cell infusions were administered without dose limiting toxicity. Infusions were well tolerated without evidence of cytokine release syndrome, pleuro-pericarditis or peritonitis. Treatment-related grade > 3 toxicities included abdominal pain (1) and back pain (1). CAR T cells were transiently detected in the peripheral blood after infusion. Two of six patients experienced stable disease by RECIST 1.1 with disease control off therapy seen in one patient for > 4 months. The change in SUV$_{max}$ of all lesions for each patient detected on ^{18}FDG-PET/CT imaging performed before and 1 month after beginning treatment was -1.9% (95% CI: -25.5% to 21.7%). In one patient, abnormal ^{18}FDG avidity seen in liver metastases at baseline was no longer detected at 1 month after therapy. **Conclusions**: Mesothelin-redirected CAR T cell therapy is well tolerated and shows preliminary evidence of antitumor efficacy in PDAC. Clinical trial information: NCT01897415.

3008 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Autologous HER2 CMV bispecific CAR T cells for progressive glioblastoma: Results from a phase I clinical trial. *First Author: Nabil M. Ahmed, Texas Children's Hosp Baylor Coll Of Medcn, Houston, TX*

Background: Glioblastoma (GBM) remains virtually incurable. T-cell therapy holds the promise to improve outcomes for GBM patients since it does not rely on the cytotoxic mechanisms of conventional therapies. We have shown in preclinical studies that HER2 and CMV are potential T-cell therapy targets for GBM. **Methods:** We report the initial results of the phase I clinical study, NCT01109095, administering autologous CMV.pp65 T cells grafted with a second generation HER2 chimeric antigen receptor (CAR; with a CD28.zeta signaling domain) to patients with progressive GBM. **Results:** Sixteen CMV-seropositive patients with HER2-positive GBM and radiological evidence of progression aged 11-70 (median age 49) were enrolled. Autologous HER2-CAR CMV T cells were successfully generated for all patients from a peripheral blood draw (maximum 90mL). T-cell products contained HER2-CAR expressing T cells as judged by FACS analysis (median: 67% (range: 46-82) %), and CMV.pp65-specific T cells as judged by IFN-gamma Elispot assays (median 985.5 (range 390 to 1292) SFC/10^5 T cells). Infusions of $1x10^6/m^2$, $3x10^6/m^2$, $1x10^7/m^2$, $3x10^7/m^2$ or $1x10^8/m^2$HER2-CAR.CMV-T cells were well tolerated without systemic side effects and no dose limiting toxicity was observed. HER2-CAR CMV T cells were detected in the peripheral blood for up to 12 weeks post infusion as judged by real-time PCR of a CAR-specific amplicon. Out of fifteen evaluable patients, 10 had progressive disease. Five out of fifteen patients had objective responses: 1 patient had a partial response with a ~62% reduction in tumor volume lasting 8 months, 1 patient had stable disease lasting 4 months and 3 patients have stable disease and are currently alive with a follow up of 18 to >24 months, after T cell infusion. **Conclusions:** This initial evaluation of the safety and efficacy of autologous HER2-CAR CMV bispecific T cells in patients with progressive GBM shows that infusions are safe and that cells could persist for up to 12 weeks in the peripheral blood. Clinical benefit was observed in 33% of patients setting the stage for studies that combine HER2-CAR CMV T cells with other immunomodulatory approaches to enhance their expansion and anti-GBM activity. Clinical trial information: NCT01109095.

3009 Poster Discussion Session; Displayed in Poster Session (Board #335), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Pembrolizumab (MK-3475) plus low-dose ipilimumab (IPI) in patients (pts) with advanced melanoma (MEL) or renal cell carcinoma (RCC): Data from the KEYNOTE-029 phase 1 study. *First Author: Michael B. Atkins, Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Pembrolizumab is a potent, highly selective, humanized monoclonal antibody against PD-1 that has shown robust antitumor activity against several advanced malignancies. In phase 1 testing, combination therapy with the anti–PD-1 antibody nivolumab and full-dose IPI (3 mg/kg) was seemingly associated with improved response rates but also increased toxicities (*NEJM* 2013;369:122-33). Here, we report the phase 1 data of concurrent administration of pembrolizumab and low-dose IPI in pts with advanced MEL or RCC. **Methods:** KEYNOTE-029 (NCT02089685) is a phase 1/2 study of pembrolizumab plus IPI or pegylated interferon alfa-2b (PEG-IFN). Assessment of the safety and tolerability of pembrolizumab plus PEG-IFN is ongoing. Safety and tolerability of pembrolizumab 2 mg/kg plus low-dose IPI 1 mg/kg every 3 weeks (Q3W) for 4 doses, followed by pembrolizumab 2 mg/kg Q3W for up to 2 years, were assessed. Dose confirmation continued until 18 pts completed the 6-wk observation period (Cycle 1). DLTs were evaluated in pts who completed the first cycle of combination therapy or who discontinued due to a treatment-related AE. The dose would be considered tolerable if ≤6 pts experienced DLTs. Toxicities were graded by CTCAE v4.0. Response is assessed at wk 12, every 6 wk thereafter until wk 30, and every 12 wk thereafter. **Results:** DLTs were observed in 6 of 19 evaluable pts (2 of 9 RCC pts, 4 of 10 MEL pts). All DLTs were of grade 3 severity. Two pts experienced 2 DLTs each: elevation of pancreatic enzymes and hyperthyroidism in 1 patient and lipase elevation and pneumonitis in another patient. The remaining DLTs were ALT/AST elevation (n = 2), colitis (n = 1), and uveitis (n = 1). Responses have been observed in MEL and RCC pts. Additional safety and preliminary efficacy data will be available for presentation. **Conclusions:** Pembrolizumab and low-dose IPI combination therapy was considered to have an acceptable safety profile in this initial safety run-in period. Based on these results, we have initiated a protocol-specified, single-arm expansion cohort to further evaluate the safety, tolerability, and preliminary efficacy of this combination in advanced MEL pts. Clinical trial information: NCT02089685.

3010 Poster Discussion Session; Displayed in Poster Session (Board #336), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Preliminary safety and activity of nivolumab and its combination with ipilimumab in recurrent glioblastoma (GBM): CHECKMATE-143. *First Author: John H. Sampson, Duke University Medical Center, Durham, NC*

Background: GBM has a grim prognosis despite current first-line therapies. Immune checkpoint inhibitors have shown antitumor activity in both solid tumors and preclinical glioma models. This study evaluates the safety/tolerability of the checkpoint inhibitors nivolumab (NIVO) and ipilimumab (IPI) in patients (pts) with a first recurrence of GBM. **Methods:** Pts were randomized to NIVO 3 mg/kg Q2W or NIVO 1 mg/kg + IPI 3 mg/kg (NIVO+IPI) Q3W followed by NIVO 3 mg/kg Q2W. Eligible pts had first recurrence of primary GBM, no prior bevacizumab treatment and KPS ≥70. The primary endpoint was safety/tolerability. This analysis reports the preliminary experience after all pts had the opportunity to complete ≥6 months (mo) of follow-up after first dose. **Results:** 20 pts were treated, 10 in each arm. All pts had prior surgical resection, radiation, and temozolomide. Median age was 57 years (range: 37-73), KPS=90 (n=13), 80 (n=2) and 70 (n=5). Median time from first GBM diagnosis was 9 mo. The median number of doses (range) received in NIVO arm was 6 (3-23). In NIVO+IPI, pts received 3 (2-8) doses of NIVO and 2 (2-4) of IPI. Drug-related adverse events (AE) in ≥3 pts were fatigue (n=3) and nausea (n=3) with NIVO and fatigue (n = 8), diarrhea (n = 7), AST and lipase increased (n = 5 each), vomiting and ALT increased (n=4 each), and amylase increased, headache, hyperthyroidism, nausea and maculo-papular rash (n=3 each) with NIVO+IPI. All NIVO AEs were grade 1 or 2. Eight (80%) NIVO+IPI pts had grade 3 or 4 AEs. Drug-related AEs leading to discontinuation occurred only in NIVO+IPI pts (n = 5; 50%), including colitis, cholecystitis, diabetic ketoacidosis, confusion, and increased lipase. There were no drug-related deaths. Among 20 treated pts, OS at 6 mo. was 75%, including 7/10 NIVO pts (70%) and 8/10 NIVO+IPI pts (80%). ORR, PFS, and biomarker analysis are being evaluated. **Conclusions:** This is the first randomized study to report the safety/tolerability of checkpoint inhibitors in GBM. The AE profile of NIVO ± IPI was consistent with studies in other tumors. OS at 6 mo. is encouraging relative to comparable historical controls. Updated safety, efficacy, and biomarker data including on-treatment histopathology will be presented. Clinical trial information: NCT02017717.

3011 Poster Discussion Session; Displayed in Poster Session (Board #337), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. *First Author: Neil Howard Segal, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Outcomes are poor for patients (pts) with recurrent/metastatic (R/M) SCCHN, and new treatments are needed. An ongoing phase I/II, multicenter, open-label study (NCT01693562) is evaluating the safety and efficacy of MEDI4736 (M), a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity, in multiple solid tumor types including SCCHN. PD-L1 is expressed in SCCHN tumors and may be associated with response to anti-PD-L1 treatment. **Methods:** Pts with R/M SCCHN, an ECOG of 0 or 1, without prior anti-PD-1/PD-L1 exposure are eligible. M is administered IV every 2 weeks at 10 mg/kg for 12 months. Retreatment is permitted upon progression after 12 months. PD-L1 expression is assessed by IHC using the Ventana SP263 clone. Prior documented HPV status is collected at study entry. Response is based on investigator assessment per RECIST v1.1. Data included represent a larger population with more mature follow up than previously reported (Fury M, et al. Poster presented at ESMO 2014, 988PD). **Results:** As of 31 Oct 2014, 62 pts (mean age 58 years [range 24–96]; 86% male; 64% current/prior smokers; ECOG 0/1: 38%/62%; HPV pos/neg/unk: 40%/39%/21%), with a median of 3 prior systemic treatments (1–10), received a median of 6 doses (1–26). Drug-related AEs were observed in 60% of pts; the most frequent were fatigue (11%), diarrhea, (8%), and nausea (7%). Grade ≥ 3 related AEs were reported in 7% of pts: rash (2 pts), and increased GGT, fatigue, and tumor inflammation (1 pt each). No drug-related AEs led to discontinuation or death. No colitis or grade ≥ 3 pneumonitis was observed. Overall, 51 pts were evaluable for response with ≥ 24 weeks of follow up; ORR was 12% (25% in PD-L1+ pts), and DCR at 24 weeks was 16% (25% in PD-L1+ pts). Responses are ongoing in 5/6 responding pts, with response durations ranging from 4+ to 43+ weeks. Median duration of response has not been reached. **Conclusions:** With more mature follow up, the safety profile of M in SCCHN is manageable and consistent with previous reports. Responses are durable; ORR and DCR are higher in PD-L1+ pts. A registration program is underway in pts with SCCHN for M alone and in combination with tremelimumab. Clinical trial information: NCT01693562.

3012 Poster Discussion Session; Displayed in Poster Session (Board #338), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Efficacy based on tumor PD-L1 expression in KEYNOTE-002, a randomized comparison of pembrolizumab (pembro; MK-3475) versus chemotherapy in patients (pts) with ipilimumab-refractory (IPI-R) advanced melanoma (MEL). *First Author: Igor Puzanov, Vanderbilt University Medical Center, Nashville, TN*

Background: Pembro is an anti–PD-1 antibody approved for treating advanced MEL that progressed following IPI and, if *BRAF*^{V600} mutant, a BRAF inhibitor. In KEYNOTE-002 (NCT01704287), pembro doses of 2 mg/kg and 10 mg/kg every 3 wk (Q3W) significantly improved PFS compared with investigator-choice chemotherapy in IPI-R MEL ($P < .0001$), with no difference between pembro doses ($P = .44$). Data from KEYNOTE-001 showed that PD-L1 positivity was correlated with a higher ORR and longer PFS in MEL pts. We evaluated efficacy in PD-L1$^+$ and PD-L1$^-$ MEL pts enrolled in KEYNOTE-002. **Methods:** 540 pts with advanced IPI-R MEL were randomized 1:1:1 to pembro 2 or 10 mg/kg every 3 wk (Q3W) or chemotherapy. PD-L1 expression was assessed centrally by IHC using the 22C3 antibody. The cut point for positivity was staining in ≥1% of tumor cells. Response was assessed at wk 12 and every 6 wk thereafter (RECIST v1.1, central review). Primary end points were PFS and OS (final analysis planned after 370 deaths occur). ORR and the relationship between PD-L1 expression and efficacy were secondary end points. Data for the pembro arms were pooled. **Results:** 421/540 pts enrolled (78%) had tumors evaluable for PD-L1 expression; 291 (69%) were PD-L1$^+$, 130 (31%) were PD-L1$^-$. Pembro prolonged PFS and increased ORR compared with control in PD-L1$^+$ and PD-L1$^-$ pts (Table). Among pembro-treated pts, ORR was higher in PD-L1$^+$ pts, but the CIs were overlapping, and there was no difference in duration of response (DOR) based on PD-L1 expression. There was no prognostic effect in the control arm. **Conclusions:** Pembro improved efficacy over chemotherapy in both PD-L1$^+$ and PD-L1$^-$ IPI-R advanced MEL. These data indicate that in IPI-R MEL pts, pembro therapy should not be limited to pts with PD-L1$^+$ tumors. Clinical trial information: NCT01704287.

	Total		PD-L1$^+$		PD-L1$^-$	
	Pembro n = 361	Control n = 179	Pembro n = 193	Control n = 98	Pembro n = 93	Control n = 37
PFS, HR[a] (95% CI)	0.53 (0.43–0.65)		0.52 (0.39–0.68)		0.60 (0.38–0.94)	
6-mo PFS, %	36	16	40	13	26	22
ORR, % (95% CI)	23 (19–28)	4 (2–9)	26 (20–33)	4 (1–10)	15 (8–24)	8 (2–22)
DOR, wk, median (range)	NR (5+ – 50+)	37 (7+ – 41)	NR (5+ – 50+)	41 (18 + – 41)	NR (6+ – 48+)	37 (7+ – 37)

[a]Pembro vs control.

3013 Poster Discussion Session; Displayed in Poster Session (Board #339), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

An ongoing phase IIIb/IV safety trial of nivolumab (NIVO) in patients (pts) with advanced or metastatic non-small-cell lung cancer (NSCLC) who progressed after receiving 1 or more prior systemic regimens. *First Author: Todd Michael Bauer, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: NIVO, a fully human IgG4 programmed death-1 (PD-1), immune checkpoint inhibitor antibody, has demonstrated durable responses and tolerability in heavily pretreated pts with advanced NSCLC. Conducted mostly in community-based oncology centers, this ongoing trial explores the safety of NIVO in previously treated NSCLC pts. **Methods:** Eligible pts are enrolled in 4 subgroups: 1) squamous cell (SQ), performance status (PS) 0–1, ≥2 prior therapies; 2) SQ, PS 0–1, 1 prior therapy; 3) nonsquamous (NSQ), PS 0–1, ≥1 prior therapy; and 4) SQ or NSQ, PS 2, ≥1 prior therapy. Pts receive NIVO 3 mg/kg IV (60 min) Q2W either until progressive disease (PD)/unacceptable toxicity (Cohort A) or for 1 year with the possibility of retreatment upon disease progression (Cohort B). Primary objective is to estimate incidence of high grade (CTCAE v4.0 Grade 3–4 and 5) select treatment-related adverse events (TRAEs); exploratory efficacy assessments include ORR, PFS and OS. **Results:** From 4/16/14 to 8/15/14, 226 pts were treated and have demographic and safety data available; 179 remain on study as of 8/15. 51 pts had evaluable radiographic tumor assessments at week 9. **Conclusions:** Safety and tolerability are consistent with prior NIVO experience and no new safety signals have been identified in this trial. Immune-related toxicities are manageable in a community practice setting using previously developed safety algorithms. Early data from this large multicenter trial suggests that pts with pretreated advanced NSCLC benefit from NIVO therapy. Clinical trial information: NCT02066636.

	N=226
% male, female	55, 45
Median age (range), yrs	67 (33–91)
% SQ, NSQ	26, 74
% PS 0–1, 2	90, 9
% 1, 2, ≥3 prior therapies	21, 28, 47
Select TRAEs, % all grade, grade 3–4	
Any	13.3, 1.8
Skin	5.3, 0.4
GI	9.7, 0.9
Pulmonary[a]	1.3, 0.4
Endocrinopathies	2.7, 0
Hepatic	1.8, 0
Infusion reaction	0.9, 0
Renal	1.3, 0
1st tumor evaluation	N=51
CR	0%
PR	7 (13.7%)
SD	22 (43.1%)

[a]1 fatal drug-related respiratory failure was reported in the setting of known lymphangitic tumor spread, recurrent pulmonary embolus, bacteremia, pleural effusion and tumor progression; death classified as "Other-Multifactorial" by investigator.

3014 Poster Discussion Session; Displayed in Poster Session (Board #340), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. *First Author: Scott Joseph Antonia, Moffitt Cancer Center, Tampa, FL*

Background: The inhibitory PD-L1 and CTLA-4 pathways control T-cell activation. MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to programmed cell death-1 and CD80 with high affinity and selectivity. Tremelimumab (T) is a selective human IgG2 mAb inhibitor of CTLA-4. M and T have demonstrated acceptable safety profiles and clinical activity as single agents. M and T block distinct interactions contributing to immunosuppression and the combination may provide greater antitumor activity versus either agent alone. **Methods:** A Phase 1, open-label dose escalation and expansion study (NCT02000947) is assessing the safety/tolerability and antitumor activity of M + T combinations in pts with advanced NSCLC. **Results:** As of 4 Dec 2014, 61 pts have been treated during the dose escalation phase (table). An MTD has not yet been defined; the Cohort 5a dose exceeded the MTD (n=2 with dose-limiting toxicities; Grade [G] 3 increased AST/ALT, G4 increased lipase). 64% of pts had ≥1 drug-related AE; the most frequent were fatigue (26%), diarrhea (21%), and increased amylase (13%). 31% of pts had ≥1 G3/4 related AE; the most frequent (>5%) were diarrhea (8%) and colitis (7%). Increasing doses of T with a constant dose of M were associated with greater severity and frequency of AEs. 18% of pts had drug-related AEs leading to discontinuation; the most frequent was colitis (7%). All AEs were manageable with standard therapy, including steroids, except G4 myasthenia gravis and G5 polymyositis in 1 pt in Cohort 2a. Of 31 pts with ≥18-week scan, 8 (26%) had partial response (PR) and 11 pts (35%) had stable disease. PRs occurred in 3 of 10 pts with PD-L1-negative tumors. **Conclusions**: The combination has a manageable safety profile with evidence of clinical activity, including in PD-L1-negative disease. These data support continued study of the combination; recruitment is ongoing. Clinical trial information: NCT02000947.

	M Q4W							M Q2W		
Cohort	1a	2a	3a	3b	4	4a	5	5a	8	9
Dose M (mg/kg) + T (mg/kg)	3 + 1	10 + 1	15 + 1	10 + 3	20 + 1	15 + 3	15 + 10	20 + 3	10 + 1	10 + 3
n	3	3	11	3	6	11	9	6	3	6
Pts with ≥1 drug-related AE, n										
All grades	1	3	5	3	2	7	8	5	0	5
Grade 3/4	0	2	2	1	1	2	4	5	0	2
All grades leading to discontinuation	0	1	1	1	0	2	2	3	0	1

3015 Poster Discussion Session; Displayed in Poster Session (Board #341), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Molecular, immune and histopathological characterization of NSCLC based on PDL1 expression on tumor and immune cells and association with response to the anti-PDL1 antibody MPDL3280A. *First Author: Scott N. Gettinger, Yale School of Medicine, New Haven, CT*

Background: Programmed death ligand-1 (PD-L1) expression on tumor cells (TC) or tumor-infiltrating immune cells (IC) is associated with OS, PFS and ORR in patients with advanced NSCLC treated with MPDL3280A (Spigel et al, Spira et al, ASCO 2015, pending). In a phase I study, high PD-L1 expression on TC or IC (TC3 or IC3) was associated with a 45% ORR (RECIST v1.1) compared to a 14% ORR in patients without TC3 or IC3 NSCLC (Horn et al, ASCO 2015, pending). **Methods:** NSCLC specimens from both pre-treatment tumor samples across MPDL3280A trials (n = 498) and a non-trial cohort (n = 706) were evaluated for PD-L1 expression in TC and IC using the SP142 IHC assay. The specimens were scored as TC 0-3 and IC 0-3 based on increasing PD-L1 expression. A subset of samples was further characterized by histopathologic review, gene expression and epigenetic modifications. **Results:** TC3 or IC3, TC2/3 or IC2/3, and TC1/2/3 or IC1/2/3 tumors represented ≈ 20%, ≈ 40% and ≈ 65% of NSCLC, respectively. TC3 and IC3 tumors represented 2 distinct populations, with < 1% overlap. IC3 tumors demonstrated a high frequency of immune infiltrates within the tumor, stroma and tumor/stroma interface, with higher expression of B- and NK-cell signatures compared to TC3 tumors. In contrast, TC3 tumors featured distinct histopathologic characteristics, with a dense desmoplastic and sclerotic tumor microenvironment. TC3 tumors had a lower frequency of immune infiltrates, which when present were primarily located in the surrounding stroma. In addition, an inverse correlation was seen with PD-L1 promoter methylation and PD-L1 expression in TC, suggesting that PD-L1 may be influenced in part by epigenetic events in TC. Tumors that were TC0 and IC0 (≈ 35% of NSCLC) showed little to no evidence of immune infiltration or activation, consistent with immunologic ignorance. **Conclusions:** NSCLC can be classified into previously unrecognized, distinct molecular and histopathologic subsets that define sensitivity to treatment with PD-L1 targeted therapy. While expression of PD-L1 on TCs and/or ICs may confer sensitivity to MPDL3280A, the immunologic context and response to treatment may differ.

3016 Poster Discussion Session; Displayed in Poster Session (Board #342), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

CEA-targeted engineered IL2: Clinical confirmation of tumor targeting and evidence of intra-tumoral immune activation. *First Author: Jan H. M. Schellens, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: CEA-IL2v (RG7813) is an engineered IL-2 variant (IL-2v) with abolished IL-2Rα (CD25) binding fused to an antibody targeting Carcinoembryonic Antigen (CEA). The molecule was designed to improve the pharmacological and safety profile of IL-2 and enable tumor targeting. **Methods:** In an ongoing Phase I trial of CEA-IL2v (ranges 0.1 – 40 mg flat dose IV; schedule q1W and q2W) in patients (pts) with advanced and/or metastatic solid CEA+ tumors, extensive pharmacodynamic monitoring in peripheral blood as well as immunohistochemical (IHC) and flow cytometric (FC) analysis of pre- and on-treatment biopsy specimens (day + 4) were performed, including tests for effector (CD8+) and helper T cell (CD4+) percentage and density. In a sub-study, biodistribution was analyzed using PET imaging of ^{89}Zr-CEA-IL2v at doses of 6 and 30 mg. **Results:** Of the 11 pts treated at 30 mg, 4 had sequential tumor biopsies evaluable both by IHC and FC. An increase in the median density (IHC) of CD8+ T cells from 62.5 (7 - 90) [median (range)] to 104.2 (7 - 255) cells/ mm^2 was observed in 3/4 subjects after the 1st dose. No relevant change in the density of CD4+ T cells was detected. FC analysis confirmed the increase in CD8:CD4 ratio in the same 3/4 patients: from 0.88 (0.57 - 1.24) to 4.54 (0.36 - 7.47). Effects in peripheral blood included strong lymphocyte expansion that was mostly driven by Natural Killer (NK) and CD8+ T cells. Medians and ranges for the 11 pts before and 4 days after dosing were: NK: 168 (range: 52 - 337) vs. 655 (206 - 1569) cells/μl; CD8+: 340 (19 - 464) vs. 831 (78 – 3754) cells/μl. While there was no clear evidence of CEA-mediated tumor accumulation at 6 mg in the first 6 pts, intra-tumoral accumulation of ^{89}Zr-CEA-IL2v was observed in 2/2 pts at 30 mg. Additional studies are ongoing. **Conclusions:** Collectively, these data support the concept that reduced affinity of CEA-IL2v for IL2R-alpha together with high-affinity binding to CEA enables tumor targeting. These findings suggest that CEA-IL2v is the first tumor-targeted cytokine, which increases immune infiltration and activates NK and T cells both in the periphery and within tumors. Clinical trial information: NCT02004106.

3017 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A first-in-human dose escalation study of PEGylated recombinant human IL-10 (AM0010) in advanced solid tumors. *First Author: Jeffrey R. Infante, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: PEGylated IL-10 induces the expansion of tumor reactive CD8 T cells both in the periphery and within the tumor. In mice, PEG-IL-10 but not non-PEG-IL-10 induces the rejection of tumors and establishes immunological memory. Primary objectives of this FIH study were to establish the safety, tolerability and the MTD of AM0010. Secondary objectives were to assess anti-tumor-activity, pharmacokinetics, immunogenicity and induced immune activation. **Methods:** Patients with advanced melanoma (4), non-small cell lung cancer (1), renal cell cancer (6), colorectal cancer (16), prostate cancer (1), ovarian cancer (1) and pancreatic cancer (4) were enrolled in escalating cohorts of 3-6 patients each followed by expansion cohorts. AM0010 was self-administrated daily subcutaneously at doses of 1 to 40 μg/kg. PK, anti-drug antibodies and immune responses were monitored. **Results:** Since November 2013, 33 patients were enrolled in cohorts of 1, 2.5, 5, 10, 20, and 40 μg/kg. An MTD was not defined through the planned maximally administered dose. Common treatment related adverse events included injection site reaction, rash, fatigue, thrombocytopenia and anemia. Most adverse events were low grade. Eight G3 adverse events were observed including anemia (3), thrombocytopenia (1), rash (1), increased lipase (1), dyslipidemia (1), transaminitis (1). The half-life of AM0010 half-life is ~20 hrs and exposures increased linearly with increasing doses. IL-18 was dose dependently increased in the serum of all patients, IFNg, IL-4, GM-CSF and IL-7 were elevated at doses $>$ 20 μg/kg. Activation of CD8 T cells was observed. Ongoing immune related partial responses (irPR) were observed in one RCC patient (20 μg/kg; -71% at 22 weeks) and one ocular melanoma patient (40 μg/kg; -57% at 14 weeks). Additional 9 patients had stable disease at 8 weeks (1 melanoma (duration 24+ weeks); 2 RCC (21/13); 1 CRC (40+); 3 CRC, 1 pancreatic, 1 ovarian (13)). **Conclusions:** AM0010 has a manageable safety profile and leads to sustained and systemic Th1 immune stimulation. The pharmacodynamics and clinical activity observed support the ongoing monotherapy expansions and future combination development in a variety of advanced malignancies. Clinical trial information: NCT02009449.

3018 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A phase I study of intratumoral injection of ipilimumab and interleukin-2 in patients with unresectable stage III-IV melanoma. *First Author: Randy Christopher Bowen, University of Utah, Salt Lake City, UT*

Background: Intratumoral (IT) IL-2 is highly effective and well tolerated, but does not generate systemic immunity or response in untreated lesions. Intravenous (IV) ipilimumab (Ipi) lowers the threshold for T cell activation leading to a durable clinical response in a minority of melanoma patients, but is associated with potentially severe toxicities. Since IV Ipi doesn't have tissue distribution, circulating anti-tumor T cells activated by this drug may differ greatly from tumor-infiltrating lymphocytes (TILs) activated by IT Ipi in terms of quantity and quality. Therefore, we hypothesized that a combination of IT IL-2 and IT Ipi would effectively hyperactivate and expand TILs to engender systemic immunity with minimal toxicity. **Methods:** This was a phase I dose escalation study for Ipi with fixed dose IL-2 in patients with unresectable stage III/IV melanoma and at least one injectable lesion. A single lesion (0.5-2.0 cm) in each patient was treated with IL-2 (3 mIU) IT TIW x 2 weeks, then BIW x 6 weeks, with escalating doses of Ipi IT weekly x 8 wks. A minimum of 3 patients were enrolled at each dose level. Endpoints included safety, tumor responses, and changes in systemic T cells. **Results:** 12 patients were treated at 3 Ipi dose levels (0.5, 1, 2 mg). Treatments were well tolerated. The only grade 3 toxicity observed was injection/tumor site ulceration/necrosis, not a DLT per protocol. Other toxicities were grade 1 in nature. An abscopal effect (response in at least 1 non-injected lesion) was seen in 9/12 patients (75%). 10 patients were evaluable for response by immune-related response criteria: 4 PR (40%) and 6 PD. 1 PD was later found to be a CR by resection. The 2 nonevaluable patients had regression of multiple skin lesions. An increase in the frequency of total peripheral IFN-γ-producing CD8+ T cells was detected in 6/8 abscopal responders. Tbet+ and granzyme-B + CD8+ T cells were observed in 4/5 and 3/5 responders tested, respectively. **Conclusions:** IT injection with the combination of Ipi/IL-2 is well tolerated and generates responses in both injected and non-injected lesions in the majority of patients. We plan to conduct a phase II trial using IT Ipi/IL-2 in conjunction with systemic immunotherapy. Clinical trial information: NCT01672450.

3019 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Immunogenomics-based development of personalized immunotherapy for lung cancers. *First Author: Yataro Daigo, Research Hospital, Institute of Medical Science, The University of Tokyo, Tokyo, Japan*

Background: Oncoantigens are oncogenic and high immunogenicity proteins specifically expressed in cancers, and are promising targets for personalized immunotherapy. **Methods:** We have established a strategy to identify new oncoantigens; i) screening of genes expressed in the majority of 120 lung cancers with cDNA microarray covering 27,648 genes, ii) verification of no expression of these genes in normal tissues, iii) validation of the clinicopathological significance of their expression with tissue microarray covering 400 lung cancers, iv) characterization of their role in the growth or invasiveness of cancer cells by RNAi and cell growth/invasion assays, v) screening of the epitope peptides recognized by HLA-A*0201- or A*2402-restricted cytotoxic T lymphocyte (CTL) for clinical trials. **Results:** We identified dozens of 10-amino-acid peptides from 45 oncoantigens, each of which was a candidate to be presented on the surface of HLA-A*0201 or HLA-A*2402 that induced CTL response. We conducted a phase I study for HLA-A*2402-positive, advanced non-small cell lung cancer patients who failed to standard therapy, using the combination of three peptides from LY6K, CDCA1, and KIF20A mixed with adjuvant once a week. 20 evaluable patients have been enrolled, and this cancer vaccine therapy demonstrated tolerability and had very high immunogenicity to induce antigen-specific CTLs in cancer patients. Disease control rate including one complete response was 50%. The patients showing LY6K-specific CTL responses demonstrated a longer overall survival than those without CTL induction. The patients with CTL induction for multiple peptides were likely to show better clinical outcomes. We are also screening predictive and monitoring biomarkers for peptide vaccine therapy through immunogenomics approach by analyzing pattern of CTL response, genomic/proteomic profiles of CTLs, cancer tissues and serum, as well as genetic variation of patients and identified various candidate biomarkers detectable in cancer tissues and/or serum. **Conclusions:** Current data of the cancer vaccine therapy coupled with screening of companion diagnostics warrants further clinical studies to develop more personalized and effective immunotherapy. Clinical trial information: NCT01069575.

3020 Poster Discussion Session; Displayed in Poster Session (Board #346), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Vaccination of MSI-H colorectal cancer patients with frameshift peptide antigens: A phase I/IIa clinical trial. *First Author: Matthias Kloor, University of Heidelberg, Heidelberg, Germany*

Background: High level microsatellite instability (MSI-H) occurs in 15% of colorectal cancers as a consequence of DNA mismatch repair deficiency. MSI-H colorectal cancers are characterized by a dense immune cell infiltration. They are characteristic of the inherited HNPCC (hereditary non-polyposis colorectal cancer) or Lynch syndrome, but can also develop sporadically. DNA mismatch repair deficiency causes insertion or deletion mutations at coding microsatellites, which leads to the generation of frameshift peptide (FSP) antigens. FSP antigens are attractive targets for vaccination, because they are highly immunogenic shared antigens, which directly result from driver mutations in MSI-H cancers. To evaluate safety and immunological efficacy of FSP vaccination, we have initiated a clinical phase I/IIa vaccination trial (Micoryx). **Methods:** The protocol comprised 3 cycles of 4 subcutaneous applications of FSP antigens (frameshift variants of the coding microsatellite-containing genes AIM2, HT001, TAF1B) mixed with Montanide ISA-51 VG over a 6 month period. Inclusion criteria were history of colorectal cancer (UICC stage III or IV) who received standard chemotherapy. Phase I of the trial evaluated safety and toxicity as the primary endpoint (6 patients), phase IIa addressed the induction of cellular and humoral immune responses (16 patients). **Results:** No FSP antigen-associated severe adverse events have been observed. Significant induction of FSP-specific immune responses against one or more FSP antigens was observed in all patients vaccinated per protocol. Few patients had stage IV disease and were evaluable according to RECIST. One heavily pretreated patient with bulky metastases showed a stable disease and stable CEA levels over 7 months under the study treatment. **Conclusions:** Vaccination with FSPs is well tolerated and leads to the induction of humoral and cellular immune responses. FSP vaccination represents a promising novel approach for treatment of MSI-H colorectal cancer patients and for tumor prevention in Lynch syndrome, allowing the evaluation of the concept of preventive cancer vaccines in an ideal model scenario of a defined high-risk patient population. Clinical trial information: NCT01461148.

3021 Poster Discussion Session; Displayed in Poster Session (Board #347), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Phase I, first-in-human trial of LV305 in patients with advanced or metastatic cancer expressing NY-ESO-1. *First Author: Neeta Somaiah, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Generation of tumor-specific cytotoxic T cells (CTLs) in vivo is a major goal of cancer immunotherapy. LV305 is a replication-incompetent, integration-deficient, hybrid viral vector based on the ZVex platform designed to target dendritic cells (DC) in vivo via CD209 (DC-SIGN) and induce the full-length expression of the cancer testis antigen, NY-ESO-1, in order to generate and expand anti-cancer CTLs. In preclinical models, LV305 is a potent inducer of CTLs and anti-tumor immunity. In this first-in-human study, the safety, immunogenicity and efficacy of LV305 are being examined in patients (pts) with cancer. **Methods:** Adults with previously treated, advanced or metastatic melanoma, sarcoma, breast, lung or ovarian cancers expressing the NY-ESO-1 protein by IHC were eligible. Following a 3+3 dose escalation design, 3 pts were enrolled into 4 cohorts to receive 3 or 4 intradermal injections every 3 weeks of 10^8, 10^9 or 10^{10} vector genomes (vg) per dose. Expansion of up to 53 pts at the 10^{10}dose is underway. **Results:** During dose escalation, 12 pts with NY-ESO-1 positive sarcomas were treated. No DLT or SAEs were observed and all related AEs were CTCAE grade 1 or 2. Common AEs were fatigue (58%), injection site reaction (33%), and myalgia (33%). After review by an independent DSMB, the highest dose, 10^{10} vg, was determined to be safe. Immunogenicity data from the initial 6 pts at the low dose (10^8 vg) demonstrated increased NY-ESO-1-specific CD8 and/or CD4 T cells in 3 pts by ELISPOT, tetramer assay of unstimulated blood, and/or TCR sequencing of blood and TILs. Data indicate the induction of T cells to new epitopes and boosting of TIL TCR sequences in blood. Of these initial 6 pts, 4 had a best response of SD (range 12-34+ weeks) with 1 pt achieving regression of 13.8%, and 2 had PD. The 6 pts dosed at 10^9 and 10^{10}vg are completing therapy. **Conclusions:** LV305 demonstrated acceptable safety at all doses up to 10^{10} vg. At the lowest dose, LV305 generated strong T cell responses and preliminary evidence of anti-tumor effect. Data from the mid and high dose are pending. These encouraging results will be followed by studies of LV305 (10^{10} vg) alone, in prime/boost with G305 (NY-ESO-1 protein-TLR4 agonist) and with anti-PD-1 therapy. Clinical trial information: NCT02122861.

3022 Poster Session (Board #348), Sat, 8:00 AM-11:30 AM

Utility of FDG-PET/CT in lymphoma patients undergoing immunotherapy with autologous CTL019 T-cells. *First Author: Nirav Niranjan Shah, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Molecular imaging with FDG-PET/CT (PET/CT) is an established modality for response assessment in lymphoma patients (pts) undergoing treatment (Tx). However, pts treated with novel immunotherapies may have false positive PET/CT findings due to tumor site and systemic inflammation. In particular, Tx with CTL019cells(autologous chimeric antigen receptor modified T-cells redirected at CD19) can be complicated by 'cytokine release syndrome' (CRS) due to a severe systemic inflammatory reaction. Infiltration of tumors by activated CTL019 cells may impact radiographic and functional imaging findings. The role of PET/CT in pts treated with CTL019has not previously been described. **Methods:** We performed a pilot, single arm, prospective study to explore the utility of early PET/CT in pts with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) undergoing Tx with CTL019 T-cells. Pts had PET/CT prior to CTL019infusion and then early PET/CT at 1 month (m) post-Tx. The primary outcome was the amount/change in metabolically active tumor volume (MTV) and FDG uptake. Secondary outcomes included the association of early PET/CT with formal response assessment by 3 m CT scan and the effect of CRS on PET/CT results. **Results:** We enrolled 6 pts (DLBCL 4; FL 2). 5 of 6 had baseline PET/CT with active disease. 4 of 6 pts developed CRS but all resolved symptoms prior to the 1 m scan. On the 1 m PET/CT, 3 had response (CR or PR) and 3 had disease progression (PD). There was 100% correlation of early PET/CT result with 3 month CT response assessment (Table). Development of CRS did not confound PET/CT findings. **Conclusions:** In DLBCL and FL pts on Tx with CTL019, early PET/CT may predict response to this novel immunotherapy. The development of CRS did not influence image assessment at 1 m. We plan to include early PET/CT in future CTL019 lymphoma studies to better define its role in this setting.

Subject	Disease	CRS N=No Y=Yes	Pre-Tx Total MTV (cc)	Post-Tx Total MTV (cc)	Absolute change in MTV(cc)	Post-Tx PET/CT Deauville Score/Response	3 m CT response
13	FL	N	54.7	0	-54.7	1/CR	CR
16	DLBCL	Y	0	32.7	+ 32.7	5/PD	PD
12	DLBCL	Y	91.2	22.9	-68.3	4/PR	PR
22	DLBCL	Y	255.9	1625.3	+ 1369.4	5/PD	PD
19	FL	Y	451.6	0	-451.6	2/CR	CR
25	DLBCL	N	121.3	369.8	+ 248.5	5/PD	PD

3023 Poster Session (Board #349), Sat, 8:00 AM-11:30 AM

Phase I, open-label, multi-ascending dose trial of avelumab (MSB0010718C), an anti-PD-L1 monoclonal antibody, in Japanese patients with advanced solid tumors. *First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in phase I/II trials. Here we report on the safety and tolerability of avelumab in a phase I dose escalation study (NCT01943461) in Japanese patients (pts) with advanced solid tumors. **Methods:** Dose escalation (3+3 design) was performed for 3 dose levels (DL 3, 10, and 20 mg/kg). The dose limiting toxicity (DLT) evaluation period was 3 weeks. **Results:** A total of 17 pts (4 gastric, 4 melanoma, 3 NSCLC, 2 CRC, 2 GIST, 1 esophageal, 1 MBC) were enrolled, with 5, 6, and 6 pts treated with avelumab at 3, 10, and 20 mg/kg, Q2W, respectively. Median age was 62 years (range 30–74) and all had ECOG PS 0 or 1, with a median of 4 prior lines of therapy (range 1–9). Treatment-emergent adverse events (TEAEs) occurred in 16/17 pts (94.1%), of which 11 (64.7%) were treatment-related. The most frequent related TEAEs ($\geq$ 10%) were infusion-related reactions (5, 29.4%), stomatitis (4, 23.5%), maculopapular rash (4, 23.5%), decreased white blood cell count (3, 17.6%), pyrexia (2, 11.8%), headache (2, 11.8%), and anemia (2, 11.8%). Two pts had grade 3 TEAEs (not related). No pt experienced a DLT. Two pts had confirmed partial responses (1 melanoma, 1 esophageal), and 5 had stable disease for $>$ 3 months. To date, 12 pts (70.6%) have discontinued treatment: 10 (58.8%) for progression, 1 (5.9%) for death, and 1 (5.9%) for other reason. Five pts (29.4%) remain on treatment. All 17 pts were evaluable for PK analysis. Half-life was 88.6, 121.8, and 114.0 h for dose levels 3, 10, and 20 mg/kg, respectively. The parameters C_{max} and AUC were approximately proportional with dose, showed low variability, and were similar to those previously obtained in Caucasian pts. **Conclusions:** Avelumab can be safely administered to Japanese pts in doses up to 20 mg/kg Q2W. Additional phase II/III studies to evaluate the clinical activity of avelumab at 10 mg/kg Q2W in select tumor types are currently being planned. *Proposed INN. Clinical trial information: NCT01943461.

3024 Poster Session (Board #350), Sat, 8:00 AM-11:30 AM

Phase I study of MEDI0639 in patients with advanced solid tumors. *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: MEDI0639 is an investigational monoclonal antibody that selectively binds to Delta-like ligand 4 (DLL4) and blocks its ability to bind to and activate signaling through the Notch receptors, potentially inhibiting tumor growth by multiple mechanisms. **Methods:** This study (NCT01577745) included patients (pts) with advanced solid tumors who had ECOG performance status 0–1 and adequate organ function. MEDI0639 10–200 mg was given every 21 days with a 3+3 dose-escalation design. Primary objective was to determine maximum tolerated dose (MTD) and safety. Other objectives included pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity (IG), and antitumor activity. **Results:** As of Jan 7, 2015, 20 pts were enrolled (median age 61y [range 40–83y]; median number of prior therapies: 5). The most common tumors were colorectal (n = 5), small cell lung cancer (n = 4), and melanoma (n = 4). No dose-limiting toxicities were identified through the 150 mg dose; the 200 mg dose is currently being evaluated. Of 20 safety-evaluable pts, the most common treatment-related adverse events (trAEs) were increased aspartate aminotransferase, increased brain natriuretic peptide (BNP), and fatigue (n = 3 each). Grade 3/4 trAEs were observed in 3 pts (acute myocardial infarction [AMI], atrial fibrillation [AF], ventricular dilatation [VD], and ventricular hypokinesia [VH] in 1 pt; lower abdominal pain in 1 pt, and hypertension in 1 pt), and 3 pts had serious trAEs (AMI, AF, VD, VH in 1 pt; diplopia in 1 pt; hemorrhagic diarrhea (HD), chest discomfort, and back pain in 1 pt). One pt discontinued due to a trAE (AMI). The trAEs of interest consistent with the mechanism of action included AMI (n = 1), hypertension (n = 2), increased BNP (n = 3), and HD (n = 1). No treatment-related deaths occurred. Of 19 efficacy evaluable pts, partial response was observed in 1 pt with melanoma; 7 pts had stable disease lasting ≥ 12 weeks. Preliminary PK was nonlinear at doses < 100 mg, and PD showed target engagement at the doses tested. IG has not been observed. **Conclusions:** MEDI0639 150 mg did not exceed the MTD. Enrollment at the 200 mg dose level is ongoing. The safety profile is consistent with the mechanism of action and appears to be manageable. Preliminary evidence of antitumor activity was observed. Clinical trial information: NCT01577745.

3025 Poster Session (Board #351), Sat, 8:00 AM-11:30 AM

Baseline serum predictors of clinical response to CTLA4 inhibitor therapy in melanoma patients. *First Author: Krisztian Homicsko, University Hospital Lausanne, CHUV, Lausanne, Switzerland*

Background: A CTLA4 specific antibody (Ipilimumab, Yervoy) has been approved as first line therapy for metastatic melanoma. Despite long-term benefit for a subpopulation (~20%) of patients, the majority will unfortunately not benefit. To date, only VEGFA levels have been suggested as a potential predictive marker in serum. In the current study we set out to identify serum protein marker/s that could identify patients benefiting from ipilimumab. **Methods:** We performed a retrospective discovery analysis of serum samples obtained before melanoma patients started Ipilimumab treatment. We selected 5 responder and 5 non-responder patients. Response was evaluated based on the first CT scan (W12) after the first course of Ipilimumab therapy. The protocol was approved by the local IRB. Samples were analyzed for 440 proteins using the RayBio Quantibody Multiplex ELISA platform. Results are being verified in a validation cohort of 12 patients. **Results:** Out of 440 proteins, 29 showed a statistically significant difference ($p < 0.05$, two-tailed Student t-test), with 7 proteins upregulated and 22 downregulated in responders. VEGFA levels were not predictive ($p = 0.4246$). One particular protein showed the most significant difference and was undetectable in 5 out of 5 responders, while 4 out of 5 non-responders in the discovery cohort had the protein expressed. In this cohort, this protein showed a positive predictive value (PPV) of 83% and also a negative predictive value of 100%. We will also present the ongoing analyzes of 12 additional pretreatment samples as a validation cohort. We generated a 10-protein signature, which we are comparing with the single protein predictor. Multivariate analyzes of markers and clinical parameters are ongoing to confirm that protein B alone or the 10-protein signature is a better predictor of response and survival. Recruitment of additional patients in this translational protocol is ongoing. **Conclusions:** The finding that a serum protein or a protein signature predicts clinical response to ipilimumab warrants further validation in larger prospective studies. (The use of protein B and/or the 10-protein signature as predictors of response to anti-CTLA4 therapy is pending patent application).

3026 Poster Session (Board #352), Sat, 8:00 AM-11:30 AM

Correlation of gene expression signatures and clinical outcomes in patients with advanced gastric cancer treated with pembrolizumab (MK-3475). *First Author: Veena Shankaran, University of Washington, Seattle, WA*

Background: Pembrolizumab, an anti–PD-1 monoclonal antibody, has shown antitumor activity in advanced gastric cancers. Hypothesis testing of 4 prespecified multigene immune expression signatures enriched for T-cell mediated interferon signaling and antigen presentation genes was used to evaluate associations with clinical outcomes in patients with gastric cancer enrolled in KEYNOTE-012, a multicohort, phase 1 study of pembrolizumab in patients with PD-L1$^+$tumors. **Methods:** 33 of 39 pembrolizumab-treated advanced gastric cancer patients had RNA expression profiling data of sufficient quality. RNA was extracted from formalin-fixed, paraffin-embedded samples and analyzed using the NanoStringnCounter system. Hypothesis testing was conducted on 4 prespecified signatures ("Interferon-gamma," "TCR-signaling," "Expanded-immune," and "Denovo") that were constructed based on analyses in patients with melanoma and prior to linking any NanoString data to clinical outcome data. **Results:** In the patients with NanoString data, ORR was 30%. For ORR, all 4 signatures showed a P value <0.10 (Table). For PFS, all signatures achieved $P<$ 0.05. All signatures showed a general pattern such that pts with very low signature scores did not respond. ROC analyses suggest that cutoffs with high sensitivity and a resultant high negative predictive value (NPV) can readily be achieved. The cutoff associated with the Youden Index of the ROC curve for the Interferon-gamma signature yielded a positive predictive value (PPV) of 45% with a NPV at 92%. **Conclusions:** Immune response signatures were associated with clinical benefit from anti–PD-1 therapy with pembrolizumab in patients with advanced gastric cancer enrolled in KEYNOTE-012. Clinical trial information: NCT01848834.

	Nominal One-Sided P[a]	
Signature	ORR N = 33	PFS N = 33
IFNγ (6 gene)	0.077	0.032
TCR Signaling (13 gene)	0.034	0.024
Expanded Immune (18 gene)	0.062	0.049
Denovo (33 gene)	0.068	0.037

[a]From logistic or Cox regression for ORR and PFS, respectively.

3027 Poster Session (Board #353), Sat, 8:00 AM-11:30 AM

TCR use and cytokine response in PD-1 blockade. *First Author: Jesse M Zaretsky, UCLA, Los Angeles, CA*

Background: PD-1 blockade releases effector T-cells in the tumor microenvironment, but little is known on the effects in peripheral blood. We used T cell receptor (TCR) sequencing and multiplex serum cytokine analysis to assess treatment-induced changes and correlation with clinical response. **Methods:** Patients with metastatic melanoma were administered PD-1 inhibitor pembrolizumab (MK-3475) across three clinical trials at UCLA (NCT01295827, NCT01704287, NCT01866319). Among those consenting to blood collection (UCLA IRB#10-000870), we selected cases with paired samples (baseline and at second dose), yielding 19 responders and 22 non-responders per irRECIST. Peripheral TCRs were sequenced by immunoSEQ assay (Adaptive Biotechnology). Serum cytokines were analyzed by Milliplex 38 Cytokine kit (HCYTMAG-60K-PX38). Mann-Whitney and Wilcox signed-rank tests evaluated group differences and treatment effects. **Results:** Unlike previous reports with CLTA4 blockade, anti-PD-1 treatment itself did not cause a net expansion in unique TCR repertoire size ($p = 0.42$). However, post treatment samples in responders had significantly more unique TCRs compared to non-responders ($p = 0.022$). Fold change in the number of clones comprising the top 25% of total TCR reads, a metric which minimizes noise from rare clonotypes, differed significantly between groups ($p = 0.015$, MW), showing a net decrease in non-responders but no net change in responders ($p = 0.013$ vs $p = 0.77$, WSR). Among serum cytokines, higher FGF-2 ($p < 0.01$) and eotaxin ($p = 0.04$) levels at baseline correlated with response, as did a post treatment decrease in relative levels of IL-8 ($p < 0.01$), MCP-1 ($p < 0.01$) and FGF-2 ($p = 0.01$). Changes in FGF-2 correlated with IL-8 and MCP1 (Spearman rho $\sigma = 0.35$, $p = 0.03$ and $\sigma = 0.70$, $p < 0.0001$). Among all study patients there was a mean increase in IP-10 ($p < 0.001$), IL-12.p40, IL-10, and TNF-a (all $p < 0.05$), and decrease in MDC ($p = 0.037$). **Conclusions:** Greater diversity of post-treatment peripheral T-cell repertoire favorably correlates with response to PD-1 inhibition, and differs from the non-specific increase observed with CTLA4 blockade. Of 38 circulating cytokines analyzed, 8 showed treatment induced changes, of which a decrease in FGF-2, MCP1, and IL-8 correlated with response.

3028 Poster Session (Board #354), Sat, 8:00 AM-11:30 AM

Biomarker analysis of patients treated with anti-CD19 chimeric antigen receptor (CAR) T cells. *First Author: Adrian Bot, Kite Pharma Inc, Santa Monica, CA*

Background: CAR engineered autologous T cell therapy has shown promising efficacy in B cell malignancies in an ongoing phase 1 study (Kochenderfer et al. J Clin Oncol 2014, ASH 2014). Anti-CD19 CAR T cell product characteristics and pharmacodynamic markers from patients in this study were correlated with clinical results. **Methods:** Patients with relapsed/refractory B cell malignancies received conditioning with fludarabine and cyclophosphamide, then anti-CD19 CAR T cells engineered with a CAR comprising CD28 and CD3-zeta signaling domains. Product T cells were characterized as such, or upon co-culture with CD19+ tumor cells, by flow cytometry and multiplex cytokine analysis. Pre- and post-CAR T cell infusion peripheral blood mononuclear cells (PBMCs) and sera were also evaluated. **Results:** To date, 11 anti-CD19 CAR T cell products, and PBMCs and serum samples from 7 patients have been evaluated. Five had an objective response to anti-CD19 CAR T cell treatment. Product T cells comprised central memory, peripheral memory and effector T cells. Upon co-culture with CD19+ tumor cells, these CAR T cells produced T_1, T_2, pro-inflammatory, homeostatic and effector cytokines, and chemokines. The treated patients showed induction of key homeostatic and inflammatory cytokines upon conditioning, as well as increased levels of immune effector molecules (granzymes, perforin) during the first 2 weeks after CAR T cell treatment. Additionally, the clinical responders showed *in vivo* expansion of CAR+ T cells to a range of 15-300 CAR+ PBMC/μL within 14 days after T cell treatment. Further analyses are ongoing. **Conclusions:** Detailed biomarker analysis from patients treated with anti-CD19 CAR T cells, may provide insight to clinical outcomes and guide the design of T-cell therapies.

3029 Poster Session (Board #355), Sat, 8:00 AM-11:30 AM

Immunological long-term follow-up of neuroblastoma stage IV patients after anti-GD2 CH14.18 antibody treatment. *First Author: Simone Kayser, University Children's Hospital, Tübingen, Germany*

Background: Neuroblastoma stage IV is associated with low cure rates. Treatment with the GD2 antibody ch14.18 could improve the long-term overall survival. Apart from GD2 other tumor antigens (TA) are expressed in neuroblastoma and studies implicated that T-cell responses to TA are associated with a better outcome. For the present study we analyzed the immune response in long term neuroblastoma survivors treated with anti GD2 ch14.18. **Methods:** Blood and serum of 17 neuroblastoma long-term survivors after GD2 therapy with $>$ 5 years follow up (patients group) and 17 age and gender matched healthy donors (control group) were analyzed. Serum was analyzed for antibodies binding to neuroblastoma cell lines and antibodies to a nominal antigen GD2. T cells were stimulated with overlapping peptides of the tumor antigens (TA) NY-ESO-1, WT-1, Survivin, MAGE-A1 and two mimotope peptides to GD2 for 10 days and analyzed for IFN-γ secretion in flow cytometry. **Results:** T-cell responses to at least one TA could be found in 82% of healthy and in 93% of patients with no significant difference in the number of TA responders between the two groups to any of these TA (Fisher´s exact test). In contrast, T-cell responses to at least one of the GD2 mimotopes were found in 53% of neuroblastoma survivors but in 0% of healthy donors. Moreover, even priming with GD2 mimotope loaded dendritic cells did not induce a T-cell response in healthy donor cells. No differences between patient and control group could be detected in binding of antibodies to neuroblastoma cell lines and no GD2-specific antibodies were detected in patients and controls. **Conclusions:** Survivors of neuroblastoma treated with anti-GD2 ch14.18 demonstrated robust T-cell responses to neuroblastoma associated TA that was comparable to healthy donors. This could enable patients to attack minimal residual disease efficiently. Moreover more than half of the patients had T-cell responses to GD2 which could be an effect of the GD2 antibody therapy. Our results show that involvement of the cellular immune system might have an impact on the better outcome of this treatment in stage IV neuroblastoma patients.

3030 Poster Session (Board #356), Sat, 8:00 AM-11:30 AM

Association of epithelial-mesenchymal transition with an immunosuppressive, inflammatory tumor microenvironment with elevated levels of checkpoint inhibitors in lung adenocarcinoma. *First Author: Yanyan Lou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Promising results in the treatment of NSCLC have been seen with agents targeting immune checkpoints, such as programmed cell death 1 (PD-1) or programmed cell death 1 ligand (PD-L1). However, only a select group of patients respond to these interventions. The identification of biomarkers that predict clinical benefit to immune checkpoint blockade is critical to successful clinical translation of these agents. Epithelial-mesenchymal transition (EMT) is a key process driving metastasis and drug resistance. Previously we have developed a robust EMT gene signature, highlighting differential patterns of drug responsiveness for epithelial and mesenchymal tumor cells. **Methods:** We conducted an integrated analysis of gene expression profiling from three independent large datasets, including The Cancer Genome Atlas (TCGA) of lung and two large datasets from MD Anderson Cancer Center, Profiling of Resistance patterns and Oncogenic Signaling Pathways in Evaluation of Cancers of the Thorax (PROSPECT) and the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE-1). Comprehensive analysis of mRNA gene expression, reverse phase protein array (RPPA), immunohistochemistry and in vivo mouse models were analyzed. **Results:** EMT is highly associated with an inflammatory tumor microenvironment in lung adenocarcinoma, independent of tumor mutational burden. We found immune activation co-existent with elevation of immune checkpoint molecules, including PD-L1, PD-L2, PD-1, TIM-3, BTLA and CTLA-4, along with increases in tumor infiltration by Foxp3+ regulatory T cells in lung adenocarcinomas that displayed an EMT phenotype. Similarly, IL-6 and indoleamine 2, 3-dioxygenase (IDO) were elevated in these tumors. Furthermore, we demonstrate that in murine models, many of these changes are recapitulated by modulation of the miR-200/ZEB1 axis, a known regulator of EMT. **Conclusions:** This study demonstrates EMT might represent a potential biomarker to select the patients who will benefit from immune checkpoint blockade agents and other immunotherapies in NSCLC and possibly other cancers.

3031 Poster Session (Board #357), Sat, 8:00 AM-11:30 AM

Exploratory analysis of clinical and translational factors associated with the inflamed phenotype in HNSCC. *First Author: Narendiran Rajasekaran, Center for Clinical Sciences Research Stanford, Stanford, CA*

Background: Immunotherapy with PD-1/PD-L1 axis blockade shows encouraging activity in head and neck squamous cell carcinoma (HNSCC). T-cell inflammation and gamma interferon driven gene expression patterns delineate a group of tumors that are most likely to benefit from anti-PD-1 therapy (Seiwert ASCO 2015, Keck CCR 2015). We examined two large, genetically annotated cohorts (TCGA & CHGC) in order to identify putative clinical and translational biomarkers that may predict benefit from anti-PD-1/anti-PD-L1 therapy in patients with HNSCC. **Methods:** 424 HNSCC tumors from the TCGA cohort were used to calculate a continuous score for tumor inflammation/inflamed mesenchymal phenotype (Keck CCR 2015). Respective scores were then correlated with available clinical, and translational characteristics. We used a second cohort, the Chicago Head and Neck Cancer Genomics cohort (CHGC) N = 132 for validation. In particular we focused on HPV status, tobacco use, anatomic site, stage, gender, race, and mutational burden for discovery of novel biomarkers/associations for HNSCC immunotherapy. **Results:** HPV status was moderately associated with inflamed phenotype in both cohorts (58/55) of HPV-positive tumors showed a high degree of inflammation, which only 30%/34% of HPV-negative tumors showed this. Smoking status, race, gender, anatomic site (controlling for HPV status), and stage did not correlate with the inflamed phenotype. The highest mutational burdens were seen in inflamed tumors, however correlation was weak. **Conclusions:** 'Inflamed phenotype' is a candidate predictive biomarker of clinical benefit from anti-PD-1 treatment and HPV status correlates with inflamed phenotype. In this study none of other the examined clinical or pathologic features including mutational burden demonstrated predictive characteristics of a therapeutic biomarker to PD-1/PD-L1 blockade.

3032 Poster Session (Board #358), Sat, 8:00 AM-11:30 AM

A phase I dose-escalation clinical trial of a peptide-based human papillomavirus therapeutic vaccine with *candida* skin test reagent as a novel vaccine adjuvant for treating women with biopsy-proven cervical intraepithelial neoplasia 2/3. *First Author: Mayumi Nakagawa, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Non-surgical treatments for cervical intraepithelial neoplasia 2/3 (CIN2/3) are needed as surgical treatments have been shown to double preterm delivery rate. An investigational human papillomavirus (HPV) therapeutic vaccine, PepCan, consists of four current good manufacturing production-grade peptides covering the HPV type 16 E6 protein and *Candida* skin test reagent as a novel adjuvant. **Methods:** The study was a single-arm, single-institution, dose-escalation Phase I clinical trial, and patients with biopsy-proven CIN2/3 were eligible for vaccination. Four injections were administered intradermally every 3 weeks in limbs, and loop electrical excision procedure (LEEP) was performed 12 weeks after the last injection for treatment and histological analysis. Six subjects were enrolled at each dose level, and dose escalation was allowed as long as less than two subjects demonstrated dose-limiting toxicities. **Results:** Six subjects at each of four dose levels (50, 100, 250, and 500 mcg per peptide) were accrued, and none of the subjects experienced any dose-limiting toxicities. The most common adverse events were injection site reactions. Vaccine-induced immune responses to E6 were detected in 65% of recipients (significantly in 43%), and systemic T-helper type 1 (Th1) cells were significantly increased after 4 vaccinations ($p = 0.02$). The best histological response was seen at the 50 mcg dose level with a regression rate of 83% (n = 6), and the overall rate was 52% (n = 23). **Conclusions:** PepCan has been shown to be safe, and able to induce HPV-specific immune responses and Th1 cells. *Candida*, which has been shown *in vitro* to induce interleukin-12 secretion, is likely responsible for the increased Th1 cells, and should be considered as a candidate adjuvant for other vaccines. A Phase II clinical trial to assess the full effect of PepCan is warranted using the 50 mcg per peptide dose. Clinical trial information: NCT00569231.

3033 Poster Session (Board #359), Sat, 8:00 AM-11:30 AM

Immunotoxin therapy in animal model of HuD antigen positive small cell lung cancer. *First Author: Bo Wang, Albert Einstein College of Medicine, New York, NY*

Background: Small cell lung cancer (SCLC) is a highly aggressive form of lung cancer. Most patients exhibit clinically detectable metastases at diagnosis and have an extremely poor prognosis despite combined modality therapy. HuD-antigen is a neuronal RNA-binding protein that is expressed in 100% of SCLC tumor cells. High levels of circulating anti-HuD antibodies in patients appear to be linked to spontaneous remission of their SCLC. This suggests that the HuD-antigen might be a potential molecular target for SCLC immunotargeting therapy. **Methods:** We constructed a new antibody-toxin compound (BW-2) comprised of mouse-anti-human-HuD mAb bound to saporin and tested the compound in vitro in the NCI-H69 SCLC cell line. In vivo SCLC experiments utilized male athymic nude mice (NCRNUM) xenografted with NCI-H69 cells. Tumor xenografted mice received a single intravenous or intratumoral injection of BW-2, while control tumor xenografted mice were treated with either anti-HuD antibody or saporin alone. Normal C57BL/6 mice were used to test for potential neurological side effects from BW-2. **Results:** In vitro experiments showed a high level of HuD+ tumor cell specific cytotoxicity in the presence of BW-2 immunotoxin and minimal HuD- cell cytotoxicity only at much higher concentrations of BW-2. Immunotoxin therapy in a nude mouse model of human SCLC demonstrated clear tumor shrinking while control tumor xenografted mice demonstrated rapid tumor volume expansion. Tumor volume in immunotoxin treated mice regressed for several weeks. Neurological testing revealed no manifestations of neurological disease in normal C57BL/6 mice even at doses of BW-2 as high as 10mg/kg. **Conclusions:** Our findings demonstrate in vitro and in vivo effectiveness of anti-HuD immunotoxin therapy for HuD+ SCLC. This approach to tumor antigen specific immunotargeting therapy may one day provide an additional treatment for SCLC.

3034 Poster Session (Board #360), Sat, 8:00 AM-11:30 AM

Results of the phase IIb part of TIME study evaluating TG4010 immunotherapy in stage IV non-small cell lung cancer (NSCLC) patients receiving first line chemotherapy. *First Author: Elisabeth A. Quoix, Hôpitaux Universitaires de Strasbourg, Strasbourg, France*

Background: TG4010 is an immunotherapy using an attenuated and modified poxvirus (MVA) coding for MUC1 and interleukin-2. A previous study showed that the baseline level of Triple Positive Activated Lymphocytes (TrPAL, CD16+CD56+CD69+) might be a predictive biomarker for TG4010 efficacy in NSCLC. **Methods:** TIME is a double blind, placebo-controlled phase IIb/III study. The phase IIb part compared first line chemotherapy combined with TG4010 or placebo and further assessed the predictive value of baseline level of TrPAL. Eligibility criteria included stage IV NSCLC not previously treated, MUC1+ tumor by immunohistochemistry (IHC), PS $\leq$ 1. TG4010 10^8pfu or placebo was given SC weekly for 6 weeks (w), then every 3w up to progression in immediate combination with chemotherapy. Primary endpoint was progression-free survival (PFS). **Results:** 222 patients (pts) were randomized 1:1. In pts with normal TrPAL the study met the primary endpoint of having a Bayesian probability for HR < 1 being $> 95\%$. PFS was significantly improved in the TG4010 arm in pts with low TrPAL (152 pts HR = 0.66 [CI95% 0.46-0.95] p = 0.013) while it was not the case in pts with high TrPAL (70 pts HR = 0.97 [CI 95% 0.55-1.73] p = 0.463). In addition, PFS was also significantly improved in pts with non-squamous tumors (196 pts HR = 0.69 [CI95% 0.51-0.94] p = 0.009) as well as in pts with non-squamous tumors and low TrPAL (131 pts HR = 0.61 [CI95% 0.42-0.89] p = 0.005). In this last group PFS at 9 months was 37% with TG4010 versus 18% with placebo. Overall survival (OS) data show an improvement in line with that observed for PFS and will be presented at the time of the meeting. Preliminary data on the effect of PDL1 expression by IHC in the tumor support the activity of TG4010 whether the tumor is positive or negative for PDL1 expression. Frequency and severity of adverse events were similar in both treatment arms. **Conclusions:** These results provide additional data supporting the efficacy of TG4010, particularly in patients with non-squamous tumors and/or a low level of TrPAL at baseline. The phase III part of the TIME study will continue in patients with non-squamous tumors and with OS as primary endpoint. Clinical trial information: NCT01383148.

3035 Poster Session (Board #361), Sat, 8:00 AM-11:30 AM

Comprehensive analysis of variation of tumor infiltrating lymphocytes during neoadjuvant chemotherapy in triple-negative breast cancer. *First Author: Carlos Castaneda Altamirano, Instituto Especializado De Enfermedades Neoplasicas, Lima, Peru*

Background: Tumor infiltrating lymphocytes(TIL) have a predictive and prognostic role in Triple Negative Breast Cancer (TNBC).There is little data regarding specific lympohcyte subsets. In this study we evaluated the association between clinicopathologic variables and TIL identified by either H&E (total TIL) or immunohistochemistry (TIL subsets) in TNBC patients receiving neoadjuvant chemotherapy (NAC). **Methods:** We evaluated stromal TIL in whole sections and in 5 HPF of a 0.6 cm tumor cylinder before and after NAC in a cohort of 100 TNBC patients. **Results:** Median age:49y,inflammatory(29%),pCR(30%),recurrences(42%),death(45%) and median follow-up(37.5m).TIL percentage by H&E is similar in the whole slide and in the 0.6 cylinder in post NAC homogeneous tumor(ICC = 0.731) but not in post NAC heterogeneous(ICC = 0.065) or preNAC tumor(ICC = 0.017). Quantitative counting and percentage calculating of TIL was significantly correlated in every subset(IHC):CD3,CD4,CD8 and FOXP3 in Pre(r:0.4982-0.6918,$p < 0.05$) and PostNAC(r:0.5387-0.7733,$p < 0.05$). The median percentage of total TIL in pre- and post-NAC specimens were 40 and 20%($p < 0.0001$), respectively. DFS $>$ 32 m and OS $>$ 41m are associated to higher preNAC TIL by H&E(40 vs 20%,p = 0,007)(40 vs 30%,p = 0.033). Media H&E TIL was not associated with age(40 vs 20%,p = 0.14), inflammatory features of pre-NAC(40 vs 35%,p = 0.64) or pCR in PostNAC samples(20 vs 20%,p = 0.63).TIL in PostNAC samples was not associated to DFS(p = 0.24) nor OS(p = 0.59).The CD4/CD3 ratio tend to be lower in pre-NAC samples with pCR(0.14 vs 0.24, p = 0.06) and lower in post-NAC samples with pCR(0.33 vs 0.07,p = 0.009).The CD8/CD4 ratio was higher in pre-NAC samples with pCR(2.75 vs 0.99,p = 003) and lower in post-NAC samples with pCR(2.09 vs 3.66,p = 0.008). **Conclusions:** TIL in PreNAC predicts pCR and Survival.TIL in 0.6 cm cylinder differs from whole slide and percentage correlates with absolute TIL calculation.CD4/CD3 and CD8/CD4 ratio evaluated by counting technique appears to predict pCR.

3036 Poster Session (Board #362), Sat, 8:00 AM-11:30 AM

Phase I/II study of tecemotide cancer immunotherapy for Japanese patients with unresectable stage III non-small cell lung cancer (NSCLC). *First Author: Hiroshi Nokihara, National Cancer Center Hospital, Tokyo, Japan*

Background: Tecemotide is a MUC1 antigen-specific cancer immunotherapy. We report results from a phase I/II study of tecemotide in Japanese patients (pts) with no disease progression (PD) after primary chemoradiotherapy (CRT) for stage III NSCLC. **Methods:** The phase II part of the study evaluated efficacy using the treatment schedule and dose confirmed in the phase I part. Eligible pts had unresectable stage III NSCLC with no PD after CRT (platinum-based chemotherapy and ≥ 50 Gy radiotherapy). In the phase II part, pts were randomized (2:1, double-blind) to tecemotide (930ug lipopeptide) or placebo (PBO) via subcutaneous administration weekly x8 then q6 weeks until PD or withdrawal. Cyclophosphamide 300–600mg/m^2 x1 or saline was given 3 days before first tecemotide or PBO dose, respectively. The primary endpoint was overall survival (OS). **Results:** A total of 172 pts were enrolled in the phase II part from Feb 2010 to Feb 2012, with 114 randomized to tecemotide and 58 to PBO. In the ITT population, baseline characteristics were well balanced between both arms. The majority (94%) of pts received concurrent CRT. Median OS was 32.4 vs 32.2 months with tecemotide vs PBO (HR 0.95, 95% CI 0.61–1.48, p = 0.828). Secondary endpoints were progression-free survival: 11.6 vs 8.0 months (HR 0.95, 95% CI 0.66–1.37, p = 0.773); time to progression: 11.3 vs 7.0 months (HR 0.94, 95% CI 0.65–1.35, p = 0.723); time to treatment failure: 8.0 vs 6.2 months (HR 1.07, 95% CI 0.75–1.54; p = 0.700). A predefined subgroup analysis showed no OS improvement with tecemotide vs PBO in the subgroups examined. Tecemotide was associated with a higher incidence of grade 3/4 adverse events vs PBO, but no new safety concerns were identified. No treatment-related grade 3/4 injection site reactions were detected. **Conclusions:** In this study, the design of which was comparable to the global phase III START trial, tecemotide maintenance therapy did not improve OS compared with PBO in Japanese patients with stage III NSCLC; in addition, no improvement in secondary endpoints was observed. Tecemotide was well tolerated, with no clinically relevant increase in adverse events. Clinical trial information: NCT00960115.

3037 Poster Session (Board #363), Sat, 8:00 AM-11:30 AM

Pharmacokinetics and myeloid effector cell engagement of an engineered IgA antibody against the epidermal growth factor receptor. *First Author: Thomas Valerius, Division of Stem Cell Transplantation and Immunotherapy, 2nd Department of Medicine, Kiel, Germany*

Background: IgA antibodies play an important role in bridging adaptive and innate immunity. There is increasing evidence that FcαRI-dependent engagement of myeloid cells appears to be crucial to activate mechanisms like phagocytosis or antibody-dependent cell-mediated cytotoxicity and that myeloid cells constitute important effector cells in cancer and cancer immunotherapy. Here, we describe an Fc engineering approach to further improve the immunotherapeutic potential of IgA antibodies. **Methods:** Recombinant IgA antibodies against the epidermal growth factor receptor (EGFR) were produced by co-transfecting CHO-K1 cells with vectors encoding the 225 variable and Igα heavy and κ light chain constant regions, respectively. An Fc engineered IgA2 antibody was generated by mutating two N-glycosylation sites and by removing two free cysteines. The resulting antibody was compared to wild type IgA2 regarding biochemical characteristics as well as Fab and Fc-mediated effector functions. Additionally, serum half-life and in vivo efficacy in a xenogeneic FcαRI-transgenic tumor model were evaluated. **Results:** Rational engineering of an IgA2 antibody resulted in monomeric molecules with improved biochemical characteristics, identical Fab- and Fc- mediated effector functions, but with significantly lower levels of terminal galactose. This molecule demonstrated lower asialoglycoprotein-receptor (ASGPR) binding and subsequently improved pharmacokinetics in mice. Compared to wild type IgA, this novel molecule displayed enhanced therapeutic efficacy against A431 tumor cells in vivo, which required human FcαRI-dependent myeloid effector cell engagement. **Conclusions:** These results demonstrate that an Fc engineered IgA antibody against EGFR displayed improved immunotherapeutic efficacy, which may overcome limitations (stability, pharmacokinetics, in vivo efficacy) of wild type IgA antibodies. Thus, these results promote the concept of FcαRI-dependent engagement of myeloid effector cells as a promising approach for antibody-based tumor immunotherapy.

3038 Poster Session (Board #364), Sat, 8:00 AM-11:30 AM

Antibody dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody, avelumab (MSB0010718C), on human tumor cells. *First Author: Kwong-Yok Tsang, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. In addition to disruption of immune suppressive signaling induced by the binding of PD-L1 on tumor cells with PD-1 on tumor infiltrating immune cells, avelumab was designed to mediate antibody dependent cellular cytotoxicity (ADCC). Other anti-PD-1/anti-PD-L1 monoclonal antibodies (mAbs) undergoing clinical evaluation are either of the IgG1 isotype and modified to remove ADCC activity or of the IgG4 isotype, which does not mediate ADCC. We present data from preclinical studies examining the ability of avelumab to induce ADCC and factors affecting tumor cell sensitivity to this mechanism. **Methods:** The ability of avelumab to induce lysis of human carcinoma cells was assessed using whole peripheral blood mononuclear cells (PBMCs) or purified natural killer (NK) cells as effectors. PD-L1 expression was reported as % positive tumor cells and mean fluorescence intensity (MFI) as determined by flow cytometry. **Results:** Using PBMCs as effectors, avelumab induced ADCC in 8/18 human carcinoma cell lines; tumor cell lysis positively correlated with the percentage of PD-L1 positive tumor cells and PD-L1 MFI. Lysis was increased when NK cells were used as effectors. Pretreating tumor cell lines with IFN-γ increased PD-L1 expression, but augmented lysis in only 4/10 cell lines. Preactivating NK cells with IL-12, however, increased lysis, suggesting a potential for synergy by combining avelumab with IL-12–based therapy. Little or no lysis was observed in NK-mediated ADCC assays vs whole PBMCs or dendritic cells isolated from PBMCs. A tumor cell line insensitive to lysis by CD8$^+$T cells was lysed by ADCC using NK cells and avelumab. **Conclusions:** Avelumab induced lysis of many human tumor cell lines via ADCC. Further clinical trials are necessary to determine whether the additional mechanism of inducing tumor lysis by ADCC will result in enhanced clinical activity compared with similar agents without ADCC activity.

3039 Poster Session (Board #365), Sat, 8:00 AM-11:30 AM

Phase I study to evaluate the safety and tolerability of MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody, in Japanese patients with advanced solid tumors. *First Author: Haruo Iguchi, Clinical Research Institute, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan*

Background: Immune-suppressing molecules can be exploited by tumor cells to suppress immune responses to cancer. Programmed cell death-1 (PD-1) is an inhibitory regulator of T-cell activation. The ligand to PD-1, PD-L1, is upregulated in several tumor types. MEDI4736 is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity. **Methods:** This Phase 1, multicenter, open-label study (NCT01938612) is evaluating the safety, PK, and clinical activity of MEDI4736 in Japanese patients (pts) with advanced solid tumors. Pts (≥ 20 years) with ECOG performance status 0–1 who are refractory or intolerant to standard treatment or for whom no standard treatment exists are eligible. MEDI4736 was given IV every 2, 3, or 4 wks (q2/3/4w) using a 3+3 dose escalation, followed by a dose-expansion phase that includes further pts at or below the maximum tolerated dose. Treatment continues for up to 12 months; retreatment is possible upon progression after 12 months. Disease response was assessed by RECIST v1.1. **Results:** As of 27 November 2014, 22 pts were enrolled across 5 dose levels. Drug-related adverse events (AEs) ≥ Grade (G) 2 were pneumonitis (G2; 3 mg/kg q2w), oral stomatitis (G2; 3 mg/kg q2w), constipation (G2; 3 mg/kg q2w), hypothyroidism (G2; 15 mg/kg q3w), eruption (G2, 20 mg/kg q4w), skin atheroma (G2, 1 mg/kg q2w), mucositis (G2; 3 mg/kg q2w), and serum-free triiodothyronine decreased (FT3; G3; 10 mg/kg q2w); all n = 1. There were no G4 drug-related AEs. G2 pneumonitis and G3 low serum FT3 were considered serious drug-related AEs. 1 pt discontinued due to an AE; G1 pneumonitis. No drug-related deaths or dose-limiting toxicities (DLTs) were reported. Of 19 evaluable pts with ≥ 1 post-baseline CT assessment, 1 pt (10 mg/kg q2w) had a partial response, and 6 pts had stable disease (n = 2 at 1 mg/kg q2w, and n = 1 each at 3 mg/kg q2w, 10 mg/kg q2w, 15 mg/kg q3w, and 20 mg/kg q4w). **Conclusions:** Initial results indicate no DLTs, 7 G2- and 1 G3-related AEs, and clinical activity for MEDI4736 in Japanese pts with advanced solid tumors. Based on these data, an expansion phase, including biliary tract cancer, SCCHN, and esophageal tumors, is underway. Clinical trial information: NCT01938612.

3040 Poster Session (Board #366), Sat, 8:00 AM-11:30 AM

Strategies for clinical development of monoclonal antibodies beyond first-in-man trials: Tested doses and rationale for dose selection. *First Author: Marie Vinches, Institut régional du Cancer de Montpellier - Val d'Aurelle, Montpellier, France*

Background: We conducted a comprehensive survey (*J. Clin. Oncol.*, in press) on the design, implementation and outcome of first-in-human trials (FIHT) of monoclonal antibodies (mAbs) over the last decade. We showed that, due to the limited observed toxicity, the maximum tolerated dose was infrequently reached and therefore the recommended phase II dose (RP2D) for subsequent clinical trials was only tentatively defined. **Methods:** In order to evaluate strategies of mAb development beyond FIHT, we performed a MEDLINE search to identify articles reporting single agent trials of mAbs whose FIHT was published between April 1, 2003 and April 1, 2013. For each mAb, we examined the doses tested in these non-FIH trials (NFIHT) with regard to the corresponding FIHT results, as well as the rationale for dose selection in NFIHT. **Results:** Sixty-nine NFIHT of 36 mAbs were selected for analysis, of which 30 were phase I, 37 phase II and 2 phase III trials. For each mAb, the number of trials ranged from 1 to 8. In phase I NFIHT, the maximum administered dose (MAD) coincided with the FIHT MAD for the tested mAb in 12 cases (40%), and the ratio between the NFIHT and FIHT MAD ranged from 0.28 to 2. An RP2D was indicated in only 14 phase I NFIHT (47%) and coincided with the FIHT RP2D or MAD for the tested mAb in 2 and 8 trials, respectively. The ratio between the phase I NFIHT RP2D and the FIHT RP2D or MAD ranged from 0.33 to 2 and from 0.28 to 2, respectively. While a FIHT RP2D was available for the tested mAb in 22 phase II-III NFIHT (56%), the dose actually administered was the FIHT RP2D in only 11 trials (28%) and the FIHT MAD in 12 other trials (31%). In the 16 phase II-III NFIHT (41%) in which the tested dose was different from FIHT RP2D or MAD, a rationale for dose selection was indicated in few cases, reporting former pharmacokinetics data (4 trials) or safety issues (1 trial). **Conclusions:** The RP2D and the MAD determined in FIHT is infrequently used in the subsequent clinical development of mAbs. The rationale beyond dose selection in phase II and III trials of mAbs is often unclear in published papers, a fact that represents a weakness in the development of this class of drugs, and may lead to wrong-dosing.

3041 Poster Session (Board #367), Sat, 8:00 AM-11:30 AM

Adoptive immunotherapy of acute myeloid leukemia (AML) with allogenic CAR t-cells targeting CD123. *First Author: Roman Galetto, Cellectis, Paris, France*

Background: Chimeric antigen receptor (CAR)-redirected T-cells have given rise to long-term durable remissions and remarkable objective response rates in patients with refractory leukemia, raising hopes that a wider application of CAR technology may lead to a new paradigm in cancer treatment. A limitation of the current autologous approach is that CAR T-cells must be manufactured on a "per patient basis". We have developed a standardized platform for manufacturing T-cells from third-party healthy donors to generate allogeneic "off-the-shelf" engineered CAR+ T-cell–based frozen products. **Methods:** Allogeneic CAR+ T cell products have been generated using Transcription Activator-Like Effector Nuclease (TALEN) gene editing technology to inactivate the TCRa constant (TRAC) gene, eliminating the potential for T-cells bearing alloreactive TCR's to mediate Graft versus Host Disease (GvHD). Editing of the TRAC gene can be achieved at high frequencies, up to 80% of TCRab negative cells. This allows the efficient production of TCR-deficient T-cells that no longer mediate alloreactivity in a xeno-GvHD mouse model. In addition, T-cells are engineered to co-express the RQR8 gene as a safety feature, with the aim of rendering them sensitive to the monoclonal antibody rituximab. **Results:** In this work we present the adaptation of this allogeneic platform to the production of T cells targeting CD123, the transmembrane alpha chain of the interleukin-3 receptor, which is expressed on tumor cells in patients with Acute Myeloid Leukemia (AML). To identify an effective CAR, we have screened multiple antigen recognition domains in the context of different CAR architectures to identify candidates displaying activity against cells expressing variable levels of the CD123 antigen. Furthermore, experiments in an orthotopic AML mouse model using UCART123 cells demonstrate important anti-tumor activity *in vivo*. **Conclusions:** The ability to carry out large scale manufacturing of allogeneic, non alloreactive CD123 specific T-cells from a single healthy donor can offer the possibility of an off-the-shelf treatment that would be immediately available for administration to a large number of AML patients.

3042 Poster Session (Board #368), Sat, 8:00 AM-11:30 AM

Tremelimumab, a fully human anti-CTLA-4 monoclonal antibody, optimal dosing regimen for patients with unresectable malignant mesothelioma (MM). *First Author: Rajesh Narwal, MedImmune, Gaithersburg, MD*

Background: Tremelimumab (T) is a selective human IgG2 mAb inhibitor of CTLA-4 that promotes T-cell activity though CTLA-4 inhibition. The primary objective of this analysis was to project the optimal T dosing regimen for a Phase (Ph) 2b study in MM. **Methods:** Retrospective population PK (N = 654; Ph 1–3; 0.01 to 15 mg/kg single dose/Q90D/Q4W) and exposure-OS (N = 293; Ph3; 15 mg/kg Q90D) analyses were performed using data from metastatic melanoma studies (A3671001/NCT00086489/NCT00254579/NCT00257205). PK (N = 40) and efficacy (N = 58) data were collected from a Ph2 study of T (NCT01649024/NCT01655888) following 2 dosing regimens: 15 mg/kg Q90D and 10 mg/kg Q4W. Modeling and simulations were performed in NONMEM and CTS software. **Results:** PK profiles were adequately described in the population model, resulting in parameters similar to a typical mAb with modest variability and indicating no need for dose adjustments. The exposure-OS analysis of a Ph3 study in melanoma showed better OS in patients with higher exposure compared to lower exposure (mOS of 18.4 vs 9 months). T did show clinical benefit in the Ph3 melanoma study; however, the primary endpoint was not met. One potential reason could be the sub-optimal dose of 15 mg/kg Q90D. Following 15 mg/kg Q90D, exposure was below the target trough level of ~30 μg/mL for about half of the dosing interval, with almost all patients below the LLOQ at the end of dosing interval. PK simulations indicated more frequent dosing of 10 mg/kg Q4W could maintain exposure at or above the target trough level in > 90% patients over the entire dosing interval and could yield higher OS. Based on these evaluations, a 10 mg/kg Q4W regimen extension arm was added in an ongoing ISS study exploring 15 mg/kg Q90D. Data from this ISS study confirmed similar PK for both schedules in melanoma and MM. A 10 mg/kg Q4W dose yielded higher exposure and could be associated with better clinical outcome in MM. The dosing regimen of 10 mg/kg Q4W for 6 months followed by 10 mg/kg Q12W is currently being tested. **Conclusions:** An optimal dosing regimen of 10 mg/kg Q4W T was identified based on integrated data analysis. This dosing regimen is currently being evaluated in an ongoing Ph2b study in MM. Clinical trial information: A3671001/NCT00086489/NCT00254579/NCT00257205/NCT01649024/NCT01655888.

3043 Poster Session (Board #369), Sat, 8:00 AM-11:30 AM

T-cell therapy in metastatic melanoma: TIL 1383I TCR transduced T cells after infusion and activity in vivo. *First Author: Courtney Regan, Loyola University Medical Center, Maywood, IL*

Background: Studies in adoptive T-cell transfer have suggested that persistence of the transduced T-cells is central to the viability of this therapeutic option. The objectives of this phase I clinical trial using TCR TIL 1383I transduced T cells in stage IV melanoma patients include measuring of persistence and monitoring the behavior of tumor-reactive T-cells in vivo. **Methods:** Peripheral blood mononuclear cells (PBMCs) were isolated from three melanoma patients, activated with anti-hCD3 with rhIL2 and rhIL15, transduced with lentivirus encoding the TIL 1383I TCR, and expanded to treatment numbers. The transduced cells were suspended in 5% human albumin and infused over 30 minutes. The infusion was preceded by lymphodepletion with fludarabine and cyclophosphamide and followed with low dose IL-2 for one week. A modified CD34 cassette in the vector enabled monitoring of the transduced T cells in the patient's PBMC post-infusion. PBMCs were collected from patients on days 1, 3, 5, 7, 14, 25, 35 and monthly up to 3 months and then every 1-3 months as clinically indicated. The presence of transduced T-cells at each time point was measured by staining with anti-CD34 mAb and analyzed using a BD LSRFortessa flow cytometer. **Results:** Transduced T-cells were detected in the blood of all three patients post infusion. Clinical activity was demonstrated in two patients – one in the form of tumor shrinkage and another with development of progressive vitiligo. **Conclusions:** Previous studies with TIL suggest better T-cell engraftment, persistence, and therapeutic efficacy with homeostatic proliferation after lymphodepletion. Out results confirm that the infused TIL 1383I TCR transduced T-cells could be detected up to 6 months after infusion and demonstrate activity. Clinical trial information: NCT01586403.

3044 Poster Session (Board #370), Sat, 8:00 AM-11:30 AM

Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with metastatic or locally advanced solid tumors: assessment of safety and tolerability in a phase I, open-label expansion study. *First Author: Karen Kelly, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. The primary objective of this phase I, open-label, parallel-group expansion study (NCT01772004) was to assess the safety and tolerability of avelumab in patients (pts) with metastatic or locally advanced solid tumors. **Methods:** Pts with advanced or metastatic disease (including NSCLC, gastric, ovarian, breast, and melanoma; ECOG PS 0-1 at trial entry) were treated with avelumab at 10 mg/kg Q2W until confirmed complete response (CR), progression, unacceptable toxicity, or withdrawal. Adverse events (AEs) were evaluated by CTCAE v4.0. **Results:** In total, 480 pts treated with avelumab were followed-up for at least 4 weeks (wks) by Nov 5, 2014 and assessed in this interim analysis (median age, 60 years [range 29-85]; ECOG PS 0 [40.6%], 1 [59.0%], 3 [0.2%], or unknown [0.2%]; median of 2 prior treatments [range 1-≥ 4]). Drug-related treatment-emergent AEs (TEAEs; all grades) occurred in 68.8% of pts, with the most frequent being fatigue (20.2%), nausea (12.9%), infusion-related reaction (IRR) (9.8%), diarrhea (6.9%), chills (6.9%), decreased appetite (6.3%), pyrexia (5.6%), influenza-like illness (5.2%), and arthralgia (5.0%). Drug-related TEAEs resulted in treatment discontinuation in 34 pts; of these, 8 were due to an IRR. Drug-related grade ≥ 3 TEAEs were reported in 12.3% (n = 59); the most common of these were anemia (5), fatigue (5), increased GGT (4), IRR (4), increased lipase (4), and decreased lymphocytes (3). AEs that were potentially immune-related were observed in 11.7% of pts, with the most common being hypothyroidism (4.0%) and pneumonitis (1.5%). **Conclusions:** Avelumab demonstrated an acceptable safety profile in a heavily pretreated population across a range of tumor types. Development of avelumab as a monotherapy and in combination is ongoing. *Proposed INN. Clinical trial information: NCT01772004.

3045 Poster Session (Board #371), Sat, 8:00 AM-11:30 AM

A phase II study of novel three peptides combination with gemcitabine as a first-line therapy for advanced pancreatic cancer (VENUS-PC study). *First Author: Hiroaki Tanaka, Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan*

Background: The novel HLA-A*2402-binding peptides derived from KIF20A (RAB6KIFL) belong to the kinesin superfamily of motor proteins, which play critical roles in the trafficking of molecules and organelles during the growth of pancreatic cancer. A phase I cancer vaccination trial using KIF20A determined its safety and immunogenicity in advanced pancreatic cancer (PC) patients (J Immunother 2014;37:36-42). We further performed a phase II trial using not only KIF20A but also an antiangiogenic cancer vaccine targeting VEGFR1 (vascular endothelial growth factor receptor 1) and VEGFR2. This revealed the safety and immunogenicity in advanced colorectal cancer as presented at the 2011 ASCO Oral Abstract Session (J Transl Med. 2014; 12:63). We try to evaluate the benefit of the cancer vaccination in combination with gemcitabine (GEM) as first-line therapy in advanced PC patients. **Methods:** Sixty-eight chemotherapy naïve PC patients were enrolled to evaluate primarily the one year survival rate, and secondarily overall survival. Each of the three peptides was mixed with 1ml of Incomplete Freund's adjuvant and subcutaneously administered weekly. GEM was administered at a dose of 1000 mg/m^2 on days 1, 8, and 15 in a 28-day cycle. All enrolled patients received the therapy without knowing the HLA-A status, and the HLA genotypes were revealed at analysis point and then, the endpoints were evaluated between the HLA-A*2402 positive and HLA-A*2402 negative group. **Results:** Between June 2012 and May 2013, a total of 68 patients were enrolled in this study. No severe adverse effects of grade 3 or higher related to these three peptides were observed. The one year survival rate was 30.3%. Median survival time was 9.2months. Response rate was 11.8% and disease control rate was 73.5%, respectively. The HLA genotype will be revealed in March 2015 and the endpoints compared between HLA-A*2402 positive and negative group will be presented at this meeting. **Conclusions:** These results suggest that this combination therapy will be feasible and promising for the treatment of advanced pancreatic cancer. Clinical trial information: UMIN000008082.

3046 Poster Session (Board #372), Sat, 8:00 AM-11:30 AM

Effect of denileukin diftitox (DD) on vaccine-induced T-cell responses and depletion of Tregs in melanoma. *First Author: Jason John Luke, University of Chicago, Chicago, IL*

Background: Depletion of CD25+ Tregs improves anti-tumor immunity in preclinical models. DD is a recombinant fusion protein of hIL-2 and diptheria toxin fragment that also kills CD25+ T cells. Prior clinical trials of DD suggested reduction of FoxP3+ Tregs, improved immune responses, and some clinical responses. We evaluated the effect of DD prior to vaccination in patients (pts) with metastatic melanoma. **Methods:** Pts were randomized to 4-peptide vaccine (250 mcg of Melan-A, gp100, MAGE3 and NA17 with GM-CSF 125 mcg emulsified in Montanide) alone or after single dose of DD (18 mcg/kg). Vaccine was given every 2 weeks for 3 doses and absent progression continued every 2 weeks. Toxicity was evaluated by CTCAE and response by RECIST. Pts were HLA-A2+ with stage IIIC/IV melanoma. Any prior therapy, standard biochemical parameters and no history of autoimmunity were allowed. Blood and tissue biopsy (when possible) were obtained pretreatment and after 3 vaccinations for immunologic assessments. **Results:** 17 pts were enrolled (7 receiving DD, 41%). Characteristics included (median) age:63, M:14; ECOG:1; cutaneous: mucosal (15:2), M status A:B:C% (6:29:65), pretreated 83%. There were no drug-related G3-4 adverse events. 9 pts (4 DD: 5 vaccine only) showed clinical benefit (1 PR, 8 SD). Time to progression was 4.9 months for DD, 4.4 mo for non-DD. Flow cytometry showed that DD did not affect total Tregs in peripheral blood (p = 0.76). ELISPOT assays revealed that in some pts peptide vaccination augments the number of Ag-specific CD8 T cells in the blood but DD did not increase Ag-specific CD8 T cell response. On-treatment biopsy from DD and non-DD treated pts showed no depletion of intratumoral Foxp3+ T cells by RT-PCR. ELISA for IL2R-alpha demonstrated that outcomes were not impacted by soluble CD25 level (p = 0.13). **Conclusions:** In contrast with previous studies,DD did not effectively deplete Tregs, augment T cell responses or improve clinical activity in pts with melanoma. Clinical trial information: NCT00515528.

3047 Poster Session (Board #373), Sat, 8:00 AM-11:30 AM

Safety and tolerability results from a phase I study of MEDI4736, a human IgG1 anti-programmed cell death-ligand-1 (PD-L1) antibody, combined with gefitinib in patients (pts) with non-small-cell lung cancer (NSCLC). *First Author: Ben C. Creelan, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: MEDI4736 is a human IgG1 monoclonal antibody which blocks PD-L1 binding to PD-1 and CD-80 with high affinity and selectivity. A Phase I open-label multicenter study was initiated to evaluate MEDI4736 combined with the EGFR tyrosine kinase inhibitor (TKI) gefitinib in NSCLC (NCT02088112). Dose escalation phase data are reported. **Methods**: Key eligibility criteria included: locally advanced/metastatic NSCLC of any *EGFR* mutation status, relapsed/refractory/intolerant of standard treatment; ≤ 4 prior therapies. Cohort A received MEDI4736 3 mg/kg (starting dose) every 2 weeks plus gefitinib 250 mg once-daily (QD). If no dose-limiting toxicities were observed, Cohort B received MEDI4736 at a higher dose of 10 mg/kg every two weeks plus gefitinib 250 mg QD. Primary endpoint: safety/tolerability and recommended dose of the MEDI4736 plus gefitinib combination. Secondary endpoints included: tumor response (RECIST 1.1); pharmacokinetics (PK); immunogenicity. **Results**: Of 10 pts (Cohort A = 3; Cohort B = 7): 4 male; 4 Asian; median age 58.5 years. Maximum tolerated dose was not reached, and no dose limiting toxicities were observed. Adverse events (AEs) were observed in all pts; treatment-related CTC Grade 3-4 AEs in 3 pts led to study discontinuation: dyspnea/hypoxia (Cohort A; 1 pt), myalgia/fatigue and elevated ALT (Cohort B; 1 pt each). These AEs resolved upon discontinuation and standard management guidelines. Two unrelated deaths occurred in Cohort B. No PK interactions were observed nor anti-drug antibodies detected with the drug combination. Of 7 pts with ≥ 1 8-week tumor assessment; 3 pts had reduction in tumor size (Cohort A = 2; Cohort B = 1). **Conclusions**: MEDI4736 (3 and 10 mg/kg) plus gefitinib was generally well tolerated in pts with NSCLC in the escalation phase, with early clinical activity observed in these heavily pre-treated pts. Preliminary data support continued evaluation of MEDI4736 10 mg/kg with gefitinib 250 mg as the recommended expansion phase dose in pts with *EGFR* sensitized mutation-positive/TKI naïve NSCLC. **Sponsored by MedImmune, global biologics R&D arm of AstraZeneca** Clinical trial information: NCT02088112.

3048 Poster Session (Board #374), Sat, 8:00 AM-11:30 AM

Phase II randomized trial of autologous tumor lysate dendritic cell vaccine (ADC) plus best supportive care (BSC) compared with BSC, in pre-treated advanced colorectal cancer patients. *First Author: Joan Maurel, Hospital Clinic, Barcelona, Spain*

Background: No treatments are available for patients (pts) with metastatic colorectal cancer (mCRC) that progresses after all approved therapies. Autologous tumor lysate dendritic cell vaccine (ADC) has T-cell stimulatory capacity and therefore potential antitumor activity. We designed a phase II randomized trial of ADC plus BSC (arm A) compared with BSC (arm B), in pre-treated mCRC patients. **Methods:** Pts with documented mCRC and progressive disease at least to two chemotherapy regimens and ECOG performance status (PS) of 0-2, were randomized (1:1 ratio) to arm A vs B. Stratification was done by ECOG PS (0,1 vs 2) and LDH ($<$ ULN vs $>$ ULN). Arm A was administered subcutaneously days 0,10,20,40,120 and thereafter every 6 months (m) till progressive disease (PD). Radiological evaluation was planned with multidetector computed tomography (MDCT) every 2 m the first 6 m and then every 3 m till PD in both arms. Primary endpoint was progression free rate (PFR) at 4 m. Accordingly, sample size was established in 76 pts to detect differences at month 4 in the PFR of $>$ 30% (40% in the ADC arm and 10% in BSC arm) with an a error = 0.05 and a power = 0.8. **Results:** From 08/2011 to 10/2013, 61 pts were screened and 52 pts were included (28 arm A and 24 arm B). An interim analysis recommended early termination for futility. Pts characteristics were well balanced between arms. No ADC-related adverse events were reported. Immunization induces an autologous tumor-specific T-cell response in 21 of 25 (84%) treated pts. Pts with evidence of a vaccine-induced, tumor-specific immune response has a markedly higher overall survival than non-responders (220 days (d) versus 113d); p = 0.026). No objective radiological response was observed in ADC arm. Median PFS and 4 m PFR in arm A was 2.7 m (95%CI 2.3-3.2m) and 15% vs 2.3 m (95%CI 2.1-2.5m) and 21% in arm B (p = 0.628). Median overall survival was 6.2m (95%CI 4.4-7.9m) in arm A vs 4.7m (95%CI 2.3-7m) in arm B (p = 0.41). **Conclusions:** Our trial, the first randomized clinical trial comparing ADC plus BSC vs BSC in mCRC, demonstrates that ADC generates a tumor-specific immune response, but not benefit on PFR, PFS and OS compared with BSC. Clinical trial information: NCT01413295.

3049 Poster Session (Board #375), Sat, 8:00 AM-11:30 AM

A subgroup with improved overall survival from the phase 2 IMPACT study: Maintenance therapy of metastatic colorectal cancer patients with the TLR-9 agonist MGN1703. *First Author: Jorge Riera-Knorrenschild, Universitätsklinikum Giessen und Marburg, Marburg, Germany*

Background: The double-blind placebo-controlled phase 2 IMPACT trial aimed to assess the clinical efficacy, safety, and immunological effects of the potent TLR9 agonist MGN1703, given at the dose of 60 mg subcutaneously twice weekly as switch maintenance after disease control due to first-line induction chemotherapy +/- bevacizumab in patients with metastatic colorectal cancer (mCRC). **Methods:** After randomization of 59 patients the trial was prematurely closed and final analysis showed a superior effect of MGN1703 compared to placebo with hazard ratios (HR) for the primary endpoint PFS on maintenance of 0.55 (p = 0.041) and 0.56 (p = 0.070) by local investigator assessment or independent radiological review, respectively. Exploratory PFS analyses of pretreatment characteristics identified patients with normalized CEA, objective response, and the presence of activated NKT cells at the end of induction chemotherapy to benefit the most from maintenance with MGN1703. The impact of these factors on the secondary endpoint overall survival (OS) is presented here. **Results:** OS data were not mature at time of final study analysis, since only 35% of MGN1703 patients and 50% of placebo patients had an event. The HR for OS of the whole study population was 0.63 (median 22.6 vs. 15.1 months). The subgroup of patients randomized into the study with confirmed RECIST response had a HR of 0.40 (median 24.5 vs. 15.1 months), suggesting this may be the population with greater benefit. HR for patients with normalized CEA or with activated NKT cells were 0.69 and 0.43, respectively. Based on this evidence, patients with mCRC and objective response after standard induction therapy are randomized in the phase 3 IMPALA study to standard treatment or switch maintenance with MGN1703. CEA and activated NKT cells are stratification factors for the study and will be prospectively assessed. **Conclusions:** The pretreatment characteristics predictive of a PFS benefit in the IMPACT study seem to retain their value also in exploratory analyses for OS. This information has been used to design the phase 3 IMPALA study, currently recruiting patients. Clinical trial information: NCT01208194.

3050 Poster Session (Board #376), Sat, 8:00 AM-11:30 AM

CD137 co-stimulation and blocking PD-1 enhances NK cell-mediated target cell lysis by CD30/CD16A TandAb AFM13. *First Author: Xing Zhao, Tissue Engineering and Stem Cells Research Center, Department of Immunology, Guiyang Medical University, Guiyang, China*

Background: The CD30/CD16A bispecific tetravalent TandAb antibody AFM13 recruits and activates NK cells by specific binding to CD16A for targeted lysis of $CD30^+$ tumor cells. Given promising clinical activity and safety profile of AFM13 and proof-of-mechanism demonstrating dependence on the immune response, potential synergy of AFM13 and checkpoint inhibitors was evaluated. **Methods:** Efficacy was assessed by in vitro cytotoxicity with human PBMCs, enriched NKs, and $CD30^+$ target cells as well as cell line and patient-derived xenograft in vivo models with AFM13, anti-CTLA-4, anti-PD-1, or anti-CD137 antibodies. **Results:** AFM13 demonstrated higher potency and efficacy toward target and effector cells relative to other $CD30^+$ antibody formats (EC50 = 15pM). These favorable properties resulted in superior cytotoxicity when AFM13 was incubated with $CD30^+$ tumor cells and enriched NK cells. Single treatment with AFM13 at suboptimal concentrations (1 pM) induced effector-to-target cell-dependent lysis of $CD30^+$ lymphoma cells up to 40% using enriched NK cells. Immune-modulating antibodies alone mediated substantially lower lysis ($<$ 25%). However, the addition of anti-PD-1 or anti-CD137 to AFM13 strongly enhanced specific lysis up to 70%, whereas the addition of anti-CTLA-4 to AFM13 showed no beneficial effect. The most impressive increase of efficacy was observed when AFM13 was applied together with a combination of anti-PD-1 and anti-CD137. In vivo, synergy of AFM13 and CPI combination was observed with each CPI tested and augmented with anti-PD1 (regression in 9/10 tumors), ant-CTLA-4 (3/10), and anti-CD137 mAb (3/10) and influenced by presence of regulatory T cells, NK cells, and Th1 cytokines. **Conclusions:** Our findings support engagement of NK cells using CD30/CD16A TandAbs by binding to CD16A does not completely exploit the efficacy of NK cells. Therefore combination trials performed with companion intratumoral assessment may personalize dual-Ab therapy and augment the efficacy of AFM13 and CPIs.

3051 Poster Session (Board #377), Sat, 8:00 AM-11:30 AM

Long term survival in IMAGE 1 (Immune Modulation And Gemcitabine Evaluation 1), a randomized, open-label phase II trial comparing gemcitabine with and without IMM-101 in advanced pancreatic cancer. *First Author: Angus George Dalgleish, St. George's University of London, London, United Kingdom*

Background: Immunotherapy may produce durable responses in some patients. IMM-101, a systemic immunomodulator containing heat-killed *Mycobacterium obuense* (NCTC13365), can be combined with various forms of chemotherapy and has shown survival benefits in cancer patients. **Methods:** In IMAGE 1, survival, safety and tolerability were assessed in advanced pancreatic cancer patients (n = 110) with a WHO score of 0-2 receiving IMM-101 (0.1 mL, 10 mg/mL intradermally) + Gemcitabine (Gem) (1000 mg/m^2 q7d3) (n = 75) or Gem alone (n = 35) for a 12-cycle maximum. Patients who completed IMAGE 1 were invited to enter a follow-up study to monitor long term survival, and received IMM-101 and, at the investigator's discretion, adjunctive chemotherapy. **Results:** As previously reported, IMM-101 was associated with clinically meaningful increases in OS and PFS, with no additional burden of adverse events above those relating to chemotherapy or the underlying disease. Patients in the ITT set with metastatic disease (n = 92) benefited most with a significant increase in median OS from 4.4 months in the Gem group (n = 28) to 7 months in the IMM-101 + Gem group (n = 64) (p = 0.01; HR 0.54, 95% CI 0.33-0.87). We now report an increase in survival probability at 12 months from 11.5% in the Gem group to 22.4% in the IMM-101 + Gem group. Consistent with an increasing separation of the K-M curves, this is amplified at 18 months when the figures are 2.3% and 18.3% in the respective groups. The times corresponding to 25% probability of survival are 7.2 and 11.5 months for the Gem and IMM-101 + Gem group, respectively, an extension of 4.3 months. Of 11 metastatic patients in the ongoing follow-up study, all from the IMM-101 + Gem group, 8 survived for 18 months from randomization and 4 of these remained alive at 2 years. The longest period on study is currently 34 months. **Conclusions:** First line IMM-101 with adjunctive chemotherapy produced significant survival benefits in patients with metastatic disease. The durable responses seen in a proportion of patients are consistent with immunotherapy for other cancers but were not predicted in advanced pancreatic cancer. Clinical trial information: NCT01303172.

3052 Poster Session (Board #378), Sat, 8:00 AM-11:30 AM

Effect of human OX40 ligand fusion protein (MEDI6383) on immune cells of the humoral and cell-mediated immune response in a non-human primate model. *First Author: Michael D Oberst, MedImmune, Gaithersburg, MD*

Background: MEDI6383 is a human OX40 ligand fusion protein currently in clinical development for the treatment of advanced solid malignancies. In vitro, this OX40 agonist binds and activates the human OX40 receptor to potently induce activation and proliferation of OX40-expressing human T cells. Given that MEDI6383 binds and signals through non-human primate OX40 with similar potency as human OX40, we hypothesized that the fusion protein would mediate T cell activation in vivo in a non-human primate model. **Methods:** To test this hypothesis, a PK/PD study was conducted wherein non-human primates were administered MEDI6383, a vehicle control, or an agonist mouse anti-human OX40 monoclonal antibody (mAb). Pharmacodynamic changes in the peripheral blood were measured using flow cytometry-based immunophenotyping. **Results:** Peripheral CD4 and CD8 memory T cell activation and proliferation were observed after administration of MEDI6383, and differed quantitatively and qualitatively from that following treatment with the OX40 mAb. Likewise, MEDI6383 also induced the proliferation of peripheral B cells, suggesting an effect on T cell-to-B cell crosstalk in vivo. Other pharmacodynamic changes observed with OX40 agonism will also be presented. **Conclusions:** These findings suggest that MEDI6383 activates both humoral and cellular immune responses, activities that have the potential to boost anti-tumor immunity in the setting of human cancer.

3053 Poster Session (Board #379), Sat, 8:00 AM-11:30 AM

A retrospective analysis of high-dose aldesleukin (HD IL-2) following immune checkpoint blockade (ICB) in metastatic melanoma (MM) and metastatic renal cell carcinoma (mRCC). *First Author: Anasuya Gunturi, Beth Israel Deaconess Medical Center, Boston, MA*

Background: HD IL-2 received FDA-approval for the front-line treatment for MM and mRCC based on its ability to produce durable responses in a subset of pts. Recently, agents targeting CTLA-4 (ipilimumab, ipi) and PD-1/PD-L1 (aPD-1) have been developed and tested in these settings. As more pts are treated with ICB as front-line therapy, it becomes increasingly important to understand if HD IL-2 is safe and efficacious as salvage therapy. **Methods:** PROCLAIM (www.proclaimregistry.com) is a IL-2 observational registry with $>$ 40 participating sites consisting of a retrospective ($n = 170$, locked) and prospective cohort ($n > 343$, on-going). We queried this database to identify pts treated with HD IL-2 after receiving ipi or aPD-1 and report their safety and efficacy outcomes, compared to those who received HD IL-2 alone. **Results:** Within the database, there are 112 pts who received HD IL-2 without any prior or post ICB, 47 pts who received HD IL-2 after ipi and 4 who received HD IL-2 after aPD-1. The most common toxicities were hypotension, thrombocytopenia, and diarrhea in the HD IL-2 alone and prior ipi groups, while hypotension, nausea/vomiting, and pulmonary edema were most common in the prior aPD-1 group. In pts evaluable for AEs, 1.9% of the HD IL-2 alone group, 6.4% of the prior ipi group and none of the prior aPD-1 group developed immune-related adverse events. None of these events were grade 3/4. The ORR was 22.9% for pts treated with HD IL-2 alone, while the ORR for pts treated with HD IL-2 after ipi or aPD-1 was 17.7%. Median OS was 14 mos for HD IL-2 alone group, 16 mos for prior ipi group and 14.5 mos for prior aPD-1 group. **Conclusions:** Early patient data from the PROCLAIM database suggest that HD IL-2 is a safe treatment option for pts who have had progressive disease after prior ICB. Outcomes from additional pts as well as updated survival data will be reported. Further exploration through prospective studies is needed to determine the optimal sequence of these immunotherapies. Clinical trial information: NCT00686959.

3054 Poster Session (Board #380), Sat, 8:00 AM-11:30 AM

Targeting the Wnt5a-β-catenin pathway in the melanoma microenvironment to augment checkpoint inhibitor immunotherapy. *First Author: Brent Allen Hanks, Duke University Medical Center, Durham, NC*

Background: While checkpoint inhibitor immunotherapy has demonstrated recent success in patients with advanced melanoma, a significant fraction of these patients continue to fail therapy. The β-catenin signaling pathway plays a role in dendritic cell (DC) tolerization and regulatory T cell (Treg) differentiation however the factors responsible for inducing this pathway are unknown. **Methods:** We utilized a $BRAF^{V600E}PTEN^{-/-}$ autochthonous model of melanoma to identify melanoma-derived factors capable of driving local Treg development and the generation of an immunotolerant microenvironment. Primary human melanoma specimens were examined for expression of these candidate factors by immunohistochemistry while sentinel lymph node-derived DCs were analyzed for expression of downstream mediators of the identified signaling pathway. Based on this data, a small molecule inhibitor of the candidate signaling pathway was tested to augment the anti-tumor immune response of checkpoint inhibitors in a murine melanoma model. **Results:** We identified the Wnt5a ligand as a critical mediator β-catenin signaling in DCs and of Treg generation in the $BRAF^{V600E}PTEN^{-/-}$model. We further determined Wnt5a to be associated with expression of the Treg marker, FoxP3, in human melanoma tissues and for Wnt5a expression by primary melanomas to be associated with an improved objective response to anti-CTLA-4 antibody therapy. In addition, our work suggests that activation of the β-catenin signaling pathway in sentinel lymph node derived DCs correlates with higher tumor burden and inferior clinical outcome. Finally, we show that suppressing Wnt ligand secretion and downstream signaling by targeting the Porcn acyl transferase enzyme functions to enhance the anti-melanoma immune response and suppress melanoma growth when administered in combination with anti-CTLA-4 antibody therapy. **Conclusions:** The Wnt5a-β-catenin signaling pathway represents a novel pharmacological target within the melanoma microenvironment that is worthy of further investigation in combination immunotherapy clinical trials.

3055 Poster Session (Board #381), Sat, 8:00 AM-11:30 AM

Pharmacokinetic profile and receptor occupancy of avelumab (MSB0010718C), an anti-PD-L1 monoclonal antibody, in a phase I, open-label, dose escalation trial in patients with advanced solid tumors. *First Author: Christopher Ryan Heery, Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Reported here is the pharmacokinetic (PK) profile of avelumab and receptor occupancy (RO) from a phase I dose escalation trial (NCT01772004). Previous in vitro experiments spiking anti-PD-L1 into human whole blood samples from healthy donors confirmed that 1 mcg/mL was sufficient for $>$ 95% RO. **Methods:** In this study, dose escalation (3+3 design) was performed for 4 dose levels (DL 1, 3, 10, and 20 mg/kg). The dose limiting toxicity (DLT) evaluation period was 3 weeks. After DL safety was determined, accrual of additional patients (pts) was allowed for the purpose of generating additional safety, PK, and RO data. **Results:** 50 pts with advanced solid tumors were enrolled and treated with avelumab, Q2W. 4, 13, 13, and 20 pts were accrued to DL 1-4, respectively. Median pt age was 59 yrs (range 29-77); 19 had an ECOG PS of 0 and 29 had an ECOG PS of 1 (2 unknown).The median number of prior lines of therapy was 3 (range 1- $\geq$ 4). Data from 45 pts were evaluable for PK analysis. $C_{max}$and AUC increased linearly with dose. Half-lives were 66, 86, 92, and 115 h for DL 1, 2, 3 and 4, respectively, with no statistically significant differences between the 3 higher DLs. Trough levels at 10 mg/kg, but not at 1 and 3 mg/kg, were sufficient for $>$ 95% RO at all dosing occasions. Population PK analysis showed that a 2-compartment model with linear elimination best described the data. Covariate analysis did not demonstrate significant correlation between body-size metrics and clearance. There was no significant change in absolute lymphocyte count or in additional multiple immune cell subsets evaluated. **Conclusions:** The PK and RO data indicate the 10 mg/kg dose of avelumab achieves excellent RO with a predictable PK profile. Based on these data and the safety profile reported separately, the 10 mg/kg dose is being tested in ongoing phase II trials. *Proposed INN. Clinical trial information: NCT01772004.

3056 Poster Session (Board #382), Sat, 8:00 AM-11:30 AM

Human OX40 ligand fusion protein (MEDI6383) as a potent OX40 agonist and immuno-modulator in vitro and in vivo. *First Author: Scott A Hammond, MedImmune, Gaithersburg, MD*

Background: OX40 is a tumor necrosis factor receptor found primarily on activated T effector (Teff) cells and regulatory T (Treg) cells including lymphocytes infiltrating mouse and human tumors. Costimulation of OX40 by agonist molecules is hypothesized to improve antitumor immunity by enhancing Teff cell activity and inhibiting Treg cell suppression. MEDI6383 is a novel, agonist, human OX40 ligand fusion protein currently undergoing early phase clinical testing for the treatment of advanced solid malignancies. **Methods:** Preclinical pharmacological properties of MEDI6383 were assessed using in vitro and in vivo models. **Results:** MEDI6383 bound specifically and with high affinity to human and monkey OX40 expressed on the cell surface of T cells, and did not bind to OX40 expressed on the cell surface of either rat or mouse T cells. The OX40 signaling pathway was activated by MEDI6383, as measured by NFκB signaling in human OX40-expressing Jurkat T reporter cells. Co-culture of reporter cells with cells that express Fcγ receptors enhanced OX40 signaling, demonstrating that clustering of MEDI6383 by Fcg receptors increased the OX40 intracellular signaling strength and magnitude of response. MEDI6383 enhanced T cell receptor mediated (co-stimulatory) activation of primary human CD4+ T cells as demonstrated by the induction of cell proliferation and cytokine release, and reduced Treg cell suppression in T cell co-cultures. MEDI6383 showed no such activity in the absence of concomitant CD3/T cell receptor complex signaling. MEDI6383 demonstrated potent in vivo antitumor activity that was dependent on the addition of alloreactive human T cells in a xenograft mouse model of human cancer. Intravenous administration of MEDI6383 to rhesus monkeys in the absence of a define antigen challenge resulted in the proliferation of both CD4+ and CD8+ total memory T-cell populations as measured by induction of the cell-proliferation marker Ki67, and by an increase in absolute numbers of these T cell populations. **Conclusions:** These results demonstrate that MEDI6383 is a potent, soluble agonist of the OX40 pathway that may be utilized to boost anti-tumor immunity in patients with cancer.

3057 Poster Session (Board #383), Sat, 8:00 AM-11:30 AM

In vitro and in vivo killing of AML using tetravalent bispecific CD33/CD3 TandAbs. *First Author: Linda G. Eissenberg, Washington University School of Medicine, St. Louis, MO*

Background: Antibody-based targeting agents specific for CD33 and CD3 are evolving as promising strategies for treating AML. T550, T564, and T589 are TandAbs that are bispecific as well as tetravalent with high affinity for CD33 (McAleese and Eser, 2012, Future Oncol. 8: 687-695). **Methods:** TandAbs were incubated with purified human T cells and a VPD-450-labeled human $CD33^+$ leukemia cell line, KG-1, or the $CD33^-$ human ALL cell line, G2 (E:T = 5:1). Flow cytometry was used to evaluate target cell lysis by TandAbs (10^{-15} to 10^{-8}M for 24h at 37°C). A primary $CD33^+$ AML patient sample (5 x 10^6 PBMC; 98% blasts, 2% T cells) engrafts robustly when injected iv into NSG mice. TandAb T550 and T564 were administered iv at 5 or 50 ug/mouse qd starting 4 h after injection of primary AML cells and daily thereafter for 5 days (n = 8). On day 38 human leukemic blasts and human T cells in the blood, spleen, and bone marrow (BM) were enumerated by flow cytometry (human CD33, CD34, CD45, CD45, CD14, CD3, CD4, CD8, and 7AAD). **Results:** Incubation of TandAbs T550, T564, and T589 with human T cells efficiently lysed KG-1 cells (IC50 ~0.01, 0.5, and 5 pM respectively). Up to 40% of T cells were activated ($CD25^+$), rising with cytotoxic activity. A control TandAb with an irrelevant target, T151 ($> 10^{-7}$ M), did not cause significant killing of KG-1 in vitro. T564 induced lysis of KG-1 cells (IC50 = 5 x 10^{-12}M) but had no effect on $CD33^-$ G2 cells (1 x 10^{-8}M). In mice injected with AML cells alone $>$ 40% of spleen cells and $>$ 45% of BM cells were confirmed by FACS to be AML blasts by day +38. No human AML was detected in the peripheral blood. In contrast, after treatment with $\geq$ 5 ug of either T550 or T564, $<$ 0.1% of cells in the spleen and $<$ 1% in the BM were leukemic blasts, representing an ~3 log reduction in leukemic blasts by day +38. Treated and untreated mice had equivalent T cell numbers on day 38. **Conclusions:** T cells become activated and potently lyse tumor cells only when targeted to CD33+ leukemic cells (KG-1) and primary CD33+ AML blasts by CD33/CD3 TandAbs. In spite of the protective environments of the BM and spleen and the extremely low number of T cells infused, nearly all primary AML blasts could be eliminated in vivo.

3058 Poster Session (Board #384), Sat, 8:00 AM-11:30 AM

Population pharmacokinetic (popPK) model of pembrolizumab (pembro; MK-3475) in patients (pts) treated in KEYNOTE-001 and KEYNOTE-002. *First Author: Tara C. Gangadhar, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: The anti–PD-1 antibody pembro has efficacy in advanced cancer pts. We characterized pembro PK properties and quantified the effect of clinical factors on exposure. Immunogenicity was also assessed. **Methods:** Pooled popPK analysis was performed to characterize pembro serum concentrations over time in pts with melanoma (n = 1077), non-small cell lung cancer (n = 46), and other advanced cancers (n = 16) treated in KEYNOTE-001 and KEYNOTE-002. Simulations were performed to evaluate the magnitude of the effects of several clinical covariates on exposure. To investigate the immunogenicity potential of pembro, the development of antidrug antibodies (ADA) was determined. **Results:** A 2-compartment model with linear clearance from the central compartment adequately describes the clinical pharmacokinetics of pembro over the 1-10 mg/kg dose range (Table). No significant differences in efficacy have been observed for pembro 2 and 10 mg/kg Q3W and 10 mg/kg Q2W and Q3W. The PK profile is similar to other monoclonal antibodies, with a low clearance (0.2 L/day), limited central volume of distribution (3.8 L), and low to moderate variability (22-41%). The effect of age, sex, geographic location, baseline ECOG PS, eGFR, AST, bilirubin, albumin, glucocorticoid coadministration, tumor type and burden, and prior ipilimumab on pembro exposure is limited, as alterations of 20% or less are predicted by the popPK model. Of 268 pts evaluable for ADA, 1 ($<$1%) developed confirmed treatment-emergent ADA with no impact on efficacy or safety. **Conclusions:** The pembro PK profile indicated a low clearance and limited volume of distribution, consistent with other monoclonal antibodies. There was no clinically meaningful effect of baseline clinical factors on pembro exposure. Pembro has limited potential to elicit the formation of ADA. Clinical trial information: NCT01295827 and NCT01704287.

Median (90% prediction interval) PK parameters of pembro at steady state based on popPK model.

	Pembro Dose Regimen		
PK Parameter	**2 mg/kg Q3W**	**10 mg/kg Q3W**	**10 mg/kg Q2W**
C_{max} (μg/mL)	64.6 (43.9; 99.2)	318 (215; 488)	393 (261; 691)
C_{trough} (μg/mL)	22.3 (8.84; 50.1)	110 (40.8; 257)	185 (82; 395)
AUC_{ss}, 6 wk (μg•day/mL)	1398 (713; 2730)	6859(3403; 13712)	10353 (5308; 20137)

3059 Poster Session (Board #385), Sat, 8:00 AM-11:30 AM

Phosphatidylserine targeting antibody in combination with anti-PD-1 antibody treatment activates infiltrating T lymphocytes of the spleen and tumor microenvironment in pre-clinical models of melanoma and breast cancer. *First Author: Xianming Huang, The University of Texas Southwestern, Dallas, TX*

Background: Despite substantial progress, only a select subset of patients benefit from anti-PD-1/PD-L1 therapies. The underlying cause for these failures of immune checkpoint blockade therapy is the overwhelming, persistent and multifocal immune suppression within the tumor microenvironment. As phosphatidylserine (PS) becomes externalized to the outer leaflet of the cell's plasma membrane within the tumor microenvironment, it serves as a signaling ligand for PS receptors on immunosuppressive myeloid-derived suppressor cells (MDSCs), regulatory T cells and M2 macrophages that can occupy up to 50% of the tumor mass. Bavituximab is a chimeric monoclonal antibody that targets and inhibits PS mediated immunosuppressive signaling, supporting immune activation and reducing levels of MDSCs, re-polarizing tumor-associated macrophages from M2 to M1 phenotype, promoting the maturation of dendritic cells (DCs) and inducing potent antitumor T-cell immunity. **Methods:** A combination of bavituximab and anti-PD-1 therapy was compared in syngeneic, pre-clinical models of melanoma and breast cancer. **Results:** Our results show that the combination induces a statistically significant activation of lymphocytes in the spleen and the tumor microenvironment as well as decreases MDSCs and PD-L1 expression. In the spleen, increases were noted in T-cells producing IFN-g and IL-2 and DCs in association with decreased MDSCs over single anti-PD-1 treatment alone. Similarly, in the tumor microenvironment, the combination treatment demonstrates increases in TILs producing IFN-g, TNFα, IL-2, Granzyme B, PD-1, increased Lag-3 positive CD8 cells, CD137 (41BB) positive CD4 cells as well as a decrease in MDSCs and PD-L1 expressing TILs compared to anti-PD-1 treatment alone. **Conclusions:** Our pre-clinical results support the use of bavituximab as an immunomodulatory treatment in PD-1 sensitive and anti-PD-1 resistant/unresponsive tumors. This effect involves enhancing the activation of CD8+ TIL correlating with increased immune stimulatory components in the spleen and the tumor microenvironment.

3060 Poster Session (Board #386), Sat, 8:00 AM-11:30 AM

Activation of CD8+ tumor infiltrating lymphocytes by bavituximab in a 3D ex vivo system of lung cancer patients. *First Author: Soner Altiok, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Bavituximab is a chimeric monoclonal antibody that targets the membrane phospholipid phosphatidylserine (PS) exposed on endothelial cells and cancer cells in solid tumors. Bavituximab blocks PS-mediated immune suppression in the tumor microenvironment. **Methods:** Fresh tumor tissues from consented patients with adenocarcinoma of the lung extracted at the time of surgical resection were utilized in a proprietary 3D *ex vivo* tumor miscrosphere assay to assess the immunomodulatory effects of bavituximab and potential immunosuppressive mechanisms such as expression of PD-1, CTLA-4, LAG3, TIM3, BTLA, and adenosine A2A receptor on the CD4+ and CD8+ tumor infiltrating T-cells. 3D tumor microspheres were prepared and cells were treated *ex vivo* with $f(ab)'_2$version of bavituximab, bavituximab, docetaxel, and a combination of bavituximab and docetaxel for 36 hours within an intact tumor microenvironment. Flow cytometry analysis evaluated treatment-mediated activation of TILs and changes in CD4, CD8 and Treg (CD25+/CD127-) subpopulations. A multiplex human cytokine assay was used to simultaneously analyze the differential secretion of cytokines. Additionally, a NanoString platform containing probes to quantitate 770 immune function genes was used to determine potential positive or negative associations between expression of immune function genes and TIL activation by bavituximab. **Results:** Bavituximab induces activation of TILs in 3D *ex vivo* tumor microsphere model of lung cancer, as evaluated by a significant increase in IFNgamma, TNF-a, and GM-CSF secretion. Flow cytometry analysis revealed that this effect was associated with low PD-1 expression on CD8 cells, but did not correlate with expression of other immune inhibitory molecules. **Conclusions:** Our preliminary data support the use of bavituximab as an immunomodulatory treatment in adenocarcinoma of the lung by enhancing the activation of CD8+ TIL that correlates with increased cytokine production by lymphoid and myeloid cells. We identified PD-1 expression as a potential biomarker of response to bavituximab treatment, suggesting that the interruption of the PD-1/PD-L1 axis may enhance the bavituximab effect in lung cancer.

3061 Poster Session (Board #387), Sat, 8:00 AM-11:30 AM

A phase I/II study of ipilimumab in women with metastatic or recurrent cervical carcinoma: A study of the Princess Margaret and Chicago N01 Consortia. *First Author: Stephanie Lheureux, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Response to second-line therapy in cervical cancer (CC) is infrequent. Based on evidence of HPV-induced immune evasion, immunotherapy is an attractive strategy in CC. Ipilimumab (Ipi) is a fully humanized monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4, a molecule that acts to downregulate the T cell immune response. **Methods:** A multicenter trial was designed to evaluate Ipi IV in metastatic/recurrent cervical cancer (NCT01693783). Eligibility requirements included measurable disease progression and prior exposure to platinum therapy. A run-in phase I safety cohort was scheduled using Ipi 3mg/kg every 21 days for four cycles in 6 patients (pts). The phase II was planned in 32 pts with Ipi 10mg/kg every 21 days for four cycles; followed by four cycles of maintenance therapy (same dose) every 12 weeks for pts demonstrating radiologic response/stabilization. Primary objectives were safety and response rate at the end of cycle 4. Immune correlative studies were performed on peripheral blood pre- and post-Ipi therapy, on archival tissue, on fresh tumor obtained prior to registration and 7 days post cycle 2. **Results:** From Dec/12 to Sept/14, a total of 42 pts with a median age of 49 (23-78) were enrolled; 29 pts had squamous CC and 13 pts had adenocarcinoma. Thirty five pts had prior radiation completed $>$ 3 months prior to enrollment and 21 pts had received 2/3 prior regimens. Toxicities were manageable and Grade 3 toxicities included diarrhea (4 pts) and colitis (3 pts). Best response (RECIST 1.1) for the 34 evaluable pts (2 pts awaiting results) included: 3 PR (1 PR and 2 uPR), 8 SD and 23 PD. The median PFS was 2.5 months (95% CI: 2.3-3.2). HPV testing was positive in 33 tumors. Intratumoral CD3, CD4, CD8, FoxP3, IDO and PD-L1 expression pre and post treatment are pending. Multicolor flow cytometry on peripheral lymphocytes revealed a treatment dependent increase of ICOS, HLA-DR, CCR4, and PD-1 during initial treatment which returned to baseline during maintenance. **Conclusions:** Ipi was well tolerated in cervical cancer pts. There is a signal of activity of immunotherapy in cervical cancer. Following Ipi treatment, an immune activation has been observed. Clinical trial information: NCT01693783.

3062 Poster Session (Board #388), Sat, 8:00 AM-11:30 AM

Second generation antihistamines after breast cancer diagnosis to improve prognosis both in patients with ER+ and ER- breast cancer. *First Author: Hakan Lars Olsson, Department of Oncology, Lund, Sweden*

Background: Subgroups of patients with breast cancer (BC) could be candidates for immunological interventions. In the present investigation the role of antihistamines on prognosis of breast cancer has been studied, especially comparing first and second generation H-1 receptor antagonists due to their possible different effects on cytokines. **Methods:** The study includes all women with BC diagnosed in Sweden 2000 through 2008 (n = 54406). Dates of birth, BC diagnosis and TNM-stage were directly extracted from the cancer registry. Therapy with antihistamines was gathered from the Swedish Prescription Registry. Other registries utilised were the Cause of Death Registry, Population Registry, and the in patient or out patient registries. BC and overall survival was compared between users of antihistamines and non users. Analyses were adjusted for TNM-stage, receptor status and age at diagnosis. A late entry model was used for different types of antihistamines. **Results:** The HR for BC specific survival for the combined group of antihistamine users (n = 9777) was 0.70 (0.66-0.75). All the effect was seen for use after BC diagnosis. Results remained after adjusting for out or in patient diagnoses of allergy. In late entry models women using desloratadine (n = 1895) had a HR of 0.69 (0.52-0.91). Loratadine users (n = 2132) HR of 0.74 (0.60-0.93). Cetirizine users (n = 3001) HR of 1.13 (0.96-1.33) and Klemastine users (n = 2278) had a HR of 0.98 (0.80-1.19). Ebastin users (n = 326) had a HR of 0.50 (0.22-1.12) and Fenofexadine users (n = 145) had a HR of 0.73 (0.30–1.76). The analyses was also stratified for ER-status, but the results did not differ noticeably. Results were similar when overall survival was analysed. **Conclusions:** This population based registry study shows that women treated with second generation antihistamines have a better overall and BC specific survival compared with non users regardless of age, history of allergy, ER status and tumor stage. The results are strongest for desloratadine use and use after BC diagnosis. Second generation antihistamines could offer a nontoxic therapy for both receptor positive and negative BC. The mechanism behind this effect is presently unknown.

3063 Poster Session (Board #389), Sat, 8:00 AM-11:30 AM

A phase I study of the toll-like receptor 5 (TLR5) agonist, entolimod in patients (pts) with advanced cancers. *First Author: Hatoon Bakhribah, Roswell Park Cancer Institute, Buffalo, NY*

Background: Entolimod is a specific, TLR5 agonist derived from salmonella flagellin, with immunotherapeutic effects in preclinical cancer models. Entolimod activates innate and adaptive immune responses and mobilizes immunocytes to organs such as liver and bladder, with functional TLR5. A phase 1 trial was undertaken to evaluate entolimod's safety, tolerability, pharmacokinetics, immunoactivity, and preliminary antitumor activity. **Methods:** Pts with advanced cancers and ECOG PS of 0-1 were treated at 5 subcutaneous doses (5, 10, 15, 20, 30, 40 μg/day) over a 2-week period. PK/PD samples were obtained pre, and 2, 4, 6, 8, 24 hrs post-dose. Immune function samples were obtained pre and 24 hrs post-dose on days1, 8, 11 and 22. **Results:** 26 pts (38.4% colorectal cancer [CRC] and 19% NSCLC) were enrolled. Common toxicities were transient hypotension (9 grade 1/4, 7 grade 2/4), hyperglycemia (8 grade 1/4, 6 grade 2/4), and fever (10 grade 1/4, 3 grade 2/4). Three DLTs were observed at 40 μg/day. One pt developed grade 3 rigors and pyrexia, a 2nd pt had grade 3 transaminitis; a 3rd had grade 3 hypotension. T_{max} was 2 to 6 hrs and $t_{1/2}$ was 3 to 7 hrs with little change between 1st and subsequent doses. Pharmacogenetic analysis revealed that 6 SNPs in the TLR5 gene were associated with LFT elevations ($p < 0.05$) Induced plasma cytokines included G-CSF, IL-6, IL-8 and IL-10 with no indications of cytokine storm. Pts exhibited immune cell activation with a stable or decrease in the levels of suppressive immune cells, accompanied by increased immunostimulatory and decreased immunosuppressive cytokines. Stable disease (SD) for $>$ 6 weeks was observed in 8 pts, with 3 pts (anal, CRC and urothelial cancer) maintaining SD for $>$ 12 weeks. Neutralizing antibodies developed by the 2nd week in most pts, indicating immune memory for flagellin. **Conclusions:** The recommended phase II dose of entolimod was30 μg/day on days 1, 4, 8, 11. The clinical results corroborated pre-clinical findings and support entolimod's potential as an immunotherapeutic agent. The safety profile suggests that entolimod can be combined with chemotherapeutic, targeted, or other immunotherapeutic agents. Clinical trial information: NCT01527236.

3064 Poster Session (Board #390), Sat, 8:00 AM-11:30 AM

MyD88/CD40-based costimulation to enhance survival and proliferation of chimeric antigen receptor (CAR)-modified T cells. *First Author: Aaron E Foster, Bellicum Pharmaceuticals, Houston, TX*

Background: Treatment of B cell malignancies with CAR-modified T cells has shown remarkable efficacy, but clinical responses in solid tumors have been limited due to poor T cell persistence and expansion. We examined whether incorporation of unconventional signaling elements, derived from the "universal" toll-like receptor adaptor molecule, MyD88, and the TNF family member, CD40, into CARs could improve T cell survival, proliferation and antitumor efficacy. **Methods:** Bicistronic vectors encoding inducible Caspase-9 (iCasp9) and CD19- or Her2-targeted CARs incorporating various costimulatory domains (e.g., CD28, 4-1BB, MyD88/CD40) were generated and used to transduce T cells. CAR-T cells were assessed for antitumor function in tumor coculture assays using $CD19^+$ (Raji and Daudi) cells or $Her2^+$ (SK-BR-3) tumor cells. Efficacy was monitored in immunodeficient (NSG) mice engrafted with tumor cell lines followed by i.v. CAR-T cell injection. *In vivo* T cell proliferation, as well as elimination via iCasp9 after i.p. injection of rimiducid, was measured using bioluminescent imaging (BLI). Tumor burden was also assessed by BLI or caliper measurements. **Results:** All CAR constructs could be stably expressed in T cells (30-90% CAR expression). MC costimulation resulted in greatly increased IL-2 production compared to CARs with alternative costimulation (~2500 pg/mL and ~200 pg/mL for MC and CD28.41BB, respectively). This correlated with enhanced T cell proliferation and corresponded to better tumor elimination in coculture assays (99% elimination at a 1:1 E:T ratio within 14 days). MC costimulation also enhanced the efficacy of CAR-T therapy in $CD19^+$ and $Her2^+$ tumor models, respectively, compared to control CARs. Furthermore, T cells transduced with MC-encoding CARs could be rapidly eliminated *in vivo* (within 1 day) via iCasp9 following rimiducid administration. **Conclusions:** MyD88/CD40 represents a potent, new T cell costimulatory molecule for CAR-T cells, resulting in robust IL-2 production, improved survival and proliferation, increased antitumor activity against $CD19^+$ and $Her2^+$ tumors *in vitro* and *in vivo,* while retaining a high safety profile through the iCasp9 suicide gene.

3065 Poster Session (Board #391), Sat, 8:00 AM-11:30 AM

A phase 1 dose-escalation study of IPH2102 (lirilumab, BMS-986015, LIRI), a fully human anti KIR monoclonal antibody (mAb) in patients (pts) with various hematologic (HEM) or solid malignancies (SOL). *First Author: Norbert Vey, Institut Paoli-Calmettes, Marseille, France*

Background: Inhibitory Killer Immunoglobulin-like receptors (KIRs) negatively regulate the killing, by NK cells, of tumors expressing their HLA class I ligands. We showed safety of 1st generation mAb targeting the major inhibitory KIRs (Vey et al Blood 2012).LIRI is a 2nd generation anti KIR mAb. The objectives of this study were to evaluate the safety and PK/PD of LIRI in pretreated pts with HEM or SOL with no or slowly progressive disease. **Methods:** In the dose escalation 3+3 phase 1 part, six dose levels of LIRI were evaluated: 0.015, 0.3, 1, 3, 6, and 10 mg/kg administered q4w x 4; the time between the first 2 infusions was adjusted to KIR desaturation (KIR occupancy $<$ 30%). In a cohort expansion, pts were treated at 0.015 and 3 mg/kg q4w x 4 **Results:** Twenty and 17 patients were treated in the dose escalation and cohort expansion parts, respectively Overall median age was 62 years (33-73); 22 had HEM (5 AML, 6 CLL and 11 NHL) and 15, SOL (7 ovarian [OC], 6 breast [BC], and 2 others cancers). LIRI was generally well tolerated with no DLT in the dose-escalation; MTD was not reached. Related AEs observed in $>$ 10% of the pts included fatigue/asthenia (30% of pts), pruritus (20%), infusion related reaction (14%), headache (11%). Only one SAE (G3 urticaria, at 0.015 mg/kg) was reported as treatment-related. Release of cytokines in serum was rare and mild to moderate. Eighteen patients (49%) discontinued the study prematurely including 13 because of disease progression, 3 for AE's and 2 for other reasons. Full KIR occupancy ($>$ 95%) was sustained during $>$ 4 weeks for dose-levels $\geq$ 0.3 mg/kg. **Conclusions:** LIRI was generally well tolerated up to the highest tested dose of 10 mg/kg which was associated with prolonged KIR occupancy. Based on these results, LIRI is currently investigated in a randomized phase 2 trial as maintenance therapy for elderly pts with AML in CR1 and in several phase 1 studies in combination with other immune checkpoints inhibitors or a cytotoxic mAb.

3066 Poster Session (Board #392), Sat, 8:00 AM-11:30 AM

Preclinical efficacy studies using HuMax-Axl-ADC, a novel antibody-drug conjugate targeting Axl-expressing solid cancers. *First Author: Esther CW Breij, Genmab, Utrecht, Netherlands*

Background: HuMax-Axl-ADC is an antibody-drug conjugate (ADC) that specifically targets Axl-expressing tumor cells. Aberrant expression of Axl, a receptor tyrosine kinase, has been described in solid and hematological malignancies, in both primary tumors and metastasis. Expression and activation of Axl is associated with poor clinical prognosis in cancers of the lung, pancreas, esophagus and breast. Moreover, Axl expression has been implicated in resistance to both chemotherapy and targeted therapy. Although the mechanism behind Axl activation in cancer is not fully understood, activation through the Axl ligand Gas6 has been implicated in at least some cancers. At the cellular level, Axl is involved in tumor cell adherence, migration and epithelial-to-mesenchymal transition. **Methods:** A panel of Axl-specific ADCs was generated by conjugating human Axl antibodies with the microtubule disrupting agent monomethyl auristatin E (MMAE), through a protease-cleavable linker. Axl-ADCs were functionally characterized *in vitro*, and the anti-tumor activity was tested *in vivo* using xenograft models. **Results:** Axl-ADCs demonstrated high affinity binding to Axl and efficiently induced cytotoxicity *in vitro,* which was dependent on both Axl expression and conjugation with MMAE. In a lung cancer xenograft model, Axl ADCs were shown to have potent anti-tumor activity *in vivo*. The most potent Axl-ADCs, including HuMax-Axl-ADC, induced complete tumor regression upon treatment with a single dose of 1 mg/kg. HuMax-Axl-ADC also strongly inhibited tumor growth in a xenograft model that showed high endogenous expression of Gas6. This is in line with our observation that HuMax-Axl-ADC does not compete with Gas6 for Axl binding. Importantly HuMax-Axl-ADC was able to induce tumor regression in PDX models that, similar to many human tumor biopsies, showed Axl expression in only a subpopulation of tumor cells **Conclusions:** HuMax-Axl-ADC is a novel ADC that shows potent anti-tumor activity in solid cancer xenograft models. The results obtained in preclinical studies support further development of HuMax-Axl-ADC for the treatment of solid cancers.

3067 Poster Session (Board #393), Sat, 8:00 AM-11:30 AM

Significance of PD-L1, IDO-1, and B7-H4 expression in lung cancer. *First Author: Kurt Alex Schalper, Yale University, New Haven, CT*

Background: Expression of immune inhibitory signals such as co-regulatory ligands/receptors and tolerogenic enzymes by cancer cells limits the effectiveness of the immune surveillance. Blockade of such signals (e.g. CTLA-4 and PD-1/PD-L1) can reinvigorate the anti-tumor immune response and induce clinical benefit in a proportion of patients with advanced cancer. **Methods:** Using multiplexed quantitative immunofluorescence**,** we measured the levels of CD3 (E272-Novus), CD8 (C8/144B-DAKO), PD-L1 (E1L3N-CST), IDO-1 (1F8.2-Millipore) and B7-H4 (D1M8I-CST) in 554 stages I-IV lung carcinomas represented in two tissue microarrays, one from Yale U. (TM79 n = 204) and one from Greece (TM140 n = 350). The markers were measured in different tumor compartments based on their colocalization with pancytokeratin and DAPI. Associations between the marker levels, clinico-pathological variables and survival were determined. **Results:** PD-L1 was detected in 16.9% of cases in the Yale set and 20% of cases in the Greek collection. IDO-1 was expressed in 42.6% and 49.8%; and B7-H4 in 12.8% and 22.6% of cases, respectively. The levels of PD-L1 and IDO-1 were not consistently associated with sex, age and tumor histology. B7-H4 expression was significantly associated with squamous tumors in both collections ($P = 0.041$ and $P < 0.0001$, respectively). Elevated PD-L1 or IDO-1 was consistently associated with prominent CD3 and CD8+ T cells ($P < 0.05$), but B7-H4 was not. In univariable analysis, IDO-1 expression was significantly associated with longer overall survival in the Yale set (HR = 0.572 [CI:0.368-0.871], P = 0.009), but not in the Greek (HR = 0.883 [CI:0.636-1.220], P = 0.452). Expression of PD-L1 and B7-H4 were not significantly associated with survival. Tumors with prominent levels of one of the markers had typically low levels of the others, suggesting predominance of only one immune inhibitory pathway. **Conclusions:** PD-L1, IDO-1 and B7-H4 are differentially expressed in human lung carcinomas and have limited prognostic value. While the expression of PD-L1 and IDO-1 are associated with increased T-cells, B7-H4 is not. The high frequency of IDO-1 expression in lung tumors (~45%) suggests its potential for therapy, perhaps in combination with checkpoint inhibitors.

3068 Poster Session (Board #394), Sat, 8:00 AM-11:30 AM

Model-based analysis of the relationship between pembrolizumab (MK-3475) exposure and efficacy in patients with advanced or metastatic melanoma. *First Author: Richard Wayne Joseph, Mayo Clinic Cancer Center, Jacksonville, FL*

Background: Optimization of antibody dosing in oncology drug development is an area of growing interest. We have previously demonstrated that the dose and schedule of pembrolizumab does not correlate with clinical outcomes in melanoma. Here, we assess the relationship between steady state plasma exposure and tumor growth dynamics in patients enrolled in the KEYNOTE-001 and KEYNOTE-002 studies. **Methods:** Patients received pembrolizumab 2 mg/kg every 3 weeks (Q3W) to 10 mg/kg Q2W or Q3W. Exposure was defined as the area under the serum concentration curve (AUC) over 6 weeks. Response was defined as the change in tumor size per standard rules for measuring target lesions (ie, sum of the longest diameters). We assessed the extent of tumor growth and its reduction under pembrolizumab treatment using nonlinear mixed effects modeling; specifically, we tested whether individual exposures predict patterns of tumor response. **Results:** In this initial analysis, we found that reduction in tumor growth was best characterized by an exponential decline, with an estimated halving time of approximately 4 months. The 90th percentile of pembrolizumab exposures ranged from 0.8 to 14 g×day/L. In agreement with the flat dose-efficacy relationship observed per objective response criteria, the observed individual pembrolizumab exposures do not significantly correlate with extent of tumor reduction or overall growth patterns over time. **Conclusions:** The significant and prolonged reductions in tumor size under pembrolizumab treatment were well characterized by the tumor size dynamics model. Tumor size reductions were independent of a wide (15-fold) range of exposure to pembrolizumab, supporting 2 mg/kg Q3W as an effective dosage that achieves a level of exposure sufficient to saturate tumor response. This examination of a wide exposure range and analysis via dynamic tumor size modeling demonstrates a framework for identifying an optimally efficacious dose in oncology. Clinical trial information: NCT01295827 and NCT01704287.

3069 Poster Session (Board #395), Sat, 8:00 AM-11:30 AM

UCART19, an allogeneic "off-the-shelf" adoptive T-cell immunotherapy against CD19$^+$ B-cell leukemias. *First Author: Julianne Smith, Cellectis, Paris, France*

Background: Autologous T-cells engineered to express chimeric antigen receptors (CARs) that target specific tumor antigens are of high potential in treating different kinds of cancer. However, they must be generated on a "per patient" basis, thereby limiting the population of patients that could benefit from this approach. **Methods:** We have developed a standardized platform for manufacturing T-cells from third-party healthy donors to generate allogeneic "off-the-shelf" engineered CD19-CAR+ T-cell–based frozen products. Our platform involves the use of transcription activator-like effector nucleases (TALEN), which mediate the simultaneous inactivation of two genes through genome editing. The knockout of the TCR alpha gene eliminates TCR expression and is intended to abrogate the donor T-cell's potential for graft-versus-host disease (GvHD), while knocking out the CD52 gene makes donor T-cells resistant to the lymphodepleting agent alemtuzumab. In addition, our T-cells are engineered to co-express the RQR8 gene as a safety feature, with the aim of rendering them sensitive to the monoclonal antibody rituximab. **Results:** We have obtained proof-of-concept by manufacturing TCR/CD52-deficient RQR8+ and CD19-CAR+ T-cells (UCART19) using a good manufacturing practice–compatible process and have demonstrated that UCART19 cells were functional using in vitro assays. Furthermore, we have demonstrated that the ability of UCART19 cells to engraft into an orthotopic human CD19+ lymphoma xenograft immunodeficient mouse model. UCART19 cells exhibited antitumor activity equivalent to that of standard CD19 CAR T-cells. We also demonstrated that UCART19 cells did not mediate alloreactivity in a xeno-GvHD mouse model. Finally, the effectiveness of the rituximab-induced depletion mechanism of RQR8$^+$cells was shown in an immunocompetent mouse model. **Conclusions:** This valuable dataset supports the development of allogeneic CAR T-cells, and UCART19 will be investigated in an exploratory, first-in-human, clinical trial where refractory/relapsed CD19+ B-cell leukemia patients are to be enrolled.

3070 Poster Session (Board #396), Sat, 8:00 AM-11:30 AM

Durability and characteristics of objective tumor responses with the innate immune cell modulator Imprime PGG in combination with standard of care frontline treatment for patients (Pts) with metastatic non-squamous NSCLC. *First Author: Walburga Engel-Riedel, Hospital Cologne-Merheim, Lung clinic, University Witten/Herdecke, Cologne, Germany*

Background: Recently, we reported numeric improvements in objective tumor response (OTR) and overall survival (16.1 vs 11.6 months median; HR = 0.66) with Imprime PGG (PGG) in a randomized (2:1) phase 2 study in 92 patients (pts) with stage IV non-squamous NSCLC receiving standard of care carboplatin/ paclitaxel (C/P) and bevacizumab (B) treatment first line (Engel-Riedel W et al, Ann Onc 2014, 25(5):1-41). Here, we report on the durability and characteristics of tumor regressions. **Methods:** The impact of treatment on the burden of malignant lesions was evaluated by modified RECIST v1.0. Imaging assessments (CT of chest and abdomen every 6 wks) were reviewed centrally in an independent, blinded facility. Pts were removed from treatment upon disease progression. **Results:** PGG (vs ctrl) in combination with C/P/B achieved a 60.4% (vs 43.5%) OTR rate. Time to OTR was short (12 wks vs $>$ 18 wks) and responses were durable: median duration of response was 10.3 mos vs 5.6 mos (KM), with OTR lasting $\geq$ 12 mos in 7% vs 0% of pts in the PGG vs ctrl groups. Following completion of C/P chemotherapy, there was continued regression of lesions on maintenance treatment with PGG+B but not B alone: 6 pts (20%) in the PGG group vs 0 in the ctrl group had further $>$ 1 cm reductions in target lesions' sum of longest diameters (SLD), incl. 1 CR at 47 wks; this pt remains on treatment 2 yrs post randomization. In the PGG group, OTR were observed regardless of baseline tumor burden (up to $>$ 30cm SLD) or lesion location (incl. lung, lymph nodes, adrenals, liver). Change from baseline in target lesions (SLD) over time will be presented for each pt. 1-yr survival was 62.8% vs 42.7% with PGG vs ctrl, and 13 (vs 1) pts remained in survival follow-up at primary analysis. Safety results have been reported previously and were favorable overall. **Conclusions:** Combined use of chemotherapy, B and PGG mediated rapid and durable responses of metastatic NSCLC regardless of baseline tumor burden or lesion location. There was further regression of lesions on maintenance PGG+B. Innate immune cell modulation with PGG holds promise for pts with metastatic non-squamous NSCLC. Clinical trial information: NCT00874107.

3071 Poster Session (Board #397), Sat, 8:00 AM-11:30 AM

Safety of Imprime PGG, a novel innate immune cell modulator, in adults with stage IV non-small cell lung cancer: an integrated analysis of two randomized phase 2 studies. *First Author: Folker Schneller, Policlinic of the Klinikum rechts der Isar, Technical University Munich, Muenchen, Germany*

Background: Imprime PGG (IPGG; beta-1,3/1,6 glucan), a yeast-derived pathogen-associated molecular pattern (PAMP), can prime innate immune effector cells to kill cancer cells opsonized by therapeutic antibodies. In two recent, identically designed phase 2 trials in patients (pts) with stage IV NSCLC, IPGG in combination with frontline carboplatin/paclitaxel (C/P) chemotherapy and bevacizumab (bev) or cetuximab (cet), respectively, was associated with numeric increases in objective tumor response rates and survival. This analysis evaluates the safety of IPGG across these studies. **Methods:** Patient-level data from two identically designed, randomized phase 2 trials of patients (pts) with stage IV NSCLC were combined for safety analyses. **Results:** A total of 177 pts were enrolled (118 IPGG, 59 Control [Ctrl]) and evaluable for safety. Overall (IPGG vs Ctrl), 99.2% (vs 100%) of pts experienced at least 1 treatment-emergent adverse event (AE) over the course of the study. Grade (Gr) III/IV AEs occurred in 85.6% vs 76.3% of pts, and serious AEs in 51.7% vs 42.4% of pts, respectively. Most common Gr III/IV AEs (occurring in at least 10% of pts in either arm) included neutropenia (35.6%, 37.3%), leukopenia (10.2%, 16.9%) and thrombocytopenia (11%, 11.9%). Gr III/IV AEs occurring at a $\geq$ 2% higher frequency in the IPGG arm included nausea (4.2%, 1.7%), abdominal pain (3.4%, 0%), fatigue (4.2%, 1.7%), hypersensitivity (2.5% vs 0%), polyneuropathy (5.9%, 3.4%) and pleural effusion (2.5%, 0%). Fatal AEs were experienced by 11% vs 3.4% of pts; no event occurred in $>$ 1 pt in either arm, except general physical health deterioration (2.5%, 0%); all fatal AEs were deemed unrelated or unlikely related to IPGG. In the IPGG arm, 72% of pts experienced AEs reported as related to IPGG; of these, 10.2% were considered unlikely related and 61.9% were considered possibly or probably related to IPGG. AEs of specific interest (e.g. infusion-related reactions; immune-mediated AEs) as well as subset analyses by histology will be presented. **Conclusions:** IPGG was generally well tolerated in pts with stage IV NSCLC receiving C/P chemotherapy and cet or bev therapy frontline. Clinical trial information: NCT00874107 and NCT00874848.

3072 Poster Session (Board #398), Sat, 8:00 AM-11:30 AM

Safety, immunogenicity, and clinical activity of the immunotherapeutic vaccine, DPX-Survivac, in a Phase 1/1b trial of women with ovarian, fallopian tube, or peritoneal cancer. *First Author: Jeannine A. Villella, Winthrop-University Hospital, Mineola, NY*

Background: Survivin is important in apoptosis, proliferation, and angiogenesis. High expression has been linked to progression and drug resistance. DPX-Survivac vaccine (DPX) contains a mix of survivin HLA class I peptides designed to evoke a cytotoxic T cell response against survivin. This trial reports the safety and immune response profiles of DPX in combination with metronomic low dose oral cyclophosphamide (CPA) in ovarian cancer (OC). **Methods:** 40 Stage IIc-IV OC patients with no evidence of disease progression post-platinum chemotherapy were enrolled. Adverse events and dose limiting toxicities (DLT) were defined by CTCAE v4.03. Immune correlates (MDSCs; T regs; B cells) and vaccine induced T cell immunity (ELISpot; tetramer analysis) was assessed in purified PBMC and blood. Clinical response was assessed by CT and CA125. **Results:** 34/40 pts had an HLA match with the vaccine. Local injection site reactions (ISR) were the main DLT with 2 grade 3 skin ulcerations in cohort C. One hematological grade 3 DLT was seen in cohort 2. Immune response increased with dose (B vs C $p = 0.01$) and use of CPA (A vs C $p = 0.02$). Subsequent cohorts (Table) were de-escalated to find a dose with similar immunogenicity and reduced ISR. Skin ulcerations were not seen in Cohort 3, with a slightly lower immune response (non-significant). CD4 T cell immune responses were also seen in HLA unmatched pts. A radiological and biochemical response was confirmed in 1 pt with residual disease post-platinum therapy and correlated to a robust immune response. **Conclusions:** DPX-Survivac is well tolerated with proven immunogenicity and preliminary evidence of clinical activity. The recommended phase 2 dose is based on tolerance for localized ISR and immune response. A randomized phase 2 in consolidation/maintenance OC and open label studies in recurrent DLBCL and OC are planned. Clinical trial information: NCT01416038.

				Priming DPX			Boost DPX (0.1mL)			
Ph	Cohort	Pts (n)	CPA	Dose (ml)	n	Freq wks	n	Freq wks	Skin ulceration Grade (n)	Immune ELISpot Response 256 to > 4000 SFU/10^6 PBMC n (%)
I	A	7	N	0.5	3	3	0	0	2 (1)	3 (43)
	B	6	Y	0.1	3	3	0	0	3 (1)	3 (50)
	C	6	Y	0.5	3	3	0	0	2 (1), 3 (2)	5 (83)
Ib	1	6	Y	0.25	2	3	4	8	2 (2), 3 (1)	6 (100)
	2	9	Y	0.25	2	3	4	8	3 (1)	4 (44)
	3	6	Y	0.25	3	8	0	0	0	4 (67)

3073 Poster Session (Board #399), Sat, 8:00 AM-11:30 AM

A first-in-human phase 1 dose-escalating trial of G305 in patients with solid tumors expressing NY-ESO-1. *First Author: Amit Mahipal, Moffitt Cancer Center, Tampa, FL*

Background: A major way to expand *in vivo* tumor antigen-specific CD8 cytotoxic T cells (CTLs) is to induce and enhance the presence of CD4 helper T cells that are specific for the same antigen. G305 is recombinant full-length NY-ESO-1 protein mixed with a proprietary formulation of the synthetic TLR4 agonist, glucopyranosyl lipid A (GLA). GLA, when administered with other recombinant antigens in healthy volunteers, induces antigen-specific CD4 T and B cells and activates innate immunity. **Methods:** Adults with advanced or metastatic melanoma, sarcoma, ovarian, breast, bladder, or NSCLC expressing NY-ESO-1 by IHC were enrolled using a 3+3 dose-escalation design. Patients were dosed i.m. every three weeks for three doses. NY-ESO-1 was fixed at 250 μg and GLA was increased from 2 to 5 to 10 μg. Safety, immunogenicity, and clinical responses were assessed prior to, during, and at the end of therapy. **Results:** 12 patients were treated; mild local reactogenicity was most common (92%) and all related adverse events were CTCAE Grade 1 or 2, with no DLTs or related SAEs. Serology results show that G305 was immunogenic at all doses; 8 of 12 patients had preexisting antibody titers at baseline, 5 of which increased with treatment, and 3 of 4 with no baseline titer seroconverted. 4 of 6 patients tested to date had high baseline CD4 T cells that increased in 2 with G305 treatment; 1 of 8 tested developed antigen-specific CD8 T-cell responses. 6 of 12 patients (50%) have had SD for 2.5 to 8+ months and 6 patients progressed after a mean of 99 days with no relationship between dose, reciprocal antibody titers, or efficacy. One patient had decreasing CA125 titers and SD for 8 months, and subsequently developed brain metastases. **Conclusions:** G305 was shown to be safe and well-tolerated at doses up to 10 μg GLA and was associated with a satisfactory clinical response. Anti-NY-ESO-1 titers suggest that a 5 μg dose of G305 is suitable for subsequent trials. The immunogenicity results support the mechanism of action for G305, which is planned to complement LV305, a hybrid novel DC-tropic viral vector expressing NY-ESO-1, in a sequential prime-boost regimen to generate and expand NY-ESO-1-specific CTLs that target solid tumors. Clinical trial information: NCT02015416.

3074 Poster Session (Board #400), Sat, 8:00 AM-11:30 AM

A sugar engineered non-fucosylated anti-CD40 antibody, SEA-CD40, with enhanced immune stimulatory activity alone and in combination with immune checkpoint inhibitors. *First Author: Shyra Jane Gardai, Seattle Genetics, Bothell, WA*

Background: SEA-CD40 is a non-fucosylated, humanized IgG1 monoclonal antibody directed against human CD40. It is derived from dacetuzumab, a humanized IgG1 previously developed for B-lineage malignancies. Antibody glycosylation is essential for Fc receptor-mediated activity and nonfucosylated antibodies may show improved efficacy via increased binding to FcγRIIIa (CD16). **Methods:** Enhanced functionality of SEA-CD40 was determined through FcγRIIIa binding, immune activation, and induction of antigen-specific T-cells **Results:** While SEA-CD40 and the parent antibody dacetuzumab bind to CD40 with similar affinity, the non-fucosylated SEA-CD40 has a higher affinity for both low (158F) and high (158V) affinity FcγRIIIa. The consequence of enhanced SEA-CD40/FcγRIIIa binding is potent ADCC activity and improved agonistic signaling to antigen presenting cells (APCs). SEA-CD40 treatment of human PBMCs elicits a robust immune response consisting of proinflammatory cytokine production, APC maturation and up-regulation of co-stimulatory receptors on APCs with activity at antibody concentrations as low as 10 ng/ml. Utilizing a surrogate antibody against mouse CD40, the immune stimulatory properties of nonfucosylated anti-CD40 were confirmed *in vivo* in syngeneic tumor models. SEA-CD40 induction of antigen specific T-cells was assessed using human peripheral blood mononuclear cells (PBMCs) exposed to the M1 influenza antigen. SEA-CD40 stimulated the expansion of influenza specific T-cells and elevated their production of IFNγ. Likewise, SEA-CD40 also stimulated T-cell proliferation and IFNγ production in PBMCs from melanoma, pancreatic, or breast cancer patients in response to a mixture of the tumor-associated antigens MAGE-A1/A3. Interestingly, antigen-specific T-cell responses to both the influenza and tumor antigens were enhanced in the presence of blocking antibodies to CTLA4 or PD1. **Conclusions:** These observations demonstrate the potential of combining the non-fucosylated agonistic SEA-CD40 with immune check point inhibitors to generate more effective adaptive antitumor immune responses.

3075 Poster Session (Board #401), Sat, 8:00 AM-11:30 AM

Effect of CD137 stimulation on ibrutinib antagonism of GA101 dependent NK cell-mediated cytotoxicity. *First Author: Narendiran Rajasekaran, Center for Clinical Sciences Research Stanford, Stanford, CA*

Background: The clinical successes of BTK inhibitor Ibrutinib and Ofatumumab (GA101), a humanized, glycoengineered mAb against CD20, suggests that a combination therapy may have clinical potential. Our previous study demonstrated that Ibrutinib antagonizes ADCC in $CD20^+$ B-cell lymphoma due to Ibrutinib's irreversible binding to interleukin-2 inducible tyrosine kinase (ITK), which is required for FcR-stimulated NK cell function. (Kohrt *et al* Blood 2014, 123;12:1957). As GA101 is superior to Rituximab in induction of NK cell mediated ADCC, we hypothesized that-Ibrutinib may not antagonize GA101 and inhibition of NK cell function by Ibrutinib could be overcome by CD137 agonistic mAb enhanced NK cell function. **Methods:** Purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with Ibrutinib for 4 hours together with GA101-coated DHL4 lymphoma cells. For NK cell activation studies, the cells were primed with GA101 coated cells for 20 hours prior to CD137 mAb addition. Secretion of IFN-gamma, CD107a mobilization and cytotoxicity were assessed. **Results:** The results showed that Ibrutinib inhibited GA101 induced NK cell mediated lysis of lymphoma target cells and degranulation, although IFN gamma release was unaffected. Anti-CD137 mAb enhanced functional GA101 induced NK cell IFN gamma release, restored and enhanced degranulation and lysis of target cells that was impaired by Ibrutinib. Similar results were obtained when autologous peripheral blood mononuclear cells were cultured with CLL cells obtained from circulating tumor cells. The therapeutic efficacy of Ibrutinib and GA101 with anti-CD137 mAb was evaluated in a xenotransplant model of DHL4 lymphoma. Following tumor inoculation, athymic mice received GA101 on day 14 and oral dose of Ibrutinib twice daily and anti-CD137 mAb on day 15 with each treatment repeated weekly for a total of three weeks. Our results demonstrate that GA101 retains its potency in vivo in combination therapy with Ibrutinib and anti-CD137 mAb. **Conclusions:** Our results support a novel approach to overcome Ibrutinib inhibition of NK cell function by activation of the host immune system by CD137 stimulation that warrants clinical investigation.

3076 Poster Session (Board #402), Sat, 8:00 AM-11:30 AM

Transfer of anti-breast cancer immunity induced by infusions of bispecific antibody armed T cells and boosted with ex vivo primed T cells after stem cell transplant in metastatic breast cancer patients. *First Author: Archana Thakur, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

Background: In a recent phase I immunotherapy (IT) study in 23 women with metastatic breast cancer (MBC), 8 infusions of activated T cells (ATC) armed with anti-CD3 x anti-HER2Bi bispecific antibody (HER2Bi) given in combination with IL-2 and GM-CSF induced specific anti-SK-BR-3 breast cancer (BrCa) cytotoxicity and increased Th_1 cytokines and in IL-12 in the serum. This study investigated whether specific cellular and humoral anti-BrCa immunity is induced by infusions of HER2Bi **a**rmed **T** cell**s** (BATs) could be transferred after high dose chemotherapy (HDC) and stem cell transplant (SCT). **Methods:** BATs were cryopreserved in 8 doses for twice weekly infusions for 4 weeks along with IL-2 (3.0×10^5 IU/m^2/day) and GM-CSF (250μg/m^2 twice per week). Seven to 14 days after the last infusion of BATs, the patient was leukapheresed to obtain 8-20 x 10^9 PBMC for expansion of immune ATC. Immune ATC were harvested and cryopreserved for multiple infusions after the HDC and SCT. **Results:** Six of 8 MBC patients enrolled in the protocol completed the protocol were evaluable for transfer of cellular and humoral immunity. Five of 6 evaluable patients exhibited 2 to 40% CTL activity after vaccination with BATs and 2.5-45% up to 12 months post SCT. One of 6 evaluable patients showed poor immune responses and no evidence of transfer. Serum anti-SK-BR-3 IgG levels increased from 1 to 11μg/ml post IT and 1 and 8 μg/ml after SCT. *In vitro* antibody synthesis showed gradual increases in antibody levels after SCT. Serum cytokine profile showed changes in IL-2, IL-12, IFN-γ, MIP-1β and IP-10. No dose-limiting events for the infusions, delays in engraftment, and life-threatening infections were observed. In the one patient who rapidly progressed after SCT, CTL and IFN-γ EliSpots were absent and the serum had high levels of Th_2 cytokines. **Conclusions:** This pilot study suggests that optimal adoptive transfer of cellular and humoral immunity, induced by BAT infusions, by immune anti-breast cancer T cells after SCT accelerates not only immune reconstitution but, more importantly, enhances reconstruction of anti-tumor cellular and humoral immunity after HDC and SCT. Clinical trial information: NCT0002780 and NCT00020722.

3077 Poster Session (Board #403), Sat, 8:00 AM-11:30 AM

First interim exploratory analysis of immune response in patients with advanced non-small cell lung cancer receiving viagenpumatucel-l (HS-110) in combination with low-dose cyclophosphamide in an ongoing phase II trial. *First Author: Roger B. Cohen, University of Pennsylvania, Jenkintown, PA*

Background: Viagenpumatucel-L (HS-110), consists of an allogeneic NSCLC cell line, selected for high expression of a series of tumor antigens shared by NSCLC patients, which has been stably transfected with gp96-Ig. Cell-secreted gp96-Ig then delivers these cell-derived antigens directly to a patient's own antigen presenting cells, and shuttles those antigens to MHC-I via the cross-presentation pathway, leading to the preferential trafficking to MHC-I and exclusive activation of CD8+ cytotoxic T cells with limited or no activation of CD4+ helper T cells. Viagenpumatucel-L is currently being evaluated in a randomized phase II trial in combination with low-dose cyclophosphamide versus physician's choice chemotherapy. **Methods:** In support of the first planned exploratory analysis in this trial, the peripheral blood immune response was evaluated for the initial cohort of patients randomized to the treatment arm and treated for at least 9 weeks of therapy. Peripheral blood mononuclear cells were evaluated by flow cytometry for detection of circulating leukocyte subsets, regulatory T cells, myeloid derived suppressor cells, activated T cells and expression of immune checkpoint molecules on T cells. Cytokine and chemokine arrays from patient serum samples were also evaluated. **Results:** The combination of viagenpumatucel-L and low-dose cyclophosphamide was well tolerated in this first cohort of patients. Increased PD-1, Tim-3 and Ki67 was observed on CD8+ T cells isolated from peripheral blood over the treatment period, which may indicate CD8+ T cell activation and proliferation in response to HS-110. **Conclusions:** If these trends are observed in the full cohort of patients, the data may provide mechanistic evidence of HS-110 and support combination therapy with anti-PD-1/L1 antibodies. Clinical trial information: NCT02117024.

3078 Poster Session (Board #404), Sat, 8:00 AM-11:30 AM

An analysis of phase II and III therapeutic cancer vaccine trials and review of the successes and failures behind 10 different vaccine modalities. *First Author: Holbrook Edwin Kohrt, Stanford University, Stanford, CA*

Background: Between 1996-2014, the FDA approved 175 drugs for the treatment of various indications of oncology and despite the progress that has been made in other forms of cancer therapy, Provenge (Sipuleucel-T) is the only therapeutic vaccine that has received FDA approval for the treatment of cancer. To understand the current landscape of therapeutic oncology vaccines, an analysis of cancer vaccines under in phase 2 and phase 3 investigation was performed. **Methods:** A search of the terms "vaccine" and "cancer" or "oncology was performed on the clinicaltrials-.gov. registry and medtrack. A literature review was also performed to identify factors that have impacted the perceived success or failure of 10 different vaccines. **Results:** Database analysis of 451 phase 2 and phase 3 therapeutic cancer vaccine trials identified the most targeted indications, vaccine modalities, adjuvant and vaccine-treatment combinations and highlighted the shift in trends between studies completed prior to 2014 and those with completion scheduled after 2014. Despite the lower number of phase 3 compared to phase 2 trials, the registration of phase 3 trials between 2010 and 2014 appeared stable indicating continued investment in the development of immunotherapeutic vaccines at this stage. The review of vaccine trials revealed that patient characteristics (disease stage, HLA-type, MGMT status, antigen signature) and combination treatments had an impact on on vaccine success while the detection of immune responses was found to be important, provided parameters such as tumour antigen expression, breadth and magnitude of the response and correspondence to intra-tumour responses were considered. **Conclusions:** Identification of factors that can impact on vaccine success and their implementation into study design could ensure vaccine trials are best matched to patients most likely to benefit from the selected mode of vaccination, improving the outlook for both the patient and the development of therapeutic cancer vaccines.

3079 Poster Session (Board #405), Sat, 8:00 AM-11:30 AM

Anti-tumor efficacy and PD-L1 expression in the tumor microenvironment after poxvirus-based active immunotherapy and PD-1 blockade. *First Author: Stefanie J Mandl, Bavarian Nordic Inc., Mountain View, CA*

Background: Treatment with poxvirus-based active immunotherapies shows evidence of robust immune responses against a variety of tumor-associated antigens in preclinical and clinical studies. These active immunotherapies are in clinical trials to treat tumors expressing PSA (PROSTVAC/Phase 3), CEA and MUC-1 (CV-301/Phase 2), HER-2 (MVA-BN-HER2), and Brachyury (MVA-BN-Brachyury). Because these immunotherapies drive IFNγ-producing T cells to the tumor, we hypothesized that the tumors would upregulate PD-L1 in an attempt to evade the immune response. Thus, combination treatment of poxvirus-based immunotherapy with PD-1 axis blockade has the potential to yield therapeutic synergy against tumors in preclinical and clinical regimens. **Methods:** In therapeutic MC38-CEA and CT26-HER2 tumor models, mice were treated with CV-301 or MVA-BN-HER2, respectively, in combination with anti-PD-1 antibody. PD-L1 expression was evaluated in the tumor microenvironment by immunofluorescence and FACS. **Results:** Poxvirus-based immunotherapies induced activation and trafficking of antigen specific T cells that produce high levels of IFNγ in the tumor microenvironment.TumorPD-L1 expression was upregulated following CV-301 and MVA-BN-HER2 immunotherapy *in vivo* as measured by immunofluorescence. The PD-L1 expression was significantly elevated on tumor cells ($p < 0.01$) and infiltrating immune cells ($p < 0.05$) as measured by FACS. Combining poxvirus-based immunotherapy with PD-1 blockade in therapeutic mouse tumor models demonstrated synergistic anti-tumor efficacy. **Conclusions:** In preclinical studies, CV-301 and MVA-BN-HER2 poxvirus-based immunotherapies drive a robust, tumor-infiltrating T cell response that provokes tumor PD-L1 expression. Synergistic anti-tumor efficacy in mice resulted from combining active immunotherapy with PD-1 immune checkpoint inhibition. The potential of active immunotherapy to drive productive antigen specific T cell immunity could provide patients with PD-L1$^{neg/low}$ tumors an opportunity to benefit from PD-1/PD-L1 axis blockade when given in combination with poxvirus-based immunotherapies.

3081 Poster Session (Board #407), Sat, 8:00 AM-11:30 AM

Effect of alphavirus vaccine encoding HER2 during concurrent anti-HER2 therapies on induction of oligoclonal T cell and antibody responses against HER2. *First Author: William Rayford Gwin, Duke University, Durham, NC*

Background: Advanced HER2-overexpressing breast cancer eventually develops resistance to standard therapies; however, the HER2 receptor persists and may serve as a target for immunotherapy. We tested an immunization strategy with a novel alphaviral based vaccine encoding the extracellular and transmembrane domains of HER2 (VRP-HER2), alone and in conjunction with standard anti-HER2 agents, in patients with predominantly metastatic treatment refractory HER2-overexpressing breast cancer to determine safety, immunogenicity, and clinical activity. **Methods:** Cohort 1 (n = 4) enrolled patients not receiving any other anticancer therapy. Cohort 2 (n = 10) enrolled patients receiving either concurrent trastuzumab +/- pertuzumab, TDM-1, or Lapatinib. VRP-HER2 was given at 4 x 10^8 IU intramuscularly, every 2 weeks for three doses. Immune response specific for HER2 was determined by ELISPOT and ELISA. Progression-free survival (PFS) was defined as time to disease progression or death. Median length of follow-up for survival was calculated in patients still alive. **Results:** VRP-HER2 immunizations were well tolerated in these heavily pre-treated cohorts (median 4.5 prior therapies). There were no dose limiting toxicities or significant decreases in cardiac ejection fraction. Adverse events were predominantly grade 1 and 2, with one grade 3 AE, hyponatremia, felt not attributable to the VRP-HER2 vaccine. T cell responses specific for HER2 were detected by ELISpot in patients from cohort 1. The magnitude of the immune response was not altered by prior anti-HER2 therapy. In cohort 1, median PFS was 57 days, median overall survival (OS) was not reached, and median follow-up for OS was 26 months. In cohort 2, median PFS was 58 days, with one partial response and stable disease in two patients, median OS was not reached, and median follow-up for OS was 7 months. **Conclusions:** VRP-HER2 was safe and immunogenic alone or with concurrent anti-HER2 therapy. Future studies will combine the vaccine in prime boost strategies alone and in combination with other therapies. Clinical trial information: NCT01526473.

3082 Poster Session (Board #408), Sat, 8:00 AM-11:30 AM

Allogeneic myeloma GVAX with lenalidomide in near complete remission to enhance progression free survival. *First Author: Ivan Borrello, Johns Hopkins Univ, Baltimore, MD*

Background: We have previously shown that lenalidomide (Len) can augment vaccine efficacy to the pneumococcal conjugate vaccine (PCV), Prevnar. We now examine if vaccinating patients on Len in a near complete remission (nCR) (negative M-spike, IFE+) could improve the clinical response and generate myeloma specific immunity. **Methods:** Patients on a Len-containing regimen were eligible for enrollment if: 1) in stable nCR for at least 4 months; 2) converting from IFE negative to IFE positive; or 3) relapsing from a nCR to an M-spike <0.3g/dL. Patients continued only on single agent Len and received 4 GVAX vaccinations consisting of two allogeneic MM lines: H929, U266 admixed with K562-GM-CSF and PCV (Prevnar). Patients received 3 monthly vaccines and a boost at 6 months. **Results:** To date 34 patients have been screened. 16 patients initially in a nCR were ineligible for vaccination: 5 (31%) had disease progression and 11 (69%) became IFE negative during the 4 month observation period. 15 patients have enrolled. The table contains patient characteristics. Median follow-up is 33.9 months. Median progression free survival (PFS) of the cohort of vaccinated patients has not been reached. In contrast, PFS in the observation arm that remained on a multidrug Len-containing therapy was 10 months (p=0.0146). Vaccination with a rising M-spike was less likely to induce a durable remission. Laboratory analysis showed that patients achieving a CR had more central memory CD8 T cells at baseline in the BM and blood and greater tumor specific IFNg production in the BM. **Conclusions:** Vaccination in combination with Len appears to significantly extend the PFS in patients with a minimal disease burden. This enhanced clinical response correlates with the development of myeloma-specific immunity with the bone marrow compartment. Vaccination of MM patients with a poly-antigenic approach such as GVAX in combination with Len in nCR shows promising early clinical activity that warrants further investigation as an approach to maintaining durable clinical remissions. Clinical trial information: NCT01349569.

	Vaccination (n=15)	Observation (n=16)
Age	69 (55-81)	66 (40-83)
FISH (high risk)	0%	0%
ISS Stage III	2 (13%)	3 (19%)
IFE negative	0 (0%)	11 (69%)
Prior Therapies	1.8 (1-4)	1.8 (1-3)

3083 Poster Session (Board #409), Sat, 8:00 AM-11:30 AM

Pilot study of intratumoral G100, toll-like receptor-4 (TLR4) agonist, therapy in patients with Merkel cell carcinoma (MCC). *First Author: Shailender Bhatia, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: MCC is an aggressive skin cancer with suboptimal therapeutic options. Despite persistent expression of Merkel cell polyomavirus (MCPyV) proteins in ~80% of cases, these tumors are able to evade host immunity. G100 consists of a specific formulation of glucopyranosyl lipid-A (GLA), a TLR4 agonist, and is capable of directly activating dendritic cells (DCs), T cells and other effector cells and stimulating anti-tumor responses in preclinical models. Intratumoral (IT) G100 may overcome immune suppression mechanisms prevalent in MCC tumors and lead to effective local and systemic anti-tumor responses. **Methods:** 10 MCC patients (pts) with accessible tumor will be enrolled for G100 treatment. Pts with locoregional MCC (Cohort A) receive 1 cycle of G100 (5 mcg/day) IT on days 1, 8 followed by definitive surgery and/or radiation (RT) starting in week 4. Pts with metastatic disease (Cohort B) receive G100 (5 mcg/day) IT on days 1, 8 and 22 of a 6-week treatment cycle. For cycles 2-4, pts receive palliative RT to the injectable tumor on day 0 followed by G100 IT weekly for 6 doses. All pts have pre- and post-treatment tumor biopsies and blood samples collected for immune monitoring. **Results:** 8 pts have been enrolled to date (2 cohort A; 6 cohort B); all 8 pts have completed one or more cycles of G100. Treatment-related AEs have all been grade 1 (inflammation, pain and bruising at the injection site) or transient grade 2 (inflammation). 2/2 Cohort A pts with stage IIIB MCC are recurrence-free at 11+ and 4+ months; the first of whom had a pathologic CR after two G100 IT injections. Of 6 pts with stage IV MCC in Cohort B, 2 pts have SD after cycle 1 (one with 28% regression) and 4 pts had PD. MCPyV-specific CD8 and CD4 T cells have been isolated from tumors and peripheral blood, and correlative immune studies of frequency and functional status are in progress. **Conclusions:** In this pilot study in MCC pts, G100 has demonstrated acceptable safety and encouraging preliminary clinical efficacy. RT was recently added to cohort B and may further enhance immune and clinical responses by increasing the release of endogenous tumor antigens. G100 IT studies in other cancers and in combination with anti-PD-1 therapy are planned. Clinical trial information: NCT02035657.

3084 Poster Session (Board #410), Sat, 8:00 AM-11:30 AM

First-in-human dose-escalating trial of *E.coli* purine nucleoside phosphorylase and fludarabine gene therapy for advanced solid tumors. *First Author: Thomas Kenwise Chung, University of Alabama at Birmingham, Birmingham, AL*

Background: The use of *E. coli* purine nucleoside phosphorylase (PNP) to activate fludarabine was safe and demonstrated robust antitumor activity in preclinical studies. The regimen demonstrated cytotoxicity within neighboring tumor cells that did not incorporate PNP, an effect known as bystander killing. Given the potential of this novel therapeutic, the FDA approved this clinical trial. **Methods:** A first-in-human multi-site Phase I clinical trial (NCT 01310179; IND 14271) was initiated to evaluate the safety and efficacy of intratumoral administration of a replication-deficient adenoviral vector expressing *E. coli* PNP in combination with intravenous fludarabine. Escalating doses of fludarabine comprised the first three cohorts (15, 45, and 75 mg/m^2) and escalating virus in the fourth (10^{12} versus 10^{11} viral particles) with 75 mg/m^2 fludarabine. Primary endpoints included adverse event rates and tumor volume change from baseline to final measurement on day 56. **Results:** All 12 study subjects completed therapy without any dose limiting toxicities. Change in tumor size from baseline to final measurement demonstrated a dose-dependent response, with 5 of 6 patients in Cohorts 3 and 4 achieving tumor regression compared to 0 of 6 patients in Cohorts 1 and 2 (p = 0.018). The overall adverse event rate was not dose-dependent. Most common adverse events included pain at the viral injection site (92%), drainage/itching/burning (50%), fatigue (50%), and fever/chills/flu-like symptoms (42%). Four patients experienced decreased peripheral blood counts and three patients experienced transient liver enzyme elevations that resolved spontaneously. Analysis of serum confirmed lack of systemic exposure to fluoroadenine, the active agent generated by E. coli PNP. Antibody response to adenovirus was detected in 2 patients, suggesting that neutralizing immune response is not a barrier to efficacy. **Conclusions:** This first-in-human clinical trial found that localized generation of fluoroadenine within tumor tissues using *E. coli* PNP and fludarabine is safe and effective. The pronounced effect on tumor volume after a single treatment cycle suggests phase II studies are warranted. Clinical trial information: NCT01310179.

3085 Poster Session (Board #411), Sat, 8:00 AM-11:30 AM

An evaluation of local and systemic immune markers following intratumoral administration of a chimeric adenovirus Ad5/3-D24-GMCSF in refractory cancer patients with solid tumors. *First Author: Sari Anneli Pesonen, Oncos Therapeutics, Helsinki, Finland*

Background: Clinical studies consistently show how adenovirus, unlike other viral vectors, can both prime and boost immune responses. Consequently, adenovirus is used to develop vaccines against various human diseases, such as cancer. Adenoviruses can be armed with transgenes for further enhancement of a tumor-specific immune reaction. We present results from a phase I study describing both local and systemic immune activation following administration of ONCOS-102, a chimeric oncolytic adenovirus, in patients with refractory solid tumors. **Methods:** A total of 12 patients were treated with up to 9 intratumoral injections of ONCOS-102. Biopsies were collected at baseline, 1 and 2 months after treatment initiation to analyze tumors for the presence of tumor infiltrating lymphocytes (TILs), expression of PD-L1, and gene expression profiles. Peripheral blood mononuclear cells (PBMCs) were collected to assess antigen specificity of CD8+ T cells by IFN-gamma ELISPOT. **Results:** No dose limiting toxicity was identified. An immediate short-term increase in systemic pro-inflammatory cytokines and an infiltration of innate immune cells into tumors was seen following ONCOS-102. Furthermore, increase in tumor infiltrating $CD8^+$ T cells was seen in 11 out of 12 patients. 10 out of 12 patients showed an increase in PD-L1+ tumor and/or lymphoid cells. Two patients showing the most striking post-treatment increase in TILs showed also a systemic induction of tumor-specific CD8+ T cells (MAGE-A1, MAGE-A3, NY-ESO-1, mesothelin) while none of these tumor-recognizing T cell populations were detected at baseline. These two patients showed high expression levels for genes associated with activated Th1 cells (perforin, granzyme B, granulysin, IFN-gamma) and Th1 type immunoprofile (IRF-1, X3CL1, CXCL9, CXCL10, CCL5, CCL2) in post-treatment biopsies. **Conclusions:** Concomitant increase in CD8+ TILs and PDL1 expressing cells in tumors suggests that local ONCOS-102 treatment is able to break the immunological ignorance towards tumors by activating the immune system in advanced refractory tumors which were immunologically silent before treatment. Clinical trial information: NCT01598129.

3086 Poster Session (Board #412), Sat, 8:00 AM-11:30 AM

Immunomodulatory effects of OX40 agonists in a defined antigen challenge in cynomolgus macaques. *First Author: Stacie L Lambert, MedImmune, Mountain View, CA*

Background: Immunomodulatory antibodies targeting specific T cell costimulatory pathways have shown great potential as cancer therapeutics. OX40 agonists can enhance T cell proliferation and survival and cause tumor regressions in mouse models. While initial evaluations of pharmacodynamic activity of these compounds in non-human primate models have relied on non-specific T cell proliferation readouts (Ki67), additional sensitive biomarkers of pharmacodynamic activity would add value in evaluating optimal dosing and timing of candidate therapeutics. **Methods:** In this study, we compared the *in vivo* activity in cynomolgus macaques of intravenously infused OX40 agonist MEDI6469 (9B12, a murine IgG1 antibody) and MEDI6383, a human OX40 ligand fusion protein consisting of a dimer of OX40L trimers held together by Fcγ domains that also agonizes the OX40 receptor. Antigen-specific responses were evaluated to respiratory syncytial virus soluble F (sF) protein, which was administered intramuscularly on the same day as OX40 agonist treatment. Ki67 proliferation was additionally measured in whole blood. **Results:** Enhancement of F-specific T cell responses, serum anti-F IgG responses and functional antibodies was observed in animals that received the OX40 agonists. In addition, OX40 agonism resulted in a temporal enhancement of cellular proliferation (Ki67 staining) in CD4 and CD8 T cell memory subsets, as well as in NK cells and B cells. The strongest antigen-specific and Ki67 responses were observed in response to MEDI6383, with the exception of responses observed for NK cell proliferation which were similar between MEDI6469 and MEDI6383. **Conclusions:** Our study indicates that antigen-specific cellular and humoral responses may be useful biomarkers of OX40 agonist activity. Additionally, our study confirms that Ki67 readouts are informative in cynomolgus macaques, which was also demonstrated in separate studies using rhesus macaques.

TPS3087 Poster Session (Board #413a), Sat, 8:00 AM-11:30 AM

Phase I, open-label study of MEDI0680, an anti-programmed cell death-1 (PD-1) antibody, in combination with MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody, in patients with advanced malignancies. *First Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA*

Background: The PD-1/PD-L1 pathway plays a key role in controlling T-cell activation and may be utilized by tumor cells to evade antitumor responses. Anti-PD-1 and anti-PD-L1 antibodies have shown acceptable safety profiles and clinical activity across a range of tumor types. MEDI0680 is a humanized IgG4κ mAb specific for human PD-1 that blocks PD-L1 and programmed cell death ligand-2 (PD-L2). Blocking both PD-L1 and PD-L2 may have more efficient blockade and may be more specific for different tumor groups in comparison to blocking either one alone. MEDI4736 is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity. Anti-PD-1 and PD-L1 agents block distinct interactions contributing to immunosuppression, suggesting potential additive or synergistic effects. Preclinical data, including mouse models, support potential benefit for anti-PD-L1 and anti-PD-1 in combination. **Methods:** This phase I, multicenter, open-label study evaluates the safety of MEDI0680 in combination with MEDI4736 in patients with advanced malignancies (NCT02118337). Eligible patients ($\geq$ 18 years) will have an Eastern Cooperative Oncology Group performance status of 0-1. The primary objectives are to assess safety and tolerability, and determine the maximum tolerated dose of MEDI0680 in combination with MEDI4736. Secondary objectives include assessment of antitumor activity (including objective response rate, disease control rate, duration of response, progression-free survival, and overall survival), pharmacokinetics, and immunogenicity of the combination. Exploratory objectives include an evaluation of biomarkers within the tumor microenvironment and their relationship to tumor response, identification of genetic predictors of response or resistance, and an assessment of patient-reported outcomes. Recruitment is ongoing, with a target enrollment of approximately 150 patients across 3 centers in the United States. Clinical trial information: NCT02118337.

TPS3088 Poster Session (Board #413b), Sat, 8:00 AM-11:30 AM

A phase I, multicenter, open-label, first-in-human study to evaluate MEDI0680, an anti-programmed cell death-1 antibody, in patients with advanced malignancies. *First Author: Jeffrey R. Infante, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: Programmed cell death-1 (PD-1) is an inhibitory regulator or checkpoint of T-cell activation. Recent data from several large phase I studies have shown that targeting the PD-1/programmed cell death ligand-1 (PD-L1) axis has an acceptable safety profile, can enhance antitumor responses, and provide clinical benefit. MEDI0680 is a humanized immunoglobulin gamma 4, kappa monoclonal antibody specific for human PD-1 that blocks PD-L1 and programmed cell death ligand-2 (PD-L2). Blocking both PD-L1 and PD-L2 may provide more efficient pathway inhibition and may be more specific for different tumor groups in comparison to blocking either one alone. As well as blocking interactions between PD-1 and its ligands, MEDI0680 also improves the intrinsic functionality of T cells by triggering internalization of PD-1, thereby reducing the surface levels of PD-1 and membrane-proximal tyrosine phosphatase SHP2. **Methods:** This is an ongoing, phase I, multicenter, open-label, first-in-human, dose-escalation study (NCT02013804) evaluating MEDI0680 in patients with advanced malignancies. Eligible patients ($\geq$ 18 years) will have an Eastern Cooperative Oncology Group performance status of 0 or 1, histologically- or cytologically-confirmed melanoma or clear-cell renal cell carcinoma that is refractory to standard treatment or for which no standard treatment exists, $\geq$ 1 measurable lesion per RECIST v1.1, with prior treatment toxicities of $\leq$ grade 1. The primary objectives of the study are to assess the safety and tolerability and define the maximum tolerated dose of MEDI0680. Secondary objectives include an evaluation of the pharmacokinetic and antitumor effects of MEDI0680. Recruitment is ongoing, with a target enrollment of approximately 48 patients across 5 centers in the United States. Clinical trial information: NCT02013804.

TPS3089 Poster Session (Board #414a), Sat, 8:00 AM-11:30 AM

First-in-human study assessing safety and tolerability of REGN1979, a novel CD20xCD3 bispecific antibody, in patients with CD20+ B-cell malignancies previously treated with anti-CD20 therapy. *First Author: Carrie M. Brownstein, Regeneron Pharmaceuticals Inc, Tarrytown, NY*

Background: REGN1979 is a human bispecific antibody based on an IgG4 isotype modified to reduce Fc binding, designed to bridge CD20-expressing cells to cytotoxic T-cells by binding to the CD3 subunit of the TCR complex. Bridging results in targeted killing of CD20+ cells by T-cells that is independent of typical requirements for specific TCR recognition of a target cell. T-cell activation requires CD20, a well-validated surface target for B-cell malignancies. This MOA is distinct from that of other available anti-CD20 antibodies, and may provide additional therapeutic benefit to patients with CD20+ malignancies, including those who have relapsed after anti-CD20 therapy. REGN1979 has been shown to specifically kill CD20+ tumor cells *in vitro*, and has shown potent *in vivo* anti-tumor activity in several mouse models (established Raji tumors and B16_hCD20)(Varghese B et al. ASH 2014. Abstract 4501). In cynomolgus monkeys, REGN1979 at doses ≥ 0.01 mg/kg depleted peripheral and tissue CD20+ B-cells to similar levels achieved with significantly higher doses of rituximab (30 mg/kg). At ≥ 0.1 mg/kg, REGN1979 depleted B-cells in spleen, mesenteric lymph nodes, and thymus to undetectable levels. **Methods:** This open label, multicenter, Phase 1, FIH study (NCT02290951) uses a 3+3 dose-escalation design with a 28-day DLT observation period to assess both acute and late toxicity. Each dose level (DL) has an initial dose followed by a second and subsequent higher dose, if the initial dose was tolerated. Patients receive REGN1979 IV weekly during a 4-week induction period at their assigned DL, then monthly for 5 additional doses. There will be parallel independent dose escalation cohorts for patients with NHL and CLL at each DL. After determining the recommended dose for further study, there will be an expansion phase with independent cohorts for patients with indolent NHL, aggressive NHL, and CLL. The primary objective is to assess the safety, tolerability, and DLTs of REGN1979. Secondary objectives include characterization of the PK profile, immunogenicity, and preliminary anti-tumor activity of REGN1979. Enrollment is ongoing. Clinical trial information: NCT02290951.

TPS3090 Poster Session (Board #414b), Sat, 8:00 AM-11:30 AM

Phase I study to evaluate the safety and efficacy of MEDI4736 in combination with tremelimumab in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). *First Author: Lillian L. Siu, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Despite advances in the treatment of SCCHN, the outlook for patients (pts) with R/M disease remains poor. Development of immunotherapies to treat this disease may hold promise. High mutational burden due to tobacco and expression of human papilloma virus (HPV)-associated viral antigens is linked to immunogenicity in SCCHN tumors. Despite this immunogenicity, tumors can evade immune detection by exploiting inhibitory checkpoints. PD-L1 is up-regulated on SCCHN tumors and is associated with antitumor T-cell response inhibition. MEDI4736 (M), a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity, has shown a manageable safety profile and promising antitumor activity in R/M SCCHN (ORR 24% in PD-L1+ pts, phase I)(Fury M, et al. Poster presented at ESMO 2014, 988PD). Tremelimumab (T), a selective human IgG2 mAb inhibitor of CTLA-4, has also shown antitumor activity in several tumor types (Tarhini AA. Immunotherapy 2013;5:215–29). Preclinical data suggest that combining anti-PD-L1 and anti-CTLA-4 provides non-redundant immune checkpoint blockade and synergistic antitumor activity. Preliminary data for M + T in NSCLC show encouraging clinical activity in both PD-L1-positive and PD-L1-negative pts (Antonia S, et al. Poster presented at ESMO 2014, 1327P). Here we describe a study assessing the safety, efficacy, and potential biomarkers of response to M + T, in pts with R/M SCCHN. **Methods:** This is a phase I, multicenter, open-label study (NCT02262741) in pts (N~164) with R/M SCCHN deemed incurable by local therapy. The dose exploration phase will evaluate the combination of M + T, followed by dose expansion in treatment-naive or pretreated R/M pts. Pts will have PD-L1 status determined prior to dosing with M IV + T IV or T IV alone. The primary objective is to assess safety/tolerability of M + T and T alone. Secondary objectives are to assess antitumor activity via RECIST (including ORR, DCR, DoR, PFS, and OS), PK/PD, immunogenicity, and if clinical activity correlates with potential biomarkers, including PD-L1 expression, HPV status, and tobacco use. Recruitment is ongoing. Clinical trial information: NCT02262741.

TPS3091 Poster Session (Board #415a), Sat, 8:00 AM-11:30 AM

A phase 1b/2, open-label study to evaluate the safety and tolerability of MEDI6469 in combination with immune therapeutic agents or therapeutic mAbs in patients with selected advanced solid tumors or aggressive B-cell lymphomas. *First Author: John D. Powderly, Carolina BioOncology Institute, Huntersville, NC*

Background: Anti-CTLA-4 and anti-PD-1/PD-L1 have shown antitumor activity in 10–30% of patients (pts) with select tumors. Combinations of co-stimulatory agonists, such as OX40, and antagonist Abs against the T-cell checkpoints CTLA-4 or PD-L1 could synergize to yield higher response rates. Additionally, nonclinical models show OX40 cell surface expression is induced following activation of NK cells. OX40 ligation promotes enhanced NK cell activity, suggesting greater antitumor activity could be achieved with an OX40 agonist in combination with an anti-CD20 antibody engaging NK cells for antitumor activity. Depleting B cells with rituximab could decrease immunogenicity of murine MEDI6469 by decreasing anti-drug Ab production. MEDI6469, an agonist human OX40 receptor murine mAb, showed clinical activity in a Phase 1 study and is being evaluated as monotherapy and in combination with tremelimumab (anti-CTLA-4) or MEDI4736 (anti-PD-L1) in pts with select advanced solid tumors, or with rituximab (anti-CD20) in relapsed diffuse large B cell lymphoma (DLBCL) pts. **Methods:** This is a Phase 1b/2, multicenter, open-label study (NCT02205333) in adult pts with select advanced solid tumors refractory to standard therapy or for which no standard therapy exists, or with histologically confirmed aggressive DLBCL. The dose-escalation phase includes single-dose IV MEDI6469 monotherapy (6+3 design) and 3 combination therapies (3+3 design): single-dose IV MEDI6469 Day 1 + repeated IV doses of (1) tremelimumab, or; (2) MEDI4736 up to 12 months or until PD, or; (3) repeated IV doses of MEDI6469 and rituximab until confirmed CR plus 1 cycle or PD. The dose-expansion phase will examine MEDI6469 combination treatments at the dose levels determined during dose escalation in pts with select advanced solid tumors or DLBCL. The primary endpoints are safety and determination of the maximum tolerated dose. Secondary endpoints are PK, immunogenicity, and antitumor activity. Enrollment of up to ~212 pts (66, dose escalation; 146, dose expansion) is ongoing. Clinical trial information: NCT02205333.

TPS3092 Poster Session (Board #415b), Sat, 8:00 AM-11:30 AM

A phase Ib study of neoadjuvant immune biomarker modulation with cetuximab and motolimod in head and neck cancer (HNC). *First Author: Benjamin Alexander Kansy, University of Pittsburgh; University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: HNC is an immunosuppressive disease, with low absolute lymphocyte counts, impaired activity of effector cells such as natural killer cells (NK), and poor antigen-presenting function. The anti-EGFR monoclonal antibody cetuximab (CTX) prolongs survival in HNC, but only in a subset of patients. This limited efficacy may be due to immunosuppressive cells such as myeloid derived suppressor cells and suppressive macrophages. The clinical efficacy of CTX may be augmented by immune stimulation. Motolimod (formerly VTX-2337) is a novel Toll-like receptor 8 (TLR8) agonist which stimulates myeloid dendritic cells, monocytes, and NK cells. Preclinical data have demonstrated enhanced CTX and NK cell-mediated lysis of HNC cells and dendritic cross-priming of EGFR-specific CD8+ T cells. CTX and motolimod in HNC patients was tolerable and active in a phase Ib study, with enhanced mobilization and activation of NK cells. Our hypothesis is that the differential clinical response of HNC to treatment with CTX and motolimod reflects the role of cellular immune activation, immune escape mechanisms, and TLR8 stimulation enhancement of the immune response in the circulation and in the tumor microenvironment. **Methods:** This is a prospective phase Ib clinical trial (NCT02124850) of preoperative treatment with CTX and motolimod. The primary objective is to determine the extent to which the administration of neoadjuvant CTX plus motolimod modulates immune biomarkers in peripheral blood and HNC tumors. An exploratory objective of the study is to assess whether this modulation of biomarkers can predict anti-tumor response. Subjects must have HNC stage II–IVA and be surgical candidates. CTX and motolimod will be administered for a 3–4 week preoperative period. Immune biomarkers will be quantitatively assessed. The biomarker modulation and biopsies of skin/acneiform rash will be studied in correlation with clinical response by CT or MRI scan. Tumor apoptosis/proliferation will be assessed by biopsy pre- and post- treatment with CTX /motolimod. All patients will receive definitive surgical resection. Enrollment target is fifteen complete specimens (tumor, peripheral blood mononuclear cells and serum). Clinical trial information: NCT02124850.

TPS3093 Poster Session (Board #416a), Sat, 8:00 AM-11:30 AM

A phase I study of MEDI6383, an OX40 agonist, in adult patients with select advanced solid tumors. *First Author: Todd Michael Bauer, Sarah Cannon Research Institute / Tennessee Oncology, PLLC., Nashville, TN*

Background: Enhancing T-cell function in cancer patients (pts) through T-cell co-stimulatory pathways such as OX40 has the potential to overcome cancer-induced immune suppression. MEDI6469, a human OX40 agonist murine antibody, administered for a single cycle in a phase I clinical study showed both an acceptable toxicity profile and regression of ≥ 1 metastatic lesion in 12 of 30 treated pts(Curti B, et al. Cancer Res 2013;73:7189–98). Humanized OX40 agonists are expected to have reduced immunogenicity relative to murine antibody, which may allow for repeat-dose administration, potentially enhancing biologic and antitumor activity. MEDI6383 is a human OX40 ligand fusion protein that in preclinical models initiates an intracellular signaling cascade to enhance T-cell survival, proliferation of T cells and macrophage lineage cells, and cytokine production. **Methods:** This is a phase I, multicenter, open-label study of MEDI6383 (NCT02221960) in adult pts with select recurrent or metastatic solid tumors. In the dose-escalation phase, sequential cohorts of pts will receive 1 of up to 6 dose levels (3+3 design) of MEDI6383 IV every 2 weeks for up to 48 weeks or until progressive disease (PD). In the dose-expansion phase, tumor-type specific cohorts will be treated at the MEDI6383 dose level and treatment schedule determined during dose escalation for up to 48 weeks or until PD. Pts who achieve a response and then have PD in follow-up may have 1 round of MEDI6383 retreatment. All pts will be followed for survival through end of study. The primary endpoint is safety and determination of the maximum tolerated dose; secondary endpoints are antitumor activity (objective response and disease control by immune-related RECIST, duration of response, progression-free survival, overall survival), pharmacokinetics, immunogenicity, and pharmacodynamics. Enrollment of up to 122 pts (42 pts, dose escalation; 80 pts, dose expansion) is ongoing. Clinical trial information: NCT02221960.

TPS3094 Poster Session (Board #416b), Sat, 8:00 AM-11:30 AM

KEYNOTE-055: A phase II trial of single agent pembrolizumab in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) who have failed platinum and cetuximab. *First Author: Steven Francis Powell, Sanford Health, Sioux Falls, SD*

Background: Treatment options are limited for pts with recurrent and/or metastatic HNSCC whose disease has progressed after platinum and cetuximab therapy. Pembrolizumab (MK-3475) is a humanized IgG4 monoclonal antibody designed to block interaction between activated T-cell-specific programmed death receptor 1 (PD-1) and its ligands PD-L1 and PD-L2. Preclinical studies have shown that blocking PD-1/PD-L1 interaction promotes infiltration of activated tumor-specific effector T cells, leading to tumor cell death. In KEYNOTE-012, a phase 1b clinical study, pembrolizumab exhibited antitumor activity in patients with recurrent or metastatic, PD-L1–positive HNSCC. Treatment with intravenous pembrolizumab 10 mg/kg every 2 weeks resulted in an objective response rate (ORR) of 19.6% (confirmed and unconfirmed responses) by investigator review, and the magnitude of response was positively correlated with PD-L1 expression in the tumor tissue (P= 0.018). **Methods:** KEYNOTE-055 (NCT02255097) is a multicenter, open-label, nonrandomized phase 2 trial with the primary objective to evaluate the efficacy and safety of pembrolizumab in 150 pts with recurrent and/or metastatic HNSCC resistant to platinum and cetuximab. Pembrolizumab will be administered intravenously for up to 24 months at a dose of 200 mg every 3 weeks until disease progression or unacceptable toxicity. Eligible pts must undergo a core or excisional biopsy prior to treatment for evaluation of PD-L1. The primary efficacy parameter is ORR, with response to treatment assessed every 6-9 weeks by central radiology review using RECIST v1.1. Secondary efficacy end points include: duration of response, ORR per modified RECIST v1.1 (to account for the unique tumor response profile of pembrolizumab), ORR for HPV^+ pts, progression-free survival (PFS), and overall survival (OS). For the ORR analyses, a 97.5% confidence interval and 1-sided P value will be provided using exact binomial distribution. Kaplan-Meier statistics will assess PFS and OS. Adverse events (AEs) will be monitored and graded using CTCAE v4.0. Clinical trial information: NCT02255097.

TPS3095 Poster Session (Board #417a), Sat, 8:00 AM-11:30 AM

A Phase II multicenter trial to evaluate combination ipilimumab and high-dose IL-2 in patients with unresectable stage III and IV melanoma. *First Author: Howard Kaufman, Rush University Medical Center, Chicago, IL*

Background: High-dose (HD) IL-2 (600,000 IU.kg) and ipilimumab (3 mg/kg) are approved immunotherapy agents for selected patients with advanced melanoma and both are associated with durable responses in a small number of patients. Previous studies in a pre-clinical melanoma tumor models and in a small phase I/II dose escalation clinical trial suggested that concurrent combination treatment was associated with improved response rates, including a 17% complete response rate in the clinical trial, without an increase in toxicity. Data has also suggested that higher doses of ipilimumab may improve response rates as shown in clinical trials comparing 3 to 10 mg/kg dosing. To better define the potential benefit of this combination in patients with melanoma, this phase II multicenter, open-label, single arm trial, is being conducted (NCT02203604). **Methods:** The primary goal of this trial is to determine the clinical OR rate within the first 24 weeks. Secondary end points include safety, feasibility, overall survival, one- and two-year survival, progression-free survival, best overall response, and frequency of effector CD8+ T cells and CD4+FoxP3+ regulatory T cells in peripheral blood, and when possible in the tumor microenvironment. Adults with advanced unresectable stage III and IV melanoma and who meet criteria for high-dose IL-2 therapy are eligible. Main exclusion criteria are active brain metastases, active autoimmune diseases, concurrent systemic immunosuppressive therapy as well as prior immunotherapy with IL-2 or impilimumab. Up to 82 patients will be enrolled and receive ipilumimab (10 mg/kg) for 4 cycles (Days 1, 22, 43, 64) and high-dose IL-2 (600,000 IU/kg) for 2 cycles (Days 22-26, 43-47) followed by maintenance ipilimumab. Preliminary safety assessment will be performed on the first 6 patients before other patients are allowed to enter the study. If significant toxicity occurs in the first 6 patients ipilimumab will be dose reduced to 3 mg/kg. As of Feb 4, 2015 3 patients have been enrolled. Clinical trial information: NCT02203604.

TPS3096 Poster Session (Board #417b), Sat, 8:00 AM-11:30 AM

Phase I study evaluating high dose ADXS11-001 treatment in women with carcinoma of the cervix. *First Author: Sharad A. Ghamande, Georgia Regents Univ, Augusta, GA*

Background: This is a phase I, dose-escalation, open-label, single-center study, in subjects with carcinoma of the cervix who have failed conventional therapy. ADXS11-001 is a live attenuated *Listeria monocytogenes* (*Lm*)-LLO immunotherapy bioengineered to secret an antigen-adjuvant fusion protein (fused to HPV16 E7). The primary objective of the study is to evaluate the tolerability and safety of ADXS11-001. Secondary objectives are tumor response, progression-free survival and correlative immunologic studies. **Methods:** Subject eligibility: Women ≥ 18 years of age with histologically-confirmed, measurable and/or evaluable (defined by RECIST 1.1) persistent, metastatic, or recurrent squamous or adenocarcinoma of the cervix with documented disease progression that is not amenable to surgery or standard radiotherapy. Subjects must have received ≤ 2 prior regimens for treatment of their metastatic disease. Planned sample size is approximately 6-12 subjects. Subjects will receive ADXS11-001 every 3 weeks during a 12- week treatment cycle. Doses will be escalated in the standard 3 + 3 fashion, in two doses, starting with 5×10^9 colony forming units (cfu) to a maximum dose level of 1×10^{10} cfu. If DLT is seen in one of 3 subjects, another 3 subjects will be treated at that same dose. If DLT is seen in 2 of 6 subjects, then that dose level will be considered maximum tolerated dose (MTD) and the previous dose level will be selected as the recommended phase II dose (RP2D). Blood samples will be evaluated for immunologic effects in cycle 1 only. Treatment cycles can be repeated at the RP2D (or less) for an individual subject until a discontinuation criterion is met, including documented disease progression, intolerable side effects. The end of study will be defined as 1 year after the last subject's first treatment or until that subject has met a discontinuation criterion. Assessment of the RP2D level may be further explored in an expansion cohort of 15 subjects. Clinical trial information: NCT02164461.

TPS3097 Poster Session (Board #418a), Sat, 8:00 AM-11:30 AM

Phase I study of AMG 211/MEDI-565 administered as continuous intravenous infusion for relapsed/refractory gastrointestinal (GI) adenocarcinoma. *First Author: Elisabeth De Vries, University Medical Center Groningen, Groningen, Netherlands*

Background: The bispecific CD19-directed CD3 T-cell engager (BiTE$^{(R)}$) blinatumomab was recently approved by FDA as single-agent immunotherapy for patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. The clinical activity of blinatumomab seen with 4-week infusion regimen provides rationale for BiTE administration as continuous intravenous infusion (cIV). Experience with an EpCAM-directed BiTE first-in-human study (FIH) suggests that in solid tumor indications dose levels achieving exposure comparable to 50% or even 90% of the maximal effective concentration in in vitro might be needed to observe substantial anti-tumor activity translating into objective response (Fiedler et al, J Clin Oncol 30, 2012, abstr 2504). The CEA-directed BiTE (MEDI-565, AMG 211) inhibited the growth of CEA-expressing cancer cells in various cancer models in the presence of CD3+ T-cells and has been explored as an intermittent 3-hour infusion for 5 subsequent days in a FIH study (NCT01284231). The present study aims at cIV AMG 211 administration that will result in lower C_{max} concentrations compared to intermittent infusions. The steady state levels with potential effective exposure should range above a threshold level required for anti-tumor activity for a prolonged period of time. The therapeutic index may be improved by reduction of adverse events attributable to a higher $C_{max}$of discontinuous administration but other adverse events due to prolonged exposure will need to be assessed. **Methods:** Approximately 34 patients with relapsed/refractory GI adenocarcinomas will be treated with AMG 211 for 7, 14 or 28 days at 200-6,400 μg/day cIV infusion in repeated cycles with 2-week breaks until confirmed disease progression, occurrence of a dose-limiting toxicity (DLT) or discontinuation for other reasons. A toxicity probability interval Bayesian model will guide dose escalation after a first DLT. Study objectives include evaluation of safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy. Cohort 1 has been completed without DLT and cohort 2 started enrollment in January 2015. **ClinicalTrials.gov Identifier**: NCT02291614 Clinical trial information: NCT02291614.

TPS3098 Poster Session (Board #418b), Sat, 8:00 AM-11:30 AM

A randomized multicenter phase Ib/II study to assess the safety and the immunological effect of chemoradiation therapy (CRT) in combination with pembrolizumab (anti-PD1) to CRT alone in patients with resectable or borderline resectable pancreatic cancer. *First Author: Matthew H. G. Katz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tumor-infiltrating lymphocytes (TILs) play a major role in anti-tumor immune responses, and their presence is correlated with survival in a variety of tumors. These TILs do not reach the pancreatic cancer (PC) cells in significant numbers due to the presence of stroma and a suppressive microenvironment. One of the leading causes for immune suppression is elevated expression of PD-L1 either by the tumor cells or the surrounding regulatory cells, resulting in dysfunction of TILs. There is recent evidence to suggest that CRT can increase the presence of TILs in the PC microenvironment (PCME), leading to production of interferon-γ (IFN-γ), which could increase the expression of PD-L1 through a negative feedback loop. **Methods:** This is a prospective multicenter randomized trial that will accrue subjects with resectable or borderline resectable PC who had not received prior treatment. The primary objectives of the study are: (1) to determine the safety of neoadjuvant CRT in combination with pembrolizumab. (2) To estimate the difference in the number of TILs in PC subjects receiving neoadjuvant CRT in combination with pembrolizumab to the number of TILs in subjects receiving neoadjuvant CRT alone. This study will also investigate the effect of CRT+/- anti-PD-1 on the other effector and suppressive immune cells. Eligible subjects will be randomized 2:1 to the investigational treatment (Arm A) to receive pembrolizumab administered IV every 3 weeks on days 1, 22, and 43 during concurrent CRT with capecitabine (825 mg/m2 orally twice daily on days of radiation only) and radiation (50.4 Gy in 28 fractions over 28 days) or Arm B to receive only concurrent CRT with capecitabine. Patients without local or distant disease progression will be taken to the operative room for planned surgery (within 2 weeks of imaging). Postoperatively, resected patients will receive off study standard of care adjuvant gemcitabine (1000mg/kg IV weekly for 3 out of 4 weeks for 6 months). Post operatively resected patients will be followed for up for PFS and OS for up to 2 years. Clinical trial information: NCT02305186.

TPS3099 Poster Session (Board #419a), Sat, 8:00 AM-11:30 AM

A phase I study to evaluate the safety and tolerability of MEDI4736, an anti- programmed cell death-ligand-1 (PD-L1) antibody, in combination with tremelimumab in patients with advanced solid tumors. *First Author: Patrick Alexander Ott, Dana-Farber Cancer Institute, Boston, MA*

Background: Programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are regulators or checkpoints of T cell activation, utilized by tumor cells to evade antitumor immune responses. MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD-80 with high affinity and selectivity. Tremelimumab (T) is a selective human IgG2 mAb inhibitor of CTLA-4. Blocking each of these checkpoints is associated with antitumor effects. The mechanisms for activating PD-1 and CTLA-4 are non-redundant, suggesting the potential for additive or synergistic effects; clinical studies have shown synergistic antitumor activity of anti-PD-1/anti-PD-L1 and anti CTLA-4 as combination therapy. **Methods:** An ongoing, phase 1, multicenter, open-label study (NCT01975831) is evaluating the safety/tolerability, pharmacokinetics (PK), immunogenicity and antitumor activity of M in combination with T in patients with advanced solid tumors. The study comprises a dose-escalation phase (3+3 design) and a subsequent dose-expansion phase. Patients with non-small cell lung, cervical, head and neck, colorectal, ovarian cancers, or renal cell carcinoma are eligible. M is administered at escalating doses starting at 0.3 mg/kg (up to 10 mg/kg) every 2 wks and T is administered at escalating doses starting at 3 mg/kg (up to 10 mg/kg) every 4 wks for the first 6 cycles, then every 12 wks. Treatment may continue for up to 12 months or until progressive disease or unacceptable toxicity. The primary endpoints are safety/tolerability and identification of the maximum tolerated dose of the combination. Secondary objectives include clinical activity (tumor response by RECIST v1.1 and Immune-related Response Criteria (irRC), PFS, and OS). The study will also assess PK and pharmacodynamic parameters, serum and tissue PD-L1 expression, immune cell phenotypes, cytokine profiling, and flow. Pharmacogenomic analysis of blood and tumor samples may be performed to examine gene expression patterns following treatment. Cohort 1 has been completed without DLT. Enrollment to cohort 2 began in March 2014. Clinical trial information: NCT01975831.

TPS3100 Poster Session (Board #419b), Sat, 8:00 AM-11:30 AM

"ARMY": First-in-human study of the humanized, defucosylated monoclonal antibody (mAb) MEN1112/OBT357 targeting CD157 antigen, in relapsed or refractory (R/R) acute myeloid leukemia (AML). *First Author: Adriano Venditti, Fondazione Policlinico Tor Vergata, Rome, Italy*

Background: Defucosylated mAbs enhance antibody dependent cell-mediated cytotoxicity (ADCC) through an improved affinity for Fc receptors. MEN1112/OBT357 is a humanized, defucosylated mAb targeting Bst1/CD157, a GPI-anchored transmembrane protein highly expressed on blasts of AML patients either at primary diagnosis or relapse. Preclinical findings show that MEN1112/OBT357 has the potential to exert powerful ADCC against AML (Aud et al ASH 2014; Venditti et al ASH 2014). **Methods:** Multi-center, non-randomized, 3+3 dose escalation/expansion cohort trial of MEN1112/OBT357 intended to recruit approximately 50 adult patients (pts) with R/R AML. Refractory pts must have failed $\geq$ 1 cycle of cytotoxic chemotherapy or hypomethylating agents. A baseline WBC count $\leq$ 10 x 10^9/L is required (pre-treatment with hydroxyurea is permitted). Main exclusion criteria are acute promyelocytic leukemia, hematopoietic stem cell transplant within 3 months prior to screening and active central nervous system involvement. MEN1112/OBT357 is given intravenously at 5 incremental doses on Days 1, 8, and 15 in a 21-day cycle for a total of 2 cycles; monthly maintenance is allowed in pts achieving clinical benefit. Primary objective is to identify dose limiting toxicities and maximum tolerated dose of MEN1112/OBT357 in pts with R/R AML; secondary objectives include (1) clinical pharmacokinetics, (2) potential immunogenicity, (3) clinical activity (complete- and composite complete remission rate, best response rate, overall survival) in treated pts and (4) its correlation with target expression/saturation, natural killer cells status, ex vivo activity at baseline and clinical/biological AML features. AEs will be graded according to NCI CTCAE v. 4.03 guidelines. Study variables will be presented by dose-cohort and overall using appropriate descriptive statistics. Efficacy will be evaluated in each cohort in pts completing the first cycle and with $\geq$ 1 post-cycle assessment using modified IWG 2003 criteria. The individual study duration is 6 months. The enrolment began on December 2014. Clinical trial information: NCT02353143 Clinical trial information: NCT02353143.

TPS3101 Poster Session (Board #420a), Sat, 8:00 AM-11:30 AM

Phase I expansion cohort trial to investigate the safety and clinical activity of avelumab (MSB0010718C) in patients with metastatic or locally advanced solid tumors. *First Author: Christopher Ryan Heery, Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. **Methods:** This is a parallel group expansion trial of avelumab in patients (pts) with selected tumor indications following the determination of dose and regimen in a phase I, open label, dose escalation study. The dose escalation cohort has been completed (n = 53). Pts in 11 separate cohorts of advanced solid tumors will receive avelumab at 10 mg/kg as a 1h infusion, Q2W. Treatment will continue until disease progression, unacceptable toxicity, or if any criterion for withdrawal of investigational medicinal product occurs. In addition to evaluating tolerability, specific objectives for the expansion cohorts include: assessment of best overall response (BOR) and progression-free survival (PFS) according to RECIST 1.1; assessment of immune-related BOR and immune-related PFS using the modified Immune-Related Response Criteria; and assessment of overall survival. Association between tumor PD-L1 expression and efficacy will be evaluated and the PK/PD profile of avelumab characterized. This trial is in progress: recruitment for 2nd-line non-small cell lung cancer (n = 184), metastatic breast cancer (n = 168), colorectal cancer (n = 21), and ovarian cancer cohorts (n = 75) is complete. Recruitment for gastric/gastroesophageal junction cancer (n = 150), melanoma (n = 50), castration-resistant prostate cancer (n = 20), adrenocortical carcinoma (n = 50), mesothelioma (n = 50), urothelial carcinoma (n = 50), and 1st-line NSCLC (n = 150) is ongoing (target enrollment provided for each tumor type). Overall, > 700 pts have been enrolled across the dose escalation and current expansion cohorts (start Jan 2013, estimate end Oct 2016). NCT01772004. *Proposed INN. Clinical trial information: NCT01772004.

TPS3102 Poster Session (Board #420b), Sat, 8:00 AM-11:30 AM

Genetically engineered NY-ESO-1 specific T cells in HLA-A201+ patients with advanced cancers. *First Author: Melinda S. Merchant, Natl Cancer Inst, Bethesda, MD*

Background: NY-ESO-1 (CTAG-1B) is a cancer testis antigen associated with spontaneous and vaccine-induced immunity that can lead to improved clinical outcomes. NY-ESO-1 is not expressed in vital tissues, and is expressed in approximately 40% of ovarian, 60% of advanced myeloma, and 70% of synovial sarcoma tumors. Expression is correlated with tumor proliferation and high risk features. A human-derived affinity-optimized TCR that recognizes the NY-ESO-1 derived SLLMWITQC peptide in complex with HLA-A*0201 (NY-ESO^{c259}) has been generated, and clinically tested as previously described using adoptive T cell transfer with supportive IL-2[1] **Methods:** Multiple clinical studies were initiated in HLA-A201+ patients with NY-ESO-1 expressing tumors. NY-ESO-1^{c259}-engineered autologous T-cells are manufactured centrally, using a 12 day commercial-grade closed system, and are administered without supportive IL-2. 40 patients have been infused: 25/26 on a phase I/II study in adults with systemic or multifocal myeloma requiring autologous stem cell transplantation, and who have incompletely responded to prior therapy or have high risk features (NCT01352286); 10/30 on a pilot study in patients ≥4 years old with unresectable, metastatic or recurrent synovial sarcoma (NCT01343043); 5/20 on a phase I study in adults with refractory or platinum resistant ovarian cancer and/or that have received ≥2 lines of chemotherapy (NCT01567891). Pre-infusion lymphodepleting chemotherapy is administered, and varies in intensity across studies. Primary objectives include safety and tolerability. Secondary objectives include evaluation of gene modified cells persistence in blood and tumor biopsies, lineage and functionality of these cells over time, and monitoring for serum cytokine levels and NY-ESO-1 antigen on tumor post infusion. Response assessments are performed using RECIST (sarcoma), IMWR criteria (myeloma), or immune-related response criteria (irRC; ovarian). 1. Robbins PF, Morgan RA, Feldman SA, et al: Tumor Regression in Patients With Metastatic Synovial Cell Sarcoma and Melanoma Using Genetically Engineered Lymphocytes Reactive With NY-ESO-1. Journal of Clinical Oncology 29:917-924, 2011 Clinical trial information: NCT01343043.

TPS3103 Poster Session (Board #421a), Sat, 8:00 AM-11:30 AM

Phase I/II study of stereotactic body radiation therapy (SBRT) to metastatic lesions in the liver or lung in combination with monoclonal antibody to OX40 in patients with progressive metastatic breast cancer (mBC) after systemic therapy. *First Author: Marka Crittenden, Earle A. Chiles Research Institute, Portland, OR*

Background: Focal radiation mediates tumor regression not only through direct cell killing, but also by influencing adaptive immune responses. We and others have investigated pre-clinical murine tumor models using the combination of high dose per fraction radiation (SBRT) given in conjunction with T-cell checkpoint and co-stimulatory molecules. For instance, in established 3LL tumor in C57BL/6 mice, the combination of radiation (3 doses of 20 Gy over 10 days) followed by an agonistic OX40 antibody administered within 24 hours of the last dose of radiation cured 60% of mice. There were no cures using radiation or OX40 alone. The combination increased the percent of activated CD8+CD25+ T cell infiltrating the tumor and tumor-draining lymph nodes. We designed a translational study for patients with progressive metastatic breast cancer after systemic therapy. **Methods:** Patients with mBC, at least one liver or lung metastatic site amenable to SBRT and at least one other metastatic site that is evaluable are eligible. Patients with hormone receptor positive mBC must have received one prior anti-hormonal therapy and have progressed. Patients with hormone receptor negative mBC must have received at least one prior chemotherapy regimen. SBRT will be administered in consecutive cohorts of 3-6 patients at doses of 15 Gy x 1, 20 Gy x 1 and 20 Gy x 2 with the first dose on day 1 of anti-OX40. Anti-OX40 is administered at a dose of 0.4 mg/kg IV on days 1, 3 and 5 of a single treatment cycle. Patients are accruing to the 20Gy x 2 radiation dose presently. The primary objective is to determine the maximum tolerated dose of SBRT administered in combination with anti-OX40. Secondary objectives include response of radiated and non-irradiated tumor sites, the influence of anti –OX40 on circulating CD4+ and CD8+ T cells and the proliferation of and activity of effector and memory T cells. Exploratory studies of serum markers of cell lysis, immunogenicity and T-cell responses to breast cancer antigens are also planned. Clinical trial information: NCT01642290.

TPS3104 Poster Session (Board #421b), Sat, 8:00 AM-11:30 AM

Study of hTERT and IL-12 DNA immunotherapy using electroporation in patients with solid tumors after definitive surgery and adjuvant therapy. *First Author: Robert H. Vonderheide, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: hTERT, the human catalytic reverse transcriptase subunit of telomerase, is highly expressed in breast, lung, and pancreatic cancers. Peptides derived from hTERT can be recognized on MHC by cytotoxic T cells and mediate tumor death. In preclinical studies, TERT DNA delivered with electroporation (EP) triggered an immune response in vivo that slowed tumor growth in HPV16-associated tumor-bearing mice. The advantages of DNA-based immunotherapy include (1) strong immunogenicity exceeding those achieved by viral vectors; (2) non infectiousness of the immunogen; (3) ability for repeated dosing; and (4) relatively low cost. EP can be used to optimally and safely deliver DNA in vivo by creating a transient electric field to enhance the cellular uptake of large molecules such as DNA. Addition of IL-12 to hTERT significantly enhanced immune responses in preclinical models. We hypothesized that generation of robust T-cell immunity by immunotherapy with hTERT + IL-12 can be clinically used to reduce the risk of relapse in high-risk cancer patients in the adjuvant setting. **Methods:** This hypothesis is being tested in a phase 1 clinical trial (NCT02327468) sponsored by Inovio and opened at Abramson Cancer Center of the University of Pennsylvania. INO-1400 is a plasmid encoding *hTERT*. INO-9012 is a dual promoter plasmid encoding human *IL-12* subunits p35 and p40. INO-1400 and INO-9012 are delivered IM followed by EP with the CELLECTRA device. This is an open-label, dose escalation study in patients with lung, pancreas, or breast carcinomas at high risk of relapse. Eligible patients must have early stage ER+ or HER2+, or any stage triple negative breast cancer; or Stage IB-IIIA NSCLC; or Stage I-III pancreatic cancer. Patients will enroll ≥ 4 and ≤ 16 weeks from completion of definitive surgery and adjuvant therapy into 1 of 6 cohorts (total N = 54): dosing INO-1400 at 2 or 8 mg ± INO-9012 at 0.5 or 2 mg, with EP, once every 4 weeks for 4 total treatments. Primary Endpoints:Safety and tolerability. Secondary Endpoints:(1) Time to progression; (2) Antigen-specific T cell response by IFN-γ ELISpot and flow cytometry; (3) antigen-specific humoral responses by ELISA. Clinical trial information: NCT02327468.

TPS3105 Poster Session (Board #422a), Sat, 8:00 AM-11:30 AM

***In situ* vaccine for low-grade lymphoma: Combination of intratumoral FIt3L and poly-ICLC with low-Dose radiotherapy.** *First Author: Thomas Urban Marron, Mount Sinai Hospital, New York, NY*

Background: Lymphomas are the 5th most incident cancer in the U.S. and indolent non-Hodgkin's lymphoma (iNHL) are incurable with standard therapy. We previously completed three trials of '*in situ* vaccination' - combining low-dose radiotherapy (XRT) with intratumoral administration of a TLR9 agonist (CpG). We demonstrated induction of tumor-specific CD8 T cell responses and clinical remissions of patients' untreated sites of disease, lasting up to > 4 years. One limitation may have been the scarcity of intratumoral dendritic cells (DC). DC are uniquely able to endocytose dying (e.g. irradiated) tumor cells for cross-presentation to anti-tumor CD8 T cells. **Methods:** FIt3L– the predominant DC differentiation factor– induces tumor leukocyte infiltration and regression of lymphoma tumors pre-clinically and a new formulation of this cytokine -CDX-301- was shown to mobilize BDCA-1 and BDCA-3 DC subsets in an early phase trial. These DC subsets respond to several TLR agonists and cross-present antigens more effectively than plasmacytoid DC (the CpG-responsive DC subset). We initiated a phase I/II study of a new iteration of the *in situ* vaccine, adding FIt3L-priming and replacing the prior TLR9 agonist with the TLR3 agonist poly-ICLC (Fig 1A). The vaccine consists of: -**intratumoral FIt3L** administration to increase DC within the tumor -**low-dose XRT** to induce immunogenic tumor cell death and release tumor-associated antigens, and -**intratumoral poly-ICLC** administration to *activate* tumor antigen-loaded DC. The current study will assess two cohorts of patients (n = 15, each) with either previously untreated or relapsed/refractory iNHL to test the hypothesis that *in situ* vaccination will induce clinical remissions at distant (untreated) tumor sites. Eligibility: iNHL, either previously untreated or relapsed/refractory. Treatment: Intratumoral CDX-301 25ug/kg x 9 days. Local radiotherapy 2Gy x 2. Intratumoral poly-ICLC 2mg weekly x 8 weeks. Patients will have tumor (FNA) and blood collected for immune monitoring at weeks 0, 2, 4, 6, 8, 12 as well as pre treatment biopsy. Restaging CT scans will be done pretreatment and at week 12. Clinical trial information: NCT01976585. Clinical trial information: NCT01976585.

TPS3106 Poster Session (Board #422b), Sat, 8:00 AM-11:30 AM

Phase I study of safety and immunogenicity of ADU-623, a live-attenuated *Listeria monocytogenes* vaccine (Δ*actA*/Δ*inlB*) expressing EGFRvIII and NY-ESO-1, in patients with WHO grade III/IV astrocytomas. *First Author: Marka Crittenden, Earle A. Chiles Research Institute, Portland, OR*

Background: The neo-antigen EGFRvIII is expressed in multiple tumor types, including high-grade astrocytomas. It is associated with a poor prognosis and resistance to conventional therapies such as chemotherapy and radiation that are part of the standard treatment. We propose that immunization with a live-attenuated *Listeria*-based vaccine, ADU-623, expressing EGFRvIII and NY-ESO-1 will elicit robust tumor-specific immune responses capable of killing EGFRvIII and/or NY-ESO-1-expressing tumor cells and improve survival of the patients. In addition, ADU-623 induces a potent innate immune response that can kill transformed cells even in the absence of neo-antigens. We designed a translational vaccine study to evaluate the safety and immunogenicity of this vaccine in patients with high-grade astrocytomas after standard of care therapy or at progression. **Methods:** Patients with a pathologic diagnosis of WHO Grade III/IV astrocytic tumors that have completed standard of care external beam radiation therapy and concurrent temozolomide followed by adjuvant temozolamide or with radiographic evidence of progression following standard of care radiation and chemotherapy treatment, including those who have gone on to a second surgical resection are eligible. Patients are enrolled and assigned consecutively to one of the following ADU-623 dose level cohorts: Cohort 1 $3x10^7$ cfu, Cohort 2 $3x10^8$ cfu, or Cohort 3 $1x10^9$ cfu, each administered IV on Days 0, 21, 42 and 63. Adverse events are monitored throughout the treatment and patients are followed for up to 24 months. Patients are currently accruing to Cohort 3. The primary objective is to determine the maximum tolerated dose and characterize the safety profile of ADU-623 in patients with treated and recurrent WHO Grade III/IV astrocytomas. Secondary objectives include progression free survival, time to progression and overall survival rates in patients vaccinated with ADU-623. Exploratory studies of EGFRvIII-, NY-ESO-1-, vector-specific and innate immune responses will be performed. Clinical trial information: NCT01967758.

3500 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

A multi-center randomized controlled trial of mFOLFOX6 with or without radiation in neoadjuvant treatment of local advanced rectal cancer (FOWARC study): Preliminary results. *First Author: Yanhong Deng, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: The FOWARC study investigates whether peri-operative mFOLFOX6 chemotherapy (CT) improves disease-free survival (DFS) in locally advanced rectal cancer. **Methods:** Between 01/2011-02/2015, patients with rectal cancer within 12 cm from the anal verge, clinical stage II-III were randomly assigned to received 5-FU with radiation(RT) (control arm), or receive mFOLFOX6 with RT (FOLFOX-RT arm), or receive 4-6 cycles of mFOLFOX6 alone (FOLFOX arm), post-operative RT is allowed if needed. Primary endpoint is DFS. Here we report the preliminary results. **Results:** 495 patients were randomized (165 in each arm). 92% of patients accomplished at least 46 Gy of RT in FOLFOX-RT arm compared to 86.8% in control arm. 5% of FOLFOX arm patients received post-op RT. R0 resection rate was 90.1%, 88.2%, and 91.2%, respectively in control arm, FOLFOX-RT arm and FOLFOX arm. The pCR rate was 12.5%, 31.3% and 7.4% respectively (P = 0.001). Good down staging (ypTNM 0-1) was achieved in 34.7%, 57.8%, and 37.9% of patients respectively. Higher toxicity and post-op complications were observed in patients received RT. Similar results were seen in subgroup of patients with lesions located within 5cm from the anal verge. **Conclusions:** mFOLFOX6 concurrent with RT resulted in higher pCR rate, neoadjuvant mFOLFOX6 alone achieved similar down staging rate with less toxicity and post-op complications, compared to preoperative 5-FU with RT. Clinical trial information: NCT01211210.

	All patients			Subgroup(0-5cm)		
	Control	FOLFOX-RT	FOLFOX	Control	FOLFOX-RT	FOLFOX
Age Median(Range)	56.2(24-75)	52.0(27-73)	56.0(21-75)	56.2(24-75)	52.6(30-72)	56(28-73)
Clinical T4b(%)	8.6	8.6	3.0	11.1	8	4.8
Clinical staging III (%)	76.5	75	70.3	67.9	66.7	51.3
pCR(%)	12.5	31.3	7.4	14.3	43.2	8.8
ypTNM 0-I(%)	34.7	57.8	37.9	33.3	62.1	41.2
TRG 0-1(%)	33.2	65.6	38.5	33.3	52	26.1
R0 resection (%)	90.1	88.2	91.2	72.2	74	76.2
Sphincter preservation (%)	76.5	82.8	88.2	59.3	62	66.7
Grade 3/4 Leucopenia(%)	14.8	20.9	7.9	15.1	14.6	15.8
Grade 3/4 radiodermatitis(%)	13.6	20.0	-	17	20.8	-
Grade 3/4 radiation proctitis(%)	9.8	13.2	-	13.1	10.4	-
Anastomotic leakage(%)	24.3	18.8	6.3	20	18.4	3
Infection of incision (%)	25.7	29.9	9.5	30.8	39.5	9.1

3501 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC). *First Author: Theo Ruers, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Background: This study evaluates the benefit of combining systemic chemotherapy (CT) with local tumor destruction by RFA in patients with unresectable CRC LM up to 9 lesions and without extrahepatic disease. Overall survival (OS) at 30 months and progression free survival (PFS) results were reported (Ann Oncol. 23(10): 2619-26, 2012). We now report on OS results, after a long term median follow-up of 9.7 years. **Methods:** Between 2002 and 2007, 119 pts were randomized between CT alone (59) or RFA+CT (60). In both arms, CT consisted of 6 months FOLFOX (oxaliplatin 85mg/m2 and LV5FU2) plus, since October 2005, bevacizumab. In the CT arm resection was allowed when unresectable disease was converted by CT to resectable disease. Primary objective was a 30-months OS rate > 38% for the combined treatment group. OS and PFS were secondary endpoints. **Results:** In the RFA+CT arm, 56 pts (93.3%) received RFA which was combined with resection in 27 pts (45%), 1 pt had all metastases resected (ineligible), 2 pts were not treated at all, in 1 pt no local treatment data were available. 51 patients (85%) in the RFA+CT arm received CT compared to all 59 in the CT arm. 6 pts in the CT arm eventually underwent hepatic resection. The primary endpoint was met, 30-months OS rate was 61.7% (95% CI: 48.2-73.9) for combined treatment. However, 30-month OS for systemic treatment only was 57.6% (95% CI: 44.1-70.4), higher than anticipated. At a median follow-up of 9.7 years, 92 deaths were reported, 53 in the CT arm and 39 in the RFA+CT arm. Causes of death in the CT arm were progressive disease (49 pts), and unknown for 4 pts, and in the RFA+CT arm, progressive disease (35 pts), other causes (2 pts) and unknown (2 pts). There was a significant difference in OS in favor of the RFA+CT arm (HR = 0.58, 95% CI: 0.38-0.88, p = 0.01). Observed median OS was 45.6 months (95% CI: 30.3 – 67.8) in the RFA+CT arm vs. 40.5 months (95% CI: 27.5 - 47.7) in the CT arm. **Conclusions:** This is the first study that prospectively investigated the efficacy of RFA +CT in pts with unresectable CRC LM. In this phase II trial, RFA+CT was associated with improved long-term OS compared to CT alone. Clinical trial information: NCT00043004.

3502 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC). *First Author: Peter Gibbs, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia*

Background: The SIRFLOX study was designed to assess the efficacy and safety of combining FOLFOX chemotherapy (± bev) with SIRT using yttrium-90 (Y-90) resin microspheres as first-line treatment of pts with liver metastases from mCRC. **Methods:** SIRFLOX was an international, multicenter, open-label, RCT in chemotherapy-naïve pts with non-resectable, liver only or liver dominant (liver plus lung and/or lymph node metastases) mCRC. Arm A: mFOLFOX6 ± bev was compared to arm B: mFOLFOX6 + SIRT (SIR-Spheres; Sirtex) administered once with cycle 1 ± bev until disease progression. The primary endpoint was progression free survival (PFS) using RECIST v1.0. Stratification variables included presence of extra hepatic disease (EHD; liver only *v* liver dominant), degree of liver involvement (≤ 25% *v* > 25%), and treatment with bev (at clinician discretion). **Results:** From Oct 2006 to Apr 2013,530 pts were randomised (arm A, n = 263; arm B, n = 267), 212 (40%) had EHD. Median follow-up was 36.1 months. The median overall PFS was 10.2 *v* 10.7 months in arms A *v* B respectively (hazard ratio [HR]: 0.93; 95% CI 0.77–1.12; p=0.428) by Kaplan Meier analysis. The median PFS in the liver was 12.6 *v* 20.5 months in arm A *v* B (HR: 0.69; 95% CI 0.55–0.90; p = 0.002) by competing risk analysis. Overall response rate (PR + CR) was 68.0% *v* 76.4% in arm A *v* B, respectively (p = 0.113). Hepatic response rate was 68.8% *v* 78.7% in arm A *v* B (p = 0.042), including CR rate 1.9% *v* 6.0% (p = 0.02). The liver resection rate was 13.7% *v* 14.2% in arm A *v* B (p = 0.857). Adverse events ≥ grade 3 were noted in 73.3% *v* 85.4% of pts in arm A *v* B. Most common toxicities were hematologic; 32.9% *v* 51.2% and gastrointestinal; 21.2% *v* 32.9%, including gastric ulcer 0.0% *v*2.4%. **Conclusion:** In first-line treatment of pts with non-resectable CRC liver metastases, the addition of SIRT to standard chemotherapy failed to improve overall PFS. However, median liver PFS was significantly extended. The addition of SIRT was associated with acceptable toxicity. Overall survival analyses, combining data from SIRFLOX and two other ongoing studies in this disease setting, are awaited. Clinical trial information: NCT00724503.

3503 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance). *First Author: Kimmie Ng, Dana-Farber Cancer Institute, Boston, MA*

Background: Prospective epidemiologic data suggest that higher levels of 25-hydroxyvitamin D [25(OH)D] are associated with improved survival in patients with colorectal cancer, however the relationship between 25(OH)D and outcome in metastatic CRC (mCRC), specifically, is unknown. **Methods:** We prospectively assessed the association between plasma 25(OH)D and overall survival (OS) in previously untreated mCRC patients enrolled in CALGB/SWOG 80405, a randomized phase III trial of chemotherapy + bevacizumab, cetuximab, or both, prior to the *KRAS* wild type amendment. Progression-free survival (PFS) was a secondary endpoint. Plasma 25(OH)D levels were measured at baseline by radioimmunoassay, and dietary and lifestyle behaviors collected from self-administered questionnaires. Cox proportional hazards models were used to calculate hazard ratios (HR) adjusted for other prognostic variables. **Results:** Among 1,043 patients, median plasma 25(OH)D was 17.2 ng/mL (range 2.2-72.7). Male and black patients, those living in the northeast, patients with lower dietary and supplemental vitamin D intake, ECOG performance status 1 (vs. 0), tumoral *RAS* mutation, higher body-mass index, lower physical activity, and blood draw during the winter and spring had significantly lower levels of 25(OH)D. Patients in the highest quintile of 25(OH)D had significantly improved OS compared to those in the lowest after adjusting for pathologic and clinical prognostic factors (median 32.6 vs. 24.5 months; HR 0.65, 95% CI, 0.51-0.83; *P* trend = 0.001). Increasing concentrations of 25(OH)D were also significantly associated with improved PFS (median 12.2 vs. 10.1 months; HR 0.79, 95% CI, 0.63-0.99; *P* trend = 0.01). The results were consistent across subgroups of patient characteristics, including *RAS* status, and remained unchanged after excluding patients who died within 3 or 6 months of blood draw. **Conclusions:** Higher concentrations of plasma 25(OH)D are associated with significantly improved survival in mCRC patients treated with chemotherapy + biologics. Randomized trials of vitamin D supplementation are warranted and ongoing, and effect modification by SNPs in vitamin D pathway genes is currently being explored.

3504 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Impact of aspirin as secondary prevention in an unselected cohort of 25,644 patients with colorectal cancer: A population-based study. *First Author: Simer Bains, 1The Biotechnology Centre and Centre for Molecular Medicine Norway, Nordic EMBL Partnership, University of Oslo, Oslo, Norway, Oslo, Norway*

Background: Regular use of aspirin (acetylsalicylic acid) has been associated with reduced incidence and mortality of colorectal cancer (CRC). However, the use of aspirin as primary prevention in the general population is still being debated due to the risk of serious hemorrhagic side effects. In contrast, the use of aspirin as secondary prevention in patients with CRC may be more justified from a risk-benefit prospective, and also as we have observed that aspirin reverses tumor immune evasion mechanisms in established colorectal cancer. This study was conducted to examine the association between aspirin use after diagnosis of CRC with CRC-specific survival (CSS) and overall survival (OS) in the largest cohort ever examined. **Methods:** An observational population-based retrospective cohort study was undertaken by linking patients diagnosed with CRC from 2004 through 2011 (Cancer Registry of Norway) with the use of aspirin in the same patients (The Norwegian Prescription Database). The registries used cover more than 99% of the Norwegian population, and include all cases in an unselected manner. Exposure was defined as having received prescription for more than 6 months of aspirin after diagnosis of CRC. Multivariate Cox proportional hazard and competing risk analyses were used to model survival. The main outcome measures of the study were CSS and OS. **Results:** In total, 25,644 patients were diagnosed with CRC in the study period and 6,109 of them were defined as exposed to aspirin after the diagnosis of CRC. The median follow-up was 2.2 years. Among aspirin exposed cases (n = 6,109), a total of 2,088 (34.2%) deaths were recorded of which 1,172 (19.2%) were CRC-specific. Among non-exposed aspirin cases (n = 19,535), a total of 7,595 (38.9%) deaths were recorded of which 6,356 (33.5%) were CRC-specific. In multivariate analysis, aspirin exposure after the diagnosis of CRC was independently associated with improved CSS (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.50-0.57; $p < 0.001$) and OS (HR, 0.71; 95% CI, 0.68-0.75; $p < 0.001$). **Conclusions:** Exposure to aspirin after the diagnosis of CRC is independently associated with improved CSS and OS.

3505 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Comprehensive molecular characterization of colorectal cancer reveals genomic predictors of immune cell infiltrates. *First Author: Marios Giannakis, Dana-Farber Cancer Institute, Boston, MA*

Background: Colorectal cancer (CRC) is a molecularly heterogeneous disease that arises and progresses in the context of a complex microenvironment. Tumor immune cell infiltrates have been shown to be associated with an improved CRC-specific and overall survival. However, the genomic features of CRC that determine the number and types of immune infiltrates remain largely uncharacterized. **Methods:** We performed Whole Exome Sequencing and microsatellite instability (MSI) analysis on primary CRCs from 689 patients (pts) identified from two large prospective cohorts, the Nurses' Health Study and the Health Professionals Follow-Up Study. We also immunohistochemically characterized the immune infiltrate (peritumoral, intratumoral periglandular, Crohn's-like, tumor-infiltrating, and total lymphocyte score) and conducted tissue microarray imaging analysis for T-cell subsets (CD3+, CD8+, CD45RO+, FoxP3+). We utilized a novel computational pipeline to calculate tumor neoantigen load (peptides resulting from somatic mutations and recognized by the immune system as foreign) and subsequently correlated the tumor neoantigen load with the aforementioned immune variables and with pt survival. **Results:** When compared to microsatellite-stable cancers, MSI-high tumors expressed significantly more neoantigens ($P < 2e\text{-}16$). Tumor neoantigen load significantly correlated with total lymphocytic score in the primary CRCs ($P = 4.9e\text{-}9$) and was most significantly associated with tumor infiltrating lymphocytes ($P = 1.6e\text{-}15$). Among T-cell subsets, tumor neoantigen load was only significantly associated with the CD45RO+ T-cell subset ($P = 0.0003$). Higher tumor neoantigen load predicted significantly improved CRC-specific and overall survival ($P = 0.014$ and $P = 0.048$, respectively). **Conclusions:** In the large prospective study of molecularly characterized CRCs, tumor neoantigen load predicts greater tumor-infiltrating lymphocytes and memory T-cell infiltration and represents a novel genomic predictor of CRC survival. Our findings link tumor genomics to specific immune response elements and have implications for the therapeutic manipulation of the latter in CRC.

3506 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Analysis of DNA mismatch repair (MMR) and clinical outcome in stage III colon cancers from patients (pts) treated with adjuvant FOLFOX +/- cetuximab in the PETACC8 and NCCTG N0147 adjuvant trials. *First Author: Aziz Zaanan, Mayo Clinic and Mayo Cancer Center, Rochester, MN*

Background: The prognostic impact of deficient (d) MMR, including sporadic and familial types, in stage III colon cancer pts receiving standard adjuvant FOLFOX therapy remains unknown. We examined the association of MMR status with clinical outcome in two phase III clinical trials of adjuvant FOLFOX +/- cetuximab. **Methods:** Prospectively collected tumors from both studies were separately analyzed for MMR protein (MLH1, MSH2, MSH6) expression and mutations in *BRAF* (*V600E*). Loss of any MMR protein indicated dMMR. Methylation of the *MLH1* gene promoter was studied in tumors with loss of MLH1 and wild-type (WT) *BRAF*. Associations of MMR status with time-to-recurrence (TTR), disease-free survival (DFS) and overall survival (OS) were analyzed using a stratified Cox proportional hazards model. Multivariate models were adjusted for treatment and covariates (age, sex, tumor grade, T/N stage, tumor location, ECOG PS, *BRAF/KRAS*). **Results:** The frequency of dMMR in the overall cohort was 10.7% (499/ 4674). 3-year (yr) DFS for dMMR *vs* proficient (p) MMR pts was 75% *vs* 74% (HR = 0.87; 95% CI, 0.71-1.07; $p_{adustedj} = .196$). Among pts with complete biomarker data (N = 4339), there were 405 dMMR tumors of which 265 (65.4%) were categorized as sporadic (*BRAF* mutation or WT with *MLH1* methylation) and 140 (34.6%) as familial (*BRAF* WT and unmethylated *MLH1* or loss of MSH2 or MSH6). DFS rates of pts with sporadic and familial dMMR tumors were similar (HR, 1.15; 95% CI, 0.73-1.81; $p_{adjusted} = .54$). Pts with dMMR tumors had similar DFS rates as did pts with pMMR tumors without *BRAF* or *KRAS* mutations (Table). Consistent results were found for biomarkers and TTR and OS. **Conclusions:** In this large cohort of stage III colon cancer pts enrolled in two adjuvant trials testing FOLFOX +/- cetuximab, MMR status was not prognostic. Similar outcomes were found for sporadic and familial dMMR cases, and when each of these dMMR subtypes was compared to pMMR tumors WT for both BRAF and KRAS genes. Clinical trial information: NCT00079274.

Variable	N	3-yr DFS %	HR (95% CI)	Adjusted P value
WT *KRAS*, WT *BRAF*, pMMR,	2205	78.1	Ref	---
Sporadic dMMR	265	77.3	0.99 (0.73,1.32)	0.9263
Familial dMMR	140	77.6	0.86 (0.58,1.26)	0.4342

3507 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Prognostic value of *BRAF* V600E and *KRAS* exon 2 mutations in microsatellite stable (MSS), stage III colon cancers (CC) from patients (pts) treated with adjuvant FOLFOX+/- cetuximab: A pooled analysis of 3934 pts from the PETACC8 and N0147 trials. *First Author: Julien Taieb, Paris Descartes University, Georges Pompidou European Hospital, Paris, France*

Background: The prognostic value of BRAF and KRAS mutations in resected CC pts remains controversial due to published studies that include stage II & III, microsatellite instability (MSI) and MSS, colon and rectal tumors, and variable treatment regimens. We examined this question in prospectively collected biospecimens from MSS stage III CC pts receiving adjuvant FOLFOX +/- cetuximab. **Methods:** Tumors were analyzed for BRAF V600E and KRAS exon 2 mutations, only MSS tumors were included. Three groups were defined: BRAF Mutant, KRAS Mutant and double wild-type (WT). The analytic strategy estimated study- and arm-specific prognostic effects to assess homogeneity of results, and then analysis of pooled data. Associations of mutations with time-to-recurrence (TTR), survival after relapse (SAR) and overall survival (OS) were analysed using a stratified Cox proportional hazards model. Multivariate models were adjusted for treatment and covariates (age, sex, tumor grade, T/N stage, tumor location, ECOG PS). **Results:** Of the 5,577 pts enrolled, 3,934 tumors were MSS and evaluable for BRAF and KRAS; 279 pts were BRAF Mutant, 1,450 KRAS Mutant, and 2,205 WT. Both mutations were linked to shorter TTR and OS vs WT, and results were confirmed in multivariate analyses (table). Median SAR was 2.57, 2.09 and 1.0 year in WT, KRAS Mutant (HR: 1.20- 95%CI: 1.01-1.44, $p < 0.0001$) and BRAF mutant (HR: 3.01-95%CI: 2.32-3.93, $p < 0.0001$), respectively. No interaction was found between treatment (with or without cetuximab) and KRAS/BRAFmutations for TTR ($p = 0.38$) or OS ($p = 0.16$). **Conclusions:** In a large pooled analysis of pts with resected stage III MSS colon cancers receiving adjuvant FOLFOX, BRAFV600E or KRAS exon 2 mutations, including codons 12 or 13, are independent predictors of significantly shorter TTR, SAR and OS. Future clinical trials in the adjuvant setting should consider these mutations as important stratification factors.

	TTR			OS		
	3 y rate	HR (95% CI)	p	3 y rate	HR (95% CI)	p
WT	80.0%			91.4%		
BRAF V600E	69.7%	1.49 [1.19,1.87]	0.0005	73.9%	1.72 [1.33,2.22]	< .0001
KRAS Exon 2	69.5%	1.60 [1.40,1.83]	< .0001	86.3%	1.52 [1.29,1.79]	< .0001

3508 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): The HERACLES trial. *First Author: Salvatore Siena, Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, Milan, Italy*

Background: We conducted a phase II of trastuzumab (T) and lapatinib (L) in HER2-amplified, KRAS exon 2 wild-type, mCRC pts resistant to standard therapies (HERACLES Trial EudraCT 2012-002128-33). **Methods:** Pts progressing after fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab were eligible if tumor was HER2+ [IHC3+ or 2+ and FISH positive (HER2:CEP17 $>$ 2) in $>$ 50% cells]. L was given po qd, T iv qw at standard doses. Response was assessed q 8 wks. The primary end-point was objective response (OR, RECIST v1.1). To consider the study positive 6/27 ORs had to be observed (α = 0.05; β = 85%; H1 = 30%). Serial liquid biopsies for HER2 ctDNA (ddPCR/NGS) and ectodomain (ECD) plasma levels (ELISA) were collected until progression. **Results:** As of Jan 31 2015, 913 pts were screened, 44 found HER2+ (4.8%), and 23 eligible and evaluable: 2F/21M, median age 63 (r = 40-86), ECOG PS $\leq$ 1, median prior regimens 5 (r = 3-8). Primary endpoint was met with 8/23 ORs [7 PR, 1 PRunc (too early); ORR = 35% (95% CL 20-55)]; 7/8 ORs were observed in HER2 IHC3+ pts. Responses lasted: 8+, 12+, 14+, 24, 24.5+ 32, 54+ and 55+ weeks. Median time to progression was 5.5 months (95% CL 3.7-9.8). Toxicity was limited to G2 diarrhea, fatigue, and rash (1 G3). HER2+ ctDNA and ECD levels decreased in 2/3 ORs and 0/2 non responders and in 2/2 ORs 0/6 with SD or PD, respectively. Exploratory correlative analyses of HER2 gene dosage will be presented together with exome analysis of index cases. **Conclusions:** HER2 is amplified in 5% of WT exon 2 KRAS mCRC patients. The HERACLES trial met its primary endpoint with 8/23 objective responses in pts heavily pretreated with standard therapies, including EGFR-targeted agents, indicating that the dual anti HER2 therapy is effective and deserves further clinical assessment in earlier lines of treatment of HER2+ mCRC patients. HERACLES is funded by Associazione Italiana Ricerca Cancro. Clinical trial information: 2012-002128-33.

3509 Poster Discussion Session; Displayed in Poster Session (Board #1), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Exploring the poor outcomes of *BRAF* mutant (*BRAF* mut) advanced colorectal cancer (aCRC): Analysis from 2,530 patients (pts) in randomized clinical trials (RCTs). *First Author: Jenny F. Seligmann, University of Leeds, Leeds, United Kingdom*

Background: *BRAF*-mut aCRC pts have poor overall survival (OS). To investigate this phenomenon, we have examined individual patient data from pts treated with chemotherapy alone in 3 RCTs to identify the points on the treatment pathway at which their outcomes are inferior to *BRAF*-wt pts. **Methods:** *BRAF* was assessed in tumors of 2530 pts in 3 RCTs: COIN (n = 1284), FOCUS (n = 787) and PICCOLO (n = 459). End-points were progression free survival (PFS), response rate (RR), post progression survival (PPS) and OS. Treatments received were 1st line OxFU (COIN), 1st line FU (FOCUS) or 2ndline Irinotecan (Ir) (PICCOLO). Analyses were performed using Cox proportional hazards models and logistic regression. **Results:** 231 pts (9.1%) were *BRAF*-mut. *BRAF*-mut status conferred worse OS in both 1st-line studies (FOCUS HR = 1.55, p = 0.002; COIN HR = 1.77, p $<$ 0.001). Compared with wt, *BRAF*-mut pts treated with 1stline OxFU had inferior RR (32% vs 48%; OR = 0.51,p $<$ 0.001) and PFS (unadjusted HR = 1.34, p = 0.041, but p = 0.19 after adjustment). Following progression on 1st-line chemotherapy, *BRAF*-mut pts had shorter PPS (COIN HR = 1.99, p $<$ 0.0001; FOCUS HR = 2.13, p $<$ 0.001). However, *BRAF*-mut did not confer a disadvantage among pts pausing chemo without progression for planned chemo-free intervals (COIN, OS HR 0.97, p = 0.75; PFS HR = 1.09, p = 0.33). In COIN, *BRAF*-mut pts were less likely to receive 2nd-line treatment after 1st-line progression (39% *vs* 60%, p = 0.002). However, once started, the outcomes during or after 2nd-line chemo were not significantly inferior in *BRAF*-mut pts: in PICCOLO: RR OR = 0.75, p = 0.65; PFS HR = 1.06, p = 0.72; PPS HR = 1.13, p = 0.57). **Conclusions:** The poor survival of *BRAF*-mut pts is driven by accelerated decline following progression, and a lower probability of receiving further lines of therapy, so clinicians need extra vigilance. However, *BRAF*-mut pts may still enjoy treatment breaks when not progressing, and if treated with 2nd line chemotherapy are no less likely to benefit.

3510 Poster Discussion Session; Displayed in Poster Session (Board #2), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as initial treatment for metastatic colorectal cancer (TRIBE study): Updated survival results and final molecular subgroups analyses. *First Author: Fotios Loupakis, U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy*

Background: The phase III TRIBE study met its primary endpoint by demonstrating that first-line FOLFOXIRI plus bev significantly prolongs PFS, as compared to FOLFIRI plus bev (*Loupakis et al, N Eng J Med 2014*). At a median follow-up of 32.2 months a preliminary OS analysis indicated a borderline OS improvement with FOLFOXIRI plus bev (HR = 0.79, p = 0.054) with a consistent effect across *RAS* (*KRAS* and *NRAS* codons 12, 13, 61) and *BRAF*V600E molecular subgroups. **Methods:** 508 pts were randomized to either FOLFIRI plus bev (Arm A, N = 256) or FOLFOXIRI plus bev (Arm B, N = 252). On available samples from *RAS* and *BRAF* wild-type (wt) pts (N = 129), also *KRAS* and *NRAS* codons 59, 117 and 146 were analysed by means of Sequenom MassArray, identifying a new "all wt" population (N = 93). **Results:** At a median follow-up of 48.1 months, in the ITT population, updated median OS for Arm B vs Arm A was 29.8 vs 25.8 months (HR = 0.80, 95%CI, 0.65-0.98, p = 0.030). Estimated 5-years OS rate were: Arm B, 24.9% vs Arm A, 12.4%. Molecular results were informative for 357 pts (70.3%). All wt patients had longer OS as compared to *RAS* mutant (HR = 0.70, p = 0.006) and to *BRAF* mutant (HR = 0.24, p $<$ 0.001). The benefit from FOLFOXIRI plus bev was consistent across all molecular subgroups (Table 1). All wt pts treated with FOLFOXIRI plus bev reported a median OS of 41.7 months as compared to 33.5 months in the FOLFIRI plus bev group (HR = 0.75, 95%CI, 0.45-1.24). **Conclusions:** FOLFOXIRI plus bev significantly improves survival of metastatic colorectal cancer pts and the OS advantage increases over time. Benefit from FOLFOXIRI plus bev is independent of *RAS* and *BRAF* mutational status. All wt pts have a better outcome independently from the treatment arm. Notable results with FOLFOXIRI plus bev are achieved in all wt pts. Clinical trial information: NCT00719797.

	Arm A FOLFIRI+bev Median PFS (mos)	Arm B FOLFOXIRI+bev Median PFS (mos)	HR [95%CI]	Arm A FOLFIRI+bev Median OS (mos)	Arm B FOLFOXIRI+bev Median OS (mos)	HR [95%CI]
All wt (N = 93)	12.2	13.7	0.82 [0.53-1.26]	33.5	41.7	0.75 [0.45-1.24]
***RAS* mut (N = 236)**	9.5	12.0	0.82 [0.63-1.07]	23.9	27.3	0.95 [0.71-1.27]
***BRAF* mut (N = 28)**	5.5	7.5	0.56 [0.20-1.14]	10.8	19.1	0.60 [0.27-1.33]

3511 Poster Discussion Session; Displayed in Poster Session (Board #3), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Phase Ib study of vemurafenib in combination with irinotecan and cetuximab in patients with *BRAF*-mutated metastatic colorectal cancer and advanced cancers. *First Author: David S. Hong, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *BRAF* V600 mutations, present in 5-10% of patients (pts) with metastatic colorectal cancer (mCRC), are poor prognostic markers and are associated with a low response to the combination of cetuximab (C) and irinotecan (I). Vemurafenib (V), an oral kinase inhibitor specific to mutated V600 BRAF, demonstrated a 5% response rate in a phase I trial of pts with *BRAF*-mutated mCRC. In vitro data in CRC cell lines has shown that blockade of mutated BRAF by vemurafenib triggers compensatory activation of EGFR. Inhibition of EGFR combined with vemurafenib results in synergistic cytotoxicity in preclinical models, which is further augmented by irinotecan. The safety and efficacy of the combination in pts with *BRAF*-mutated advanced malignancies have not been defined. **Methods:** In this 3+3 phase I study, pts with *BRAF*-mutated cancers received escalating doses of V in combination with C and I over a 14-day cycle. Responses were evaluated every 4 cycles by RECIST 1.1. Adverse events (AEs) were assessed by CTCAE 4.0. **Results:** Among 19 total pts treated on study, 18 pts have mCRC: 6 at dose level 1(DL) (V- 480mg PO BID, C-250 mg/m^2 weekly and I- 180mg/m^2 every 14 days), 6 at DL 2 (increased to V-720mg PO BID), and 6 at DL3 (V-960mg PO BID). Median age was 63 yrs (42-73yrs). One DLT was observed at each DL (arthralgia in 2 pts, diarrhea in 1 pt). The MTD was determined to be DL3 (V-960 mg PO BID, C-250 mg/m^2 weekly, I-180mg/m^2 every 14 days). The most common AEs were fatigue (94%), diarrhea (89%), nausea (83%), and rash (78%). Six of the 17 evaluable mCRC pts achieved a partial response (RR 35%). Median best response was a reduction of -20% (+21% to -100%) with median duration of response of 12.5 cycles (IQR, 5-17 cycles). Seven mCRC pts remain on study. Median PFS is 7.7 months. One pt came off study due to diarrhea before restaging. Preliminary PKs and PDs will be reported. **Conclusions:** The combination of V with I and C is well tolerated in pts with *BRAF*-mutated mCRC with the MTD at V-960 mg PO BID, C-250 mg/m^2 weekly, I-180mg/m^2 every 14 days. Responses were seen in 35% of evaluable mCRC pts. A US cooperative group randomized phase II trial of I and C with or without V in *BRAF*-mutated mCRC (SWOG 1406) is ongoing. Clinical trial information: NCT01787500.

3512 Poster Discussion Session; Displayed in Poster Session (Board #4), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Randomized phase III study of adjuvant chemotherapy with S-1 versus capecitabine (cape) in patients with stage III colon cancer (CC): Results of Japan Clinical Oncology Group study (JCOG0910). *First Author: Tetsuya Hamaguchi, Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan*

Background: We previously reported the results of the JCOG0205 study, which indicated that D2/D3 lymph node dissection followed by adjuvant fluoropyrimidine (F) monotherapy resulted in better disease-free survival (DFS) and overall survival (OS) in Japan than in Western countries (*EJC 2014*). Cape is one of standard adjuvant chemotherapy for stage III CC (*NEJM 2005*). Recently, S-1 was demonstrated to be non-inferior to uracil and tegafur plus leucovorin in DFS (*Ann Oncol 2014*). This is the first report of JCOG0910, which compared S-1 with cape. **Methods:** Key eligibility criteria were: stage III, colorectal adenocarcinoma except for lower rectal cancer, R0 with D2/3 lymph node dissection, 20-80 years old. Patients were randomized to 8 courses of cape (2,500 mg/m^2/day, days 1–14, q3w) or 4 courses of S-1 (80 mg/m^2/day, days 1–28, q6w). Primary endpoint was DFS. Planned sample size was 1,550 to provide 80% power with a non-inferiority margin of hazard ratio (HR) of 1.24 and 1-sided α = 0.05; with interim analyses after 50% of the planned accrual and 1 year after completion of accrual. **Results:** Between Mar 2010 and Aug 2013, 1,564 pts were randomized to cape (n = 782) or S-1 (n = 782). Median age was 66; male/female: 52%/48%, colon/rectum: 68%/32%, number of positive nodes $\leq$ 3/4 $\leq$: 84%/16%. At the second interim analysis on Sep 2014, 48% of required events (258/535) were observed, and JCOG Data and Safety Monitoring Committee recommended early publication because S-1 was apparently inferior to cape in DFS. With median follow-up of 23.7 months for all randomized pts, 3-year DFS was 82.0% in cape and 77.9% in S-1. The HR of DFS was 1.23 (99.05% CI, 0.887–1.70) and the non-inferiority of S-1 was not demonstrated (P = 0.111). The incidence of grade 3/4 adverse events was 21.2% in cape and 12.1% in S-1. Hand-foot syndrome was common in cape, whereas diarrhea and anorexia were common in S-1. **Conclusions:** This study failed to demonstrate the non-inferior of adjuvant S-1 to cape in DFS. Adjuvant cape remains the standard treatment and S-1 should not be used for stage III CC. Clinical trial information: UMIN000003272.

3513 Poster Discussion Session; Displayed in Poster Session (Board #5), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Cochrane systematic review and meta-analysis of adjuvant therapy for stage II colon cancer. *First Author: Brandon Matthew Meyers, Juravinski Cancer Centre McMaster Univ, Hamilton, ON, Canada*

Background: Stage III disease is associated with a high risk of relapse after surgery, and adjuvant 5-fluorouracil chemotherapy (5FUc) has been shown to improve overall (OS) and disease-free survival (DFS). Whether adjuvant 5FUc confers a similar benefit in stage II colon cancer is unclear. A previous Cochrane review demonstrated that adjuvant therapy improved DFS, but not OS. An updated systematic review of the literature was undertaken, including all forms of adjuvant therapy. **Methods:** We searched Cochrane Central Register of Controlled Trials, MEDLINE(R), and EMBASE from 1/1987 - 7/2014. We scanned ASCO and ESMO annual meeting proceedings. Randomized controlled trials (RCTs) containing data on stage II colon cancer patients undergoing adjuvant therapy *vs.* observation were included. Pooled results were expressed as risk ratios (RR), with 95% confidence intervals using a random effects model. Treatments were evaluated using *a priori* defined categories, and sub-groups, of systemic chemotherapy, regional chemotherapy, and immunotherapy. **Results:** 25 RCTs met the inclusion criteria. Overall, adjuvant systemic chemotherapy did not improve OS (RR 0.93; 0.81 - 1.07). Sub-group analysis demonstrated that newer 5FUc improved OS (RR 0.85; 0.75 - 0.96) and DFS (RR 0.82; 0.72 - 0.93). Portal vein infusion (PVI), a sub-group of regional chemotherapy, improved OS (RR 0.74; 0.55 - 0.99) but not DFS (RR 0.93; 0.74 - 1.16). Heterogeneity was low for systemic chemotherapy (I^2 = 0% for all analyses), but moderate-high for PVI (I^2= 41% for OS). Tumour vaccines and edrecolomab immunotherapy resulted in OS similar to observation (RR 0.94; 0.79 - 1.12). The estimated 'optimal information size' was only reached for the category of systemic chemotherapy. **Conclusions:** 5FUc bolus injections demonstrated an improvement in OS and DFS in stage II colon cancer. Although the PVI sub-group showed a statistical benefit to OS, significant heterogeneity, and a failure to reach 'optimal information size' indicates these results are not robust. Immunotherapy had no demonstrated benefits. Further investigation is required to determine whether subsets of stage II colon cancer patient might derive additional benefit from adjuvant chemotherapy.

3514 Poster Discussion Session; Displayed in Poster Session (Board #6), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Toxicity and quality of life data from SCOT: An international phase III randomized (1:1) noninferiority trial comparing 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy. *First Author: Timothy Iveson, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom*

Background: Oxaliplatin/Fluoropyrimidine combination chemotherapy is an established adjuvant treatment for colorectal cancer (CRC). Neurotoxicity from Oxaliplatin is cumulative, dose limiting, and potentially irreversible. **Methods:** SCOT is designed to determine whether 3 months of adjuvant chemotherapy with OxMdG or XelOX (physician/patient choice) in Stage III /high risk Stage II CRC is as effective as 6 months, with less toxicity. In the initial 867 patients toxicity was graded during treatment using NCI-CTCAE. Quality of life was assessed using EORTC QLQ-C30/EQ-5D (n = 1681) and neuropathy using GOG-Ntx4 (n = 1776). **Results:** From May 2008 to Nov 2013, 6087 patients were randomized from 237 centers/6 countries. Median age was 65 years. 4972 (82%) were Stage III, 4983 (82%) had colon cancer and 4105 (67%) received XelOx. There were 31 toxic deaths (0.5%) equally distributed between the randomized arms. Toxicity profiles depended on the FU backbone with more grade 3/4 neutropenia on OxMdG (23% v 5%) and more grade 3/4 diarrhea (9% v 15 %) on XelOx. 16% overall did not complete 3 months of treatment mainly citing toxicity (56%). Peripheral neuropathy was *cumulative*, (24% grade 2/3 toxicity by 3 months; 56% by 6 months) and as measured by GOG-NTX4 persisted and was much higher at 1 year on the 6 month compared to the 3 month randomized arm (mean difference = 19 [se = 1.3]). QLQ-C30 global health status worsened during treatment and stayed more depressed in months 4-6 in the 6 month arm. By12 months the mean difference between the arms was small (2.2[0.9]); a similar pattern was seen with the QLQ-C30 functional scales. The pattern for the EQ-5D health score were also similar with small differences at 12 months (.03 [.02] respectively). **Conclusions:** Both OxMdG and XelOx were safe and well tolerated. As expected, the main toxicities did vary according to FU backbone (but this was not randomized). Quality of life worsened while patients were on treatment but recovered by 1 year despite persistent peripheral neuropathy, suggesting that current quality of life tools may not adequately capture the morbidity associated with this toxicity. Clinical trial information: ISRCTN59757862.

3515 Poster Discussion Session; Displayed in Poster Session (Board #7), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC). *First Author: Akihiko Murata, Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Japan*

Background: The ACTS-RC trial is a phase III trial designed to superiority of S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate) to UFT (uracil and tegafur), a standard treatment in Japan as adjuvant chemotherapy for curatively resected stage II/III rectal cancer. **Methods:** 20-80 aged patients (pts) with stage II/III rectal cancer who underwent curative surgery without preoperative therapy randomly assigned to receive UFT (500, or 600mg/day according to BSA on days 1 to 5 days, followed by 2 days rest) for 1 year or S-1 (80, 100, or 120mg/day according to BSA on days 1 to 28, followed by 14 days rest) for 1 year. The primary endpoint was Relapse-free survival (RFS). The 5-year RFS rate in the UFT group was assumed to be 70%. We calculated that a total enrollment of 800 pts was needed for a hazard ratio (HR) of 0.70 in the S-1 group as compared with the UFT group, with the use of the log-rank test, two-sided alpha of 0.05, and power of 0.80. **Results:** A total of 959 pts were randomly assigned between April 2006 and March 2009 (480 pts in UFT group, 479 pts in S-1 group). Median age: 63 years, upper/lower rectum: 52%/48%. The groups were balanced. At a median follow-up of 5.02 years, 5-year RFS rate was 61.7%(95%CI: 57.1-65.9%)in the UFT group and 66.4%(95%CI: 61.9-70.5%) in the S-1 group. The HR of RFS was 0.773(95%CI: 0.625-0.955) and superiority of S-1 was demonstrated (p = 0.0165). The completion rate of the protocol treatment was 61.8% in UFT group and 61.3% in S-1 group. 5-year overall survival rate was 80.2%(95%CI: 76.3-83.5%)in the UFT group and 82.0%(95%CI:78.3-85.2%) in the S-1 group. The overall incidence of grade $\geq$ 3 adverse events in UFT group and S-1 group were 11.7% and 13.4%: anemia(1.3% v 1.3%), diarrhea(2.3% v 2.6%), anorexia(1.0% v 2.6%), nausea(0.4% v 1.3%), hyperbilirubinemia (1.0% v 1.3%), AST(1.5% v 0.9%) and ALT(2.3% v 0.9%), respectively. **Conclusions:** Adjuvant chemotherapy using S-1 demonstrated improved 5-year RFS in pts with curatively resected stage II/III rectal cancer. S-1 is an additional adjuvant treatment option for these pts. Clinical trial information: C000000385.

3516 Poster Discussion Session; Displayed in Poster Session (Board #8), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

S0713: A phase II study of cetuximab (CET) added to induction chemotherapy (ICT) of oxaliplatin (OX) and capecitabine (CAP), followed by neoadjuvant chemoradiation (NACR) for locally advanced rectal cancer (LARC). *First Author: Cynthia G. Leichman, New York Univ, New York, NY*

Background: NACR for LARC has been standard for 2 decades. Pathologic complete response (pCR) associates with improved survival and is an outcome surrogate in NACR clinical trials. In modern phase III trials of NACR in LARC, pCR ranges 15-20%. CET improves response rates in KRAS wild-type (KRAS-WT) metastatic colorectal cancer. S0713 was designed to select patients (PTS) by KRAS-WT status to assess improvement in pCR with CET added to ICT and NACR for LARC. **Methods:** Eligibility: Stage II-III biopsy proven LARC, KRAS-WT, without bowel obstruction or prior therapy, adequate hematologic, hepatic and renal function, and performance status of 0-2. Peripheral neuropathy $>$ grade 2 was exclusionary. Enrollment target was 80 eligible PTS with planned interim analysis after 40 PTS received all therapy; if $<$ 7 pCR were observed at interim, the study was to close. Treatment consisted of ICT then NACR and surgery. Treatment regimen: Cycle 1: OX 50 mg/m2 day (d) 1,8,15,22,29, CET 400mg/m2 d1 then 250 mg/m2 d 8, 15, 22, 29 and CAP 825 mg/m2 p.o. BID Monday through Friday (M-F) d1-35; Rest d 36-49; Cycle 2: OX 50 mg/m2 d 50, 57, 71, 78, CET 250 mg/m2 d 50, 57, **64**, 71, 78 and CAP 825 mg/m2 p.o. BID M- F d 50-85 with radiation 180 cGy/d M-F x 5 weeks (4500 cGy) followed by 540 cGy boost x 3 (stage II; 5040cGy) or 5 (stage 3; 5400cGy). Surgery occurred 3-8 weeks after NACR. 80 eligible PTS would give a power of 90% if true pCR $>$ 35% at a significance of 0.04. The regimen would lack future interest if pCR $<$ 20%. **Results:** From February 2009 to April 2013, 83 PTS registered; 5 were ineligible; 4 not treated. 74 were available for toxicity evaluation (TOX); 72 had available data; 62 PTS (86%) had surgery. 1 grade 5 TOX and 2 grade 4 TOX occurred. 7 PTS withdrew for TOX, 2 for other reasons. 18 of 62 PTS had pCR (25%, 95% CI 16-37%). 19 PTS (26%) had microscopic cancer; 35 PTS (49%) had minor/no response (10 no surgery). **Conclusions:** ICT and NACR with CET improved pCR over historical and recent rates of ~20%. Toxicity was generally acceptable. This approach can serve as a base for adding additional agents in KRAS-WT LARC. Additional analysis for resistance genes is ongoing. Clinical trial information: NCT00686166.

3517 Poster Discussion Session; Displayed in Poster Session (Board #9), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Safety and tolerability of veliparib combined with capecitabine plus radiotherapy in patients with locally advanced rectal cancer (LARC): Final results of a phase Ib study. *First Author: Michael Michael, Peter MacCallum Cancer Centre, East Melbourne, Australia*

Background: Standard treatment for patients (pts) with LARC consists of chemoradiation followed by surgery. To achieve higher response rates and reduce risk of recurrence, further optimization is needed. Veliparib (ABT-888), a potent orally bioavailable PARP1/2 inhibitor, has been shown to enhance antitumor activity of chemotherapy and radiotherapy (RT) in preclinical models. Herein, we present the final results from a phase Ib dose-escalation study (NCT01589419) of veliparib plus capecitabine (C) and RT (C/RT) in pts with LARC. **Methods:** Stage II/III rectal cancer pts ($\geq$ 18 years) received C (p.o. 825 mg/m^2 BID) and RT (1.8 Gy QD) for approx. 5.5 weeks (5 days/week). Veliparib (p.o. 20–400 mg BID) was administered from day 2 until 2 days after RT (7 days/week). Pts underwent surgery 5–10 weeks after RT. Primary objectives were to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of veliparib plus C/RT, using an exposure-adjusted continual reassessment method. Safety, pharmacokinetics (PK), and antitumor activity were also assessed. **Results:** As of 23 Nov 2014, 32 pts (81% male, median age 57 years) received study treatment (veliparib $<$ 400 mg, n = 16; 400 mg, n = 16). Most common adverse events possibly or probably related to treatment were fatigue (41%), nausea (41%), diarrhea (25%), and vomiting (22%); grade 3/4 events were diarrhea (n = 2), anemia, lymphopenia, and pulmonary embolism (n = 1 each). Dose-limiting toxicities (grade 2) occurred in 2 pts: radiation skin injury, and nausea and vomiting, at 70 and 400 mg veliparib, respectively. The MTD was not reached. The RP2D for veliparib was 400 mg BID. Veliparib (20–70 mg BID) PK was dose proportional, with no clear impact on the PK of C. Postsurgery tumor downstaging was observed in 72% of 32 evaluable pts; 28% achieved a pathologic complete response. Sphincter-sparing surgery was performed in 70% of 30 evaluable pts. **Conclusions:** Veliparib plus C/RT had an acceptable safety profile in LARC pts and the RP2D is 400 mg BID. Veliparib showed a dose-proportional PK profile and no effect on the PK of C. The combination treatment showed promising preliminary antitumor activity. Clinical trial information: NCT01589419.

3518 Poster Discussion Session; Displayed in Poster Session (Board #10), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Compliance to chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA) according to radiotherapy (RT) dose, overall treatment time (OTT) and chemotherapy (CT) and their impact on long-term outcome: Results of ACT II. *First Author: Robert Glynne-Jones, Mount Vernon Centre for Cancer Treatment, London, United Kingdom*

Background: Concurrent CRT is standard treatment for patients with SCCA. We explored CRT compliance in ACT II, which compared 5FU/CisP with 5FU/MMC (wks 1 & 5) of a uniform RT dose (50.4Gy, 28 daily fractions (F) of 1.8Gy). **Methods:** We investigated the association between poor compliance and baseline factors (age, sex, site, T & N stage), type of CT (MMC/CisP) with progression free survival (PFS). Compliance was categorized as follows: RT, 5 groups: A = per protocol (50.4Gy in 28F in 38-42 days), B = $\leq$ 40Gy, C = 40-48.6Gy in 23-27F, D = 50.4Gy in $>$ 42 days, E $>$ 52.2Gy. CT, 2 groups: 1 = wks1 & 5 & 2 = wk1 only. **Results:** 933 and 862 of 940 pts were evaluable for RT & CT compliance respectively. Median follow-up was 5.1 yrs. Baseline characteristics of evaluable patients were similar to all 940 ACT II patients. Canal tumors, CisP, GFR$<$60 & WBC $<$ 11 were borderline significant predictors of poor wk5 CT compliance (p 0.09, 0.07, 0.06 & 0.08 respectively). Poor CT compliance at wk5 impacted significantly on PFS (treatment adjusted HR: 1.63 (95% CI: 1.23-2.17), p = 0.001). No baseline factors analyzed, or chemotherapy type, were significant independent predictors of poor RT compliance. **Conclusions:** In ACT II poor CT & RT compliance (lower dose/prolonged OTT) adversely impacted on PFS. Treatment interruptions should be minimized and prolonged OTT compensated by hyperfractionation or possibly additional dose. Intensity Modulated RT may improve compliance. Patients with poor compliance to RT/CT may need closer monitoring following treatment. Clinical trial information: 26715889.

Impact of RT compliance on PFS (N=933).

Group	Total events/ No of pts	3 y PFS rate %	Treatment-adjusted HR (95% CI)	P-value
A	221/786	76	1.00	0.0001
B	11/18	44	3.71 (2.01-6.82)	
C	11/21	56	2.26 (1.23-4.14)	
D	39/93	62	1.62 (1.15-2.28)	
E	6/15	59	1.60 (0.71-3.61)	

3519 Poster Discussion Session; Displayed in Poster Session (Board #11), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Comprehensive multiplatform biomarker analysis of 212 anal squamous cell carcinomas. *First Author: Patrick McKay Boland, Roswell Park Cancer Institute, Buffalo, NY*

Background: Squamous cell anal carcinoma is a rare, HPV-associated malignancy accounting for 2% of digestive system cancers. Usually these malignancies are detected early and successfully managed with chemoradiation. Uncommonly, these cancers recur or present with metastases. In this setting, cisplatin and 5-fluorouracil represent the only endorsed regimens. Beyond standard therapy, few therapeutic options exist. The purpose of this study is to identify other novel, potential targets and therapeutic options for this disease, utilizing a multiplatform approach. **Methods:** 212 squamous cell anal carcinoma specimenswere tested via a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ) consisting of gene sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]) and gene amplification (CISH or FISH). Tissue from a metastatic site was submitted in 80.2% of the cases. Documentation of positive HPV or HIV status was provided in six cases. **Results:** IHC overexpression was noted in MRP1 (97.6%, 81/83), EGFR (89.7%, 35/39), TOPO1 (68.3%, 123/180), MGMT (67.2%, 125/186), and PTEN (46.9%, 90/192). EGFR and HER2 were amplified (ISH) in 7.4% (5/68) and 1.8% (2/111) of cases. High mutation rates were seen in biomarkers associated with the PIK3CA/Akt pathway: PIK3CA (26.8%, 26/97), FBXW7 (11.8%, 8/68), PTEN (3.1%, 2/64), and Akt1 (1.5%, 1/68). PIK3CA exon 9 mutations were detected in 75% of all PIK3CA mutations. KRAS mutations were rare (1.8%, 2/111). Point mutations in other genes were also identified, including a few co-occurring mutations. **Conclusions:** Multiplatform tumor profiling identified several potential targets. Protein expression aberrations identified potential treatment options not routinely considered. Mutations in PIK3CA, Akt1, and FBXW7 and PTEN loss indicate potential for targeting the PI3 kinase pathway. Targeting the ErbB-family receptors, namely with anti-EGFR agents or newer generation pan-HER inhibitors, may represent another option, given EGFR and HER2 amplification as well as EGFR overexpression. Differences in anal carcinomas whose etiology is of viral origin may present different treatment options based on the driver mutations.

3520 Poster Discussion Session; Displayed in Poster Session (Board #12), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Checkpoint kinase (CHK) 1/2 inhibitor LY2606368 in a phase I, dose-expansion study in patients (pts) with metastatic squamous cell carcinoma (mSCC) of the anus. *First Author: Johanna C. Bendell, Sarah Cannon Research Institute, Nashville, TN*

Background: LY2606368 is a CHK 1/2 inhibitor. CHK1 is a multifunctional kinase essential for checkpoint control, DNA repair, cell cycle replication, and proliferation. Potent inhibition of CHK1 is predicted to generate DNA damage and mitotic catastrophe. LY2606368 was evaluated as a single agent in an expansion cohort of pts with mSCC of the anus. **Methods:** This was a phase I study in pts with advanced cancer (NCT01115790). Preliminary signs of activity in the dose-escalation phase warranted a dose-expansion cohort of pts with mSCC of the anus given LY2606368 at the maximum tolerated dose (MTD) of 105 mg/m^2 IV on day 1 of a 14-day schedule. Radiographic assessment every 6 weeks and pretreatment biopsies were obtained. Safety, tolerability, preliminary efficacy, and pharmacogenetic results are reported. **Results:** Of 26 pts enrolled, 62% had $\geq$ 2 prior regimens (median = 2 regimens; range: 1 - 13) and 92% of pts had prior radiotherapy. The most frequently reported adverse event (AE) was neutropenia, which occurred in 92% of pts (grade 4: 77%), but was of relatively brief duration; 1 pt experienced febrile neutropenia. Other drug-related AEs occurring in $>$ 20% of pts were thrombocytopenia (58%), anemia (38%), and fatigue (31%). Nonhematologic AEs included nausea (19%), diarrhea (15%), anorexia and headache (12% each), which were mostly grade 1 or 2. One pt (4%) had a CR, 3 pts (12%) had a PR, and 11 pts (42%) had SD, for an overall response rate of 15% (90% CI: 5, 32) and a disease control rate of 58% (90% CI: 40, 74). Of the 4 pts with response, 3 pts (including the pt with a CR) remain on treatment, and 1 had a prolonged duration of response (10.1 mos) before discontinuing therapy. Tissue samples were available from 14 pts with evaluable response data. Alterations of genes in the PI3K pathway occurred in 5/8 (63%) pts with clinical benefit vs 1/6 (17%) pts without (p = 0.12). **Conclusions:** The CHK 1/2 inhibitor LY2606368 demonstrated an acceptable safety profile despite a relatively high rate of transient grade 4 neutropenia. Single-agent activity was observed in pretreated mSCC of the anus, a disease with a high unmet medical need. The MTD of 105 mg/m^2 is confirmed as the recommended phase II dose. Clinical trial information: NCT01115790.

3521 Poster Session (Board #13), Mon, 8:00 AM-11:30 AM

Role of race and socioeconomic status in overall and cancer-specific survival of anal cancer patients. *First Author: Jessica Belmonte, UC Irvine Medical Center, Orange, CA*

Background: Treatment of anal cancer (AC) relies on a multidisciplinary approach and highly-coordinated care. As such, health disparities may arise in vulnerable populations. Our aim was to analyze the overall and cancer-specific survival (OS, CSS) of AC patients stratified by race/ethnicity while accounting for treatment and socioeconomic (SES) differences, as this has not been studied before. **Methods:** Incident cases of squamous cell AC were identified in the California Cancer Registry during 2004-2009. In-situ through stage IV AC were included. Univariate OS and CSS estimates were generated using Kaplan-Meier methods. Multivariate analysis (MVA) of OS and CSS were performed using Cox proportional-hazard regression models, adjusting for age, gender, SES, stage, grade, surgery, chemotherapy, and radiation therapy. **Results:** We identified 4303 incident cases of AC, including 3023 Caucasians (C), 342 African-Americans (AA), 555 Hispanics (H), 115 Asians (As) and 268 Others (O, Native American and unidentified race/ethnicity). Five-year OS for AAs was statistically shorter than for C and H counterparts (see table below). Higher SES was independently associated with a longer OS (p-trend $<$ 0.0001) and CSS (p-trend 0.0101), compared to lower SES in MVA. After adjustment for SES and other covariates, and compared to C as a referent group, AAs were observed to have an independent increased risk of mortality (for OS, HR = 1.9, 95%CI 1.5-2.3 and for CSS, HR = 1.8, CI 1.3-2.4). This risk difference (AA vs. C) was observed in each stage and significant for all except stage II. **Conclusions:** In squamous cell AC, health disparities exist between racial/ethnic groups as exemplified by worse outcomes in the AA cohort vs. other racial/ethnic groups. The differences in survival cannot be accounted for by SES alone or treatment. SES is independently associated with outcome in AC. Additional determinants of health must be identified to facilitate improvement in outcomes.

Univariate overall survival estimates (by Kaplan Meier Method).

	12 months	36 months	60 months
Caucasian	92%	80%	72%
Black	85%	71%	65%
Hispanic	92%	78%	68%
Asian	91%	79%	70%
Native American/Other	97%	94%	90%

Log-Rank P-value for the above K-M survival curves $<$ 0.0001

3522 Poster Session (Board #14), Mon, 8:00 AM-11:30 AM

Comprehensive genomic profiling of anal squamous cell carcinoma to reveal frequency of clinically relevant genomic alterations in the PI3K/mTOR pathway. *First Author: Eric M. Sanford, Foundation Medicine, Inc., Cambridge, MA*

Background: Anal squamous cell carcinoma (ASCC) is an HPV-associated rare tumor that has nearly doubled in incidence since 1973, with cisplatin-based chemotherapy as the only treatment shown to be effective for patients with metastatic disease. We performed comprehensive genomic profiling (CGP) on 70 patients with ASCC to identify the spectrum of clinically relevant genomic alterations (CRGA). **Methods:** DNA was extracted from 40 microns of FFPE sections. CGP was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 692X for the entire coding regions of 236 cancer-related genes plus 47 introns from 19 genes frequently rearranged in cancer. CRGA were defined as GA linked to FDA-approved agents or investigational agents in clinical trials. **Results:** There were 48 female and 22 male patients with a median age of 59.5 years (range 31-88). Three tumors (4%) were grade 1, 33 (47%) were grade 2, and 34 (49%) were grade 3. At the time of sequencing, 5 (7%) cases were stage II, 13 (19%) were stage III, and 47 (67%) were stage IV, with staging information unavailable for 5 (7%) patients. HPV-16 or HPV-18 was detected in 61 (87%) tumors: 59 were positive for HPV-16 and 2 were positive for HPV-18. CGP revealed 238 GA (3.4 per tumor), 111 of which were CRGA (1.6 per tumor). At least one CRGA was detected in 53 (76%) cases. The most common CRGA were in *PIK3CA* (27 cases; 39%), *PTEN* (10 cases; 14%), and *FBXW7* (8 cases; 11%). For the 9 (13%) tumors where HPV DNA was not detected, a significant enrichment of LOF mutations was observed in *TP53* (6 of 8 altered cases; p $<$ 0.0001) and *CDKN2A*(5 of 5 altered cases; p $<$ 0.0001). Clinical outcomes for PI3K/mTOR pathway-altered patients are being investigated. **Conclusions:** ASCC features a high rate of potentially targetable PI3K/mTOR pathway alterations, with 37 (53%) tumors harboring alterations in *PIK3CA*, *PTEN*, or *FBXW7*—a mutational profile similar to HPV positive head and neck and cervical SCC. The enrichment of *TP53* and *CDKN2A* alterations in tumors where HPV DNA was not detected was similarly found in HPV negative head and neck squamous cell carcinoma, suggesting a distinct route to carcinogenesis for HPV negative ASCC.

3523 Poster Session (Board #15), Mon, 8:00 AM-11:30 AM

Programmed cell death-Ligand 1 (PD-L1) expression and outcome in patients with squamous cell cancer of anal canal (SCCAC). *First Author: Swetha Gujja, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: PD-L1 expression has been associated with worse prognosis in a variety of cancers. In anal carcinoma, the prevalence of PD-L1 positivity in tumor tissue is unknown. To evaluate the influence of PD-L1 expression on prognosis of subjects with SCCAC, a retrospective analysis was conducted. **Methods:** Subjects with SCCAC were identified from tumor registry at the University of Arkansas for Medical Sciences and Kansas University between 1992 and 2011. The charts were reviewed to confirm the diagnosis, stage, treatment and outcome of the subjects. Paraffin tissue blocks of the subjects were stained for PD-L1 expression using rabbit polyclonal antibody (ab153991, ABCAM). PDL1 positivity was defined as any membranous or cytoplasmic immunoreactivity within the tumor cells. Nuclear or general blush staining only was considered negative.Kaplan-Meier curves and the Wilcoxon test were used to compare subjects positive vs. negative for PD-L1 expression for differences in Overall (OS) and Recurrence-Free (RFS) survival. **Results:** Samples from 41 subjects were evaluated for PD-L1 expression. Median age was 52 years (range 30-94). Males were 51%. There were 80% Caucasians, 15% African-Americans, 5% others. 22% were early stage (0, I, II), 48% late stage (III, IV) and 29% unknown. 93% were p16-positive by immunohistochemistry. 71% had chemo-radiation, 2.4% had chemotherapy, 17% had surgery and 10% had unknown treatment. PD-L1 positivity was seen in 62% of late/ unknown stage and 33% of early stage disease. PD-L1-positive vs. negative patients respectively had RFS medians of 1.5 vs. 4.9 years (p = 0.068) and OS medians of 2.2 vs. 7.6 years (p = 0.64). **Conclusions:** PD-L1positivity was associated with poorer RFS, with a trend towards statistical significance. OS was not significantly different between the PD-L1 positive and negative groups. However, larger sample size may show statistically significant difference in RFS and OS.

3524 Poster Session (Board #16), Mon, 8:00 AM-11:30 AM

Sequential liver and lung resection for colorectal cancer metastases: In which patients should surgery be proposed? *First Author: Muthukumarassamy Rajakannu, Centre HepatoBiliaire, Hopital Paul Brousse, Villejuif, France*

Background: Resection of colorectal cancer (CRC) liver or lung metastases is an established therapeutic strategy. However, controversies exist when metastases are found concomitantly in both the organs or when the patients, who have undergone either liver or lung resection, have a recurrence in the other organ. **Methods:** All consecutive patients operated for CRC liver and lung metastasis (LLM) at our institution from January 1990 to December 2012 were reviewed. Our policy was to propose sequential surgery of both sites with perioperative chemotherapy, provided that the strategy was potentially curative. We aimed to evaluate Overall Survival (OS) of these patients, to develop a clinical usable prognostic score and to find out if cure is possible. **Results:** A total of 150 patients (89 men - 61 women; median age - 56 years) were included in the study. Median number of LLM resected was 3 and 1 respectively. Median follow-up was 5 years (Range 0.6 - 22.8 years). Median OS, 5-year OS and 10-year OS from first metastasis resection were 6 years, 59% and 35% respectively. Multivariate analysis identified metastatic CRC at initial diagnosis [P = 0.027], Pre-Lung resection CEA level > 100 ng/ml [P = 0.007], Pre-Lung resection CA19-9 level > normal [P = 0.029], Interval between 1st liver and 1st lung resection < 24 months [P = 0.004], > 2 lung metastases resected [P = 0.049] and Non-curative lung resection [P = 0.012] were independent predictors of OS. Simultaneous presentation of LLM and perioperative chemotherapy was not associated with OS. Prognostic model was developed using 5 preoperative factors. LLM score > 3 was associated with good 5-year survival [AUROC 0.7, Sensitivity 90%, Specificity 67%]. Fifteen patients were considered as cured with > 5 years disease-free survival from the last surgery (median LLM score 7). **Conclusions:** Good long-term survival can be achieved in patients who undergo sequential resection of the liver and lung metastases from CRC with 10% being cured. LLM score is an effective way to select patients for sequential resection. Higher the score better is the survival after sequential surgery and better is the chance of cure. Conversely, the role of surgery should be questioned in patients with LLM score < 3.

3525 Poster Session (Board #17), Mon, 8:00 AM-11:30 AM

Impact of *UGT1A1* genotype on prognosis in Japanese advanced colorectal cancer patients treated by irinotecan-based regimens. *First Author: Wataru Ichikawa, Division of Medical Oncology, Showa University, School of Medicine, Tokyo, Japan*

Background: The influence of *UGT1A1*6* and *UGT1A1*28* on prognosis of irinotecan (IRI)-based regimens has been controversial, although *UGT1A1* genotypes are risk factors for IRI-related toxicities in Asians. We conducted a prospective analysis to examine the correlation between *UGT1A1* genotypes and safety/efficacy of IRI-based regimens in Japanese patients (pts) with advanced colorectal cancer (aCRC) (NCT 01039506). The validated nomogram for predicting the probability of severe neutropenia induced by IRI-based regimens was proposed based on safety analysis (ASCO 2014, Abst No. 3543). We analyzed the efficacy in terms of *UGT1A1*genotypes. **Methods:** 1,376 pts who had histologically confirmed aCRC and received IRI-based regimens were enrolled. *UGT1A1* genotypes were categorized into three groups: wild (**1/*1*), hetero (**1/*6*, **1/*28*), and homo (**6/*6*, **6/*28*, **28/*28*). The primary objective was to investigate the non-inferiority of hetero or homo to wild in progression-free survival (PFS) under the non-inferiority margin of hazard ratio (HR) of 1.25, using propensity score weighting to adjust for baseline characteristics. Progression was evaluated by investigators according to the RECIST 1.1 criteria. The association of prognosis with IRI exposure was also examined. **Results:** The efficacy analysis was performed using 1,339 pts. The prevalence of *UGT1A1* genotypes were 47% wild, 42% hetero, and 11% homo. The median PFSs according to *UGT1A1*genotypes were 6.0 (95% CI, 5.6–6.7) months (mo) in wild, 6.0 mo (5.4–6.6) in hetero, 5.6 mo (4.4–6.1) in homo. The HR of hetero to wild was 0.988 (0.864–1.130; non-inferiority p = 0.0006) and that of homo to wild was 1.202 (0.988–1.463, non-inferiority p = 0.6977). The HRs in the homo group with a starting dose not less than 80% to wild and with a dose less than 80% of the standard IRI dose were 1.037 (0.779–1.379, p = 0.8052) and 1.393 (1.106–1.754, p = 0.0049), respectively. **Conclusions:** This analysis revealed that PFS in the *UGT1A1* hetero group were non-inferior to the wild group. However, the homo group had worse PFS as compared with the wild group. The excessive dose reduction of the starting IRI dose might account for the unfavorable results in the homo group.

3526 Poster Session (Board #18), Mon, 8:00 AM-11:30 AM

Masitinib plus FOLFIRI for second line treatment of metastatic colorectal cancer: An open label phase Ib/II trial. *First Author: Julien Taieb, Paris Descartes University, Georges Pompidou European Hospital, Paris, France*

Background: Masitinib (MAS) is a selective inhibitor of c-Kit and mast cell function. Increased mast cell activity in the tumor microenvironment is linked to poor prognosis and a protumoral immune response in colorectal cancer (CRC). In vitro, MAS acts as a chemosensitizer of 5-fluorouracil and irinotecan in CRC cell lines. This trial evaluated MAS in combination with chemotherapies. We report here findings from the cohort receiving MAS + FOLFIRI. **Methods:** Patients (pts) with nonresectable, metastatic CRC after progression to first line treatment received MAS + FOLFIRI until progression, refusal or unacceptable toxicity. Patients previously treated with irinotecan were excluded. Phase 1 evaluated safety of the combination with Dose Limiting Toxicity (DLT) determining subsequent dose and recruitment. DLT was defined as grade 3 non hematological adverse event (AE) or any grade 4 AE related to MAS. Phase 2 evaluated efficacy. **Results:** Eighteen pts (50% with mutated KRAS) from 6 centers in France were treated. MAS dose was reduced from 9 to 6 mg/kg/day for the final 3 pts based on new mechanistic understanding and to minimize risk of toxicity. No DLT was reported for the phase 1 stage (3 pts) at 9 mg/kg/day. After a median follow-up of 22.8 months, median OS was 17.6 months (95%CI [8.9; 20]) and median PFS was 6.2 months (95%CI [3.1; 9.2]). Overall response rate was 28%, including 1 pt with a confirmed complete response. Efficacy was still evident in the 3 pts treated at 6 mg/kg/day with PFS of 9.2, 6.2 and 5.6 months without any grade 3-4 AE in this cohort. Overall, 6/18 pts (33%) reported grade 3-4 AE and 4/18 pts (22%) experienced serious AE. No treatment related deaths were reported. **Conclusions:** The safety profile of MAS + FOLFIRI was acceptable. Efficacy findings seem to compare favorably against historic benchmarks (see table). MAS may therefore offer patients a new active compound for mCRC. A confirmatory phase 3 trial evaluating FOLFIRI+/- MAS at 6 mg/kg/day as second line for mCRC is ongoing.

	MAS + FOLFIRI	*FOLFIRI wildtype KRAS	*FOLFIRI mutant KRAS
OS (months)	17.6	12.5	11.1
PFS (months)	6.2	3.9	4.9
Objective Response Rate	28%	10%	14%
Complete	6%	0%	0%
Partial	22%	10%	14%

* Peeters (2010) J Clin Oncol 28: 4706.

3527 Poster Session (Board #19), Mon, 8:00 AM-11:30 AM

A phase II study of NK012, a polymeric micelle formulation of SN-38, in colorectal cancer patients who had received prior oxaliplatin-based regimen. *First Author: Akihito Tsuji, Department of Medical Oncology, Kochi Health Sciences Center, Kochi, Japan*

Background: NK012 is a micelle-forming macromolecular prodrug of SN-38, an active metabolite of irinotecan. In the completed phase I study, the recommended dose was decided to be 28 mg/m^2, with a DLT of myelosuppression. This phase II study was conducted to evaluate an efficacy and safety of NK012 in patients with recurrent or metastatic colorectal cancer. **Methods:** This was a multicenter, open-label, single-arm phase 2 study. Patients with a history of oxaliplatin-based treatment against metastatic colorectal cancer, or recurrence within 6 months after the last dose of adjuvant oxaliplatin had been enrolled. NK012 (28 mg/m^2) was administered intravenously every 3 weeks. Administrations continued until disease progression. Objective clinical response was evaluated according to RECIST 1.1. The primary endpoint was overall response rate (ORR). **Results:** In the 58 patients registered, 53 patients received NK012. Median number of previous oxaliplatin-based therapy was 11.0 courses. 4.2% of patients had a history of previous irinotecan. Median treatment period was 3 courses. ORR was 3.8 %, and DCR (CR+PR+SD) was 56.0%. Median PFS and OS were 99.0 and 451 days, respectively. Major adverse drug reactions were absolute neutrophil count (ANC) decreased, of which grade 4 or more manifested in 81% of patients. Ratio of Grade 4 ANC decreased was higher in patients who had received previous oxaliplatin for more than 6 months. Grade 3 diarrhea manifested in 5.7%, but no diarrhea of Grade 4 manifested. **Conclusions:** Efficacy of NK012 against recurrent or metastatic colorectal cancer was comparable with that of irinotecan monotherapy previously reported, and disease control by NK012 was suggested. Unlike irinotecan, the major ADR was myelosuppression, with mild gastrointestinal toxicity. These safety profiles implicate a possibility of combination with less-myelotoxic anticancer agent(s) like 5-FU/LV and of being preferable to FOLFIRI. Further optimization of dosage and schedule of NK012 administration and its combination strategy would be worthwhile.

3528 Poster Session (Board #20), Mon, 8:00 AM-11:30 AM

Can we use radiofrequency ablation for liver metastases from colorectal cancer over 25 mm initially but downsized by systemic chemotherapy? *First Author: Leonor Benhaim, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Radiofrequency ablation (RFA) can be a valid treatment for liver metastases from colorectal cancer (CRLM) and is mostly dedicated to metastases unsuitable for surgical resection. Tumor size at the time of the RFA procedure is the main predictive factor for in situ recurrence (ISR) at the ablated zone. However, regardless to tumor size during procedure, the diameter of liver metastases at presentation, before chemotherapy infusion, may be predictive for ISR, although it has never been assessed. The aim of this study was to determine the risk for ISR after RFA for liver metastasis larger than 25mm initially but that have been downsized by preoperative chemotherapy. **Methods:** We retrospectively reviewed all RFA performed in patients treated for CRLM who had previously received at least one cycle of systemic chemotherapy from January 2004 to December 2012. Each tumor site treated by RFA was studied independently. Metastases were divided into 2 groups according to its size. Group1: $\leq$ 25mm before and after chemotherapy. Group 2: $>$ 25 mm before chemotherapy; 2A: $\leq$ 25mm after chemotherapy 2B: $>$ 25 mm after chemotherapy. **Results:** 133 CRLM were ablated in 83 patients after systemic chemotherapy (median follow-up 21 months). Among those patients, 57 underwent RFA combined with hepatectomy. The rate of 1-year ISR was significantly higher in group 2A than in group 1 (31.8% vs. 15.5% respectively, $p = 0.0006$). The highest rate of 1-year IRS was 63.6% in group 2B which was significantly higher than in group 1 ($p < 0.001$) and 2A ($p = 0.04$). Time to in situ recurrence (TTISR) was significantly shorter in group 2A than in group 1 (HR: 2.89; 95%CI [1.04-8.01], $p = 0.004$). The shortest TTISR was observed in group 2B. In multivariate analysis, RFA group was the only significant indicator for ISR after RFA ($p < 0.001$). **Conclusions:** Initially oversized CRLM do remain beyond the optimal indications for RFA despite downsizing and should be consider as contraindication to RFA procedure. The rate of ISR remains in this situation doubled to that of upfront small liver metastasis reaching 32%.

3529 Poster Session (Board #21), Mon, 8:00 AM-11:30 AM

Long-term follow-up of bone marrow micrometastases in colon cancer patients. *First Author: Carsten T. Viehl, Department of Surgery, Spitalzentrum Biel, Biel/Bienne, Switzerland*

Background: There is suggestive evidence from investigations with short follow-up that bone marrow (BM) micrometastases are a poor prognostic factor in colorectal cancer patients. The objective of the present prospective study was to evaluate the long-term prognosis of bone marrow micrometastases (BMM) in a large cohort of colon cancer patients. **Methods:** Overall, 144 stage I-III colon cancer patients underwent BM aspirations from both iliac crests prior to open oncologic colon resections. The BM aspirates were stained with the pancytokeratin antibody A45-B/B3, and analyzed for the presence of epithelial tumor cells by an automated cellular imaging system and by visual verification by a pathologist. Overall (OS) and disease-free survival (DFS) were analyzed by Cox proportional hazard regression analyses. **Results:** Median age was 74 years, 47% of patients were female. BMM were found in 55 patients (38%). Median follow-up was 74 months (87 months for patients who survived) with no loss to follow-up. Overall, 30 patients (21%) had a recurrence and 56 patients (39%) died. In univariate analyses, BMM-positive patients had a significantly worse OS (hazard ratio [HR] 0.61; 95% confidence interval [95%CI] 0.50,0.74; $p < 0.001$) and DFS (HR 0.61; 95%CI 0.57,0.65; $p < 0.001$) compared to BMM-negative patients. In multivariable analyses, the presence of BMM remained an independent prognostic factor for OS and DFS (table). **Conclusions:** The presence of BMM is a frequent phenomenon occurring in over one third of stage I-III colon cancer patients. The present prospective cohort study provides compelling evidence that BMM represent a significant, independent prognostic factor for DFS and OS in colon cancer patients even with long-term follow-up. The use of adjuvant chemotherapy in node negative patients with BMM may be justified. Clinical trial information: NCT00826579.

Multivariable analysis.

	OS		DFS	
	HR (95%CI)	p-value	HR (95%CI)	p-value
BM negative vs positive	**0.69 (0.59, 0.80)**	**<0.001**	**0.69 (0.65, 0.72)**	**<0.001**
Age (per 10 years increase)	2.02 (1.73, 2.35)	< 0.001	1.73 (1.58, 1.89)	< 0.001
Male vs female	1.16 (0.79, 1.71)	0.440	1.33 (1.01, 1.75)	0.044
T stage (T1/2 vs T3/4)	1.34 (0.55, 3.28)	0.519	1.18 (0.57, 2.41)	0.658
Nodal status (N0 vs N+)	0.48 (0.39, 0.59)	< 0.001	0.52 (0.42, 0.66)	< 0.001

3530 Poster Session (Board #22), Mon, 8:00 AM-11:30 AM

Phase I study of anti-VEGF receptor-3 (VEGFR-3) monoclonal antibody (mab) LY3022856/IMC-3C5 (3C5). *First Author: Wasif M. Saif, Tufts University School of Medicine Tufts Cancer Center - Medical Center, Boston, MA*

Background: Many cancers metastasize to regional lymph nodes (LN). LN involvement by tumor is an adverse prognostic factor. 3C5 is a human IgG1 mab to VEGFR-3, which is a principal mediator of lymphangiogenesis (LA). **Methods:** This was a first-in-human study (NCT01288989). Part A (A) was a dose escalation study, followed by Part B (B), a planned 15-patient (pt) colorectal (CRC) expansion cohort. The primary endpoint of A was to establish the safety profile and maximum tolerated dose of 3C5 in pts with advanced solid tumors refractory to standard therapy: for B was to establish safety, tolerability, and dose confirmation in pts with advanced refractory CRC. Secondary objectives were pharmacokinetics (PK; noncompartmental parameters), antitumor activity, and immunogenicity. Pharmacodynamics was an exploratory objective. **Results:** Between April 2011 and August 2014, 44 pts were treated (23 in A, 21 in B): median age 58 years (range 33 to 79), male 59%, white 82%, black 9%, Asian 9%; median weight 77 kg (range 52 to 132). Starting dose was 5 mg/kg weekly (qwk), escalated to 10 mg/kg qwk and 20 mg/kg qwk and reached the highest planned dose of 30 mg/kg qwk without dose limiting toxicity. Treatment-emergent adverse events (AE) of any grade occurring in more than 15% of patients were: nausea 41%, fatigue 32%, vomiting 30%, anorexia 27%, pyrexia 25%, edema 23%, urinary tract infection (UTI) 21%, constipation 18%, cough 18%, and hypoalbuminemia 16%, diarrhea 16%. The most common grade 3/4 AEs were UTI, small bowel obstruction 7% each, and nausea, dyspnea, anemia, hypomagnesemia, pneumonia, bile duct stenosis 5% each. No responses per RECIST were noted. 4 of 8 pts with CRC treated at 30 mg/kg on A had prolonged progression free survival (PFS) (10 to 39 weeks). In B, 3C5 at 30 mg/kg qwk resulted in a median PFS of 6.3 weeks (95% confidence interval = 5.1, 14.4). No significant changes in serum VEGF-C/D levels were detected from pt samples after 3C5 administration. **Conclusions:** 3C5 was well tolerated up to a dose of 30 mg/kg qwk. 3C5 does not appear to have significant anti-tumor activity as monotherapy in CRC. Future development will be considered in indications in which LA plays a prominent role. Clinical trial information: NCT01288989.

3531 Poster Session (Board #23), Mon, 8:00 AM-11:30 AM

Relationship between metformin use and recurrence and survival in patients (pts) with resected stage III colon cancer (CC) receiving adjuvant chemotherapy: Results from NCCTG N0147 (Alliance). *First Author: Preet Paul Singh, Washington University School of Medicine, St. Louis, MO*

Background: Although preclinical and epidemiological data suggest that metformin may have antineoplastic properties in CC, the impact of metformin use on pt survival in stage III CC undergoing curative resection is unknown. **Methods:** Before randomization to FOLFOX +/- cetuximab, 1958 stage III CC pts enrolled on N0147 study completed a questionnaire that included information on diabetes mellitus (DM) and metformin use. Cox models assessed the association between metformin use and outcomes of disease free survival (DFS), overall survival (OS) and time to recurrence (TTR), adjusting for clinical/pathological factors. **Results:** 1691 (86%), 115 (6%) and 152 (8%) of 1958 pts reported no history of DM, DM with metformin use, or DM with no metformin use, respectively. The two treatment arms were pooled since metformin use showed homogeneous effects on outcomes across arms. There was no difference in DFS, OS and TTR irrespective of metformin use when DM pts were compared to non-DM pts, after adjusting for tumor/pt factors (Table). Within the cohort of DM pts ($n = 267$), DFS (HR = 0.90; 95% CI: 0.59-1.35; $p = 0.595$), OS (HR = 0.99; 95% CI: 0.65-1.49; $p = 0.948$) and TTR (HR = 0.87; 95% CI: 0.56-1.35; $p = 0.534$) were similar in metformin users compared to non-users. Survival outcomes were comparable regardless of duration of metformin use (< 1, 1-5, 6-10, 11+ years) before randomization ($p = 0.361$ for DFS; $p = 0.068$ for OS). There were no interaction effects observed between metformin use and clinical/pathological factors (*KRAS*, *BRAF* mutation status, tumor site, T/N stage, gender, and age). **Conclusions:** Stage III CC patients treated with adjuvant chemotherapy who used metformin experienced similar DFS, OS, or TTR compared to non-DM pts or DM pts without metformin use.

	DFS		OS		TTR	
Group	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Non-DM	Ref		Ref		Ref	
DM, metformin use	0.95 (0.67-1.36)	0.796	1.17 (0.82-1.67)	0.383	0.91 (0.62-1.33)	0.616
DM, no metformin use	1.15 (0.86-1.54)	0.361	1.26 (0.93-1.72)	0.138	1.14 (0.84-1.57)	0.401

3532 Poster Session (Board #24), Mon, 8:00 AM-11:30 AM

***DPYD c.1905+1G>A and c.2846A>T* and *UGT1A1*28* allelic variants as predictors of toxicity: Pharmacogenetic translational analysis from the phase III TRIBE study in metastatic colorectal cancer.** *First Author: Marzia Del Re, University of Pisa Department of Clinical and Experimental Medicine, Ghezzano, Italy*

Background: Adverse drug reactions (ADRs) caused by fluoropyrimidines depend, at least in part, from DPD deficiency resulting from the loss-of-function mutations c.1905+1G > A and c.2846A > T. Moreover, irinotecan ADRs appear frequently in patients bearing the *UGT1A1*28* variant, associated with reduced UGT1A1 expression. In this study, we analyse the association between *DPYD* and *UGT* variants with ADRs by 5-fluorouracil and irinotecan in subjects enrolled within the phase III TRIBE study, whose final results have been recently reported. **Methods:** Out of 508 randomized patients, blood samples for pharmacogenetic analyses were available for 440 patients. DNA was extracted from 200 μl of blood and analyses of *DPYD* c.1905+1G > A, c.2846T > C and *UGT1A1*28* was performed by a Pyrosequencing platform (Qiagen, USA). The study was approved by the local Ethics Committee. **Results:** Each of the *DPYD* c.1905+1GA and c.2846AT genotypes were found in 5 out of 440 subjects, with a combined frequency of 2.2%. c.1905+1GA and c.2846AT had the same impact on ADRs and, taken together, patients bearing these variants (N = 10) had an increased risk of G3/4 neutropenia (OR: 4.14, p = 0.043) and stomatitis (OR: 10.36, p = 0.003) as compared to wild-type patients. Five out of 10 DPYD mutant patients experienced a G4 ADR after the first cycle of therapy. *UGT1A1*28*/**28* was found in 39/436 patients (8.9%); these patients had an increased risk of G3/4 neutropenia as compared to both *1/*1 (OR: 3.81, p < 0.001) and *1/*28 (OR: 2.28, p = 0.022) genotypes. Patients bearing *DPYD* c.1905+1GA, c.2846AT and *UGT1A1*28*/**28* (N = 49) had an increased risk of G3/4 neutropenia (OR: 2.98, p < 0.001), febrile neutropenia (OR: 2.78, p = 0.023) and G3/4 stomatitis (OR: 6.83, p < 0.001). No significant correlation with G3/4 diarrhea was found. **Conclusions:** *DPYD* c.1905+1GA, c.2846AT and *UGT1A1*28*/**28* are associated with a higher risk of G3/4 ADRs also in the TRIBE trial, underscoring the predictive role of *DPYD* and *UGT1A1* variants across various fluoropyrimidine and irinotecan-containing schedules, and therefore their potential usefulness in treatment tailoring.

3533 Poster Session (Board #25), Mon, 8:00 AM-11:30 AM

Dual targeting of vascular endothelial growth factor-A (VEGF-A) and angiopoietins (Ang) without chemotherapy in metastatic colorectal cancer (mCRC): Results of the VENGEANCE study. *First Author: Jennifer Mooi, Austin Health, Melbourne, Australia*

Background: VEGF-A and Ang play complementary roles in regulation of blood vessel growth, maturation and function. Hence we postulate that combined blockade of VEGF-A and Ang would have clinical activity in mCRC. Trebananib/AMG386 (Treb) is a peptibody that inhibits binding of Ang 1/2 to the Tie2 receptor. Previous studies have established the safety of Treb with various VEGF inhibitors including bevacizumab (Bev). **Methods:** VENGEANCE is an open label Phase II study evaluating the combination of Bev and Treb without chemotherapy as 1st line treatment of mCRC. Key eligibility criteria: patients (pts) with unresectable mCRC, no prior therapy, PS 0-2, adequate organ function, and in whom investigator considers not requiring immediate cytotoxic chemotherapy. Treatment: Bev 7.5mg/kg q3w and Treb 15 mg/kg qw. Primary endpoint: disease control rate (pts without disease progression, i.e. RECIST CR+PR+SD) at 6 mths (DC6m). 2 stage Simon design required stage I: DC6m >5/17 pts, stage II: DC6m >13 pts, for a positive study. Secondary endpoints: response rate (RR), toxicity, progression-free survival (PFS) and overall survival (OS). **Results:** 45 pts were enrolled from 4 Australian sites from Sep 2010 to Aug 2013. Med follow up is 33.7 mths. At time of analysis, 7 pts remain on study treatment (3 PR, 4 SD; duration on study 19 – 32 mths). Key AEs of interest were GI hemorrhage, TIA, cardiac ischemia, PE, GI perforation and CNS hemorrhage (2% each) and g3 hypertension (4%). **Conclusions:** Treb plus Bev showed promising activity that merits evaluation in further randomized studies, including combinations with chemotherapy. RR of the combination is greater than previously reported for Bev monotherapy (3%).The toxicity profile is manageable and the combination does not appear to increase toxicities in excess of those expected with Bev +/- chemotherapy. Clinical trial information: NCT01249521.

Endpoint outcomes.

	DC6m	ORR	Med PFS (mths)*	Med OS (mths)*
Treb + Bev (N=45)	60 % (n=27 non-PD, n=18 PD)	15.5% (n=7 PR, no CR)	9.0 (6.5 – 12.8)	33.4 (27.1 – 39.5)

*Kaplan-Meier estimates, with 95% confidence intervals

3535 Poster Session (Board #27), Mon, 8:00 AM-11:30 AM

Tumor response outcomes in first-line treatment of wild-type (WT) *RAS* metastatic colorectal carcinoma (mCRC) following modified FOLFOX6 (mFOLFOX6) + either panitumumab (pmab) or bevacizumab (bev). *First Author: Fernando Rivera, Hospital Universitario Marqués de Valdecilla, Santander, Spain*

Background: In the PEAK study, pmab + mFOLFOX6 was associated with longer overall survival (OS) than bev + mFOLFOX6 in first-line *RAS* WT mCRC. RECIST overall response rates (ORR) were similar between treatment arms. Here, we report exploratory analyses of tumor assessments beyond RECIST. **Methods:** PEAK was a randomized phase 2 study of first-line pmab + mFOLFOX6 vs bev + mFOLFOX6 in previously untreated mCRC. ORRs (investigator assessed), median duration of response (DoR; from first confirmed response to disease progression or death [secondary endpoint]) and depth of response (DpR; defined as the percentage of tumor shrinkage at nadir or progression) in *RAS* WT patients (pts) were calculated by treatment. Early tumor shrinkage (ETS) was defined as the proportion of pts with ≥ 30% tumor shrinkage at week 8 (exploratory analysis). **Results:** Overall, 169 pts with *RAS* WT mCRC were included in the ORR analysis and 154 had tumor-shrinkage data available at baseline and week 8. Significantly more pts in the pmab + mFOLFOX6 arm had ETS at week 8 vs the bev + mFOLFOX6 arm (Table). ORRs were similar in the two arms, while DoR was significantly longer and DpR significantly greater with pmab + mFOLFOX6 (Table). ≥ 30% vs < 30% tumor shrinkage at week 8 was associated with longer median PFS (HR: 0.52 [95% CI: 0.29–0.92] and HR: 0.65 [95% CI: 0.38–1.13]) and OS (HR: 0.44 [95% CI: 0.15–1.32] and HR: 0.23 [95% CI: 0.08–0.66]) for pmab + mFOLFOX6 and bev + mFOLFOX6, respectively. **Conclusions:** Although ORR appeared to be similar or only numerically improved in the pmab arm of PEAK, the responses observed appeared to occur earlier, last longer and be deeper in our exploratory analyses. This is consistent with the observed OS and PFS benefit, and with data reported earlier from the FIRE3 study. Clinical trial information: NCT00819780.

	Pmab + mFOLFOX6	Bev + mFOLFOX6	p-value
ORR (median [95% CI]), %	65 (54–75)	62 (50–72)	–
DoR (median [95% CI]), months	11.4 (9.7–13.6)	8.5 (6.3–9.3)	0.0142
ETS, % patients	64	45	0.0232
DpR (median [IQR]), %	65 (48–87)	46 (29–62)	0.0007

CI = confidence interval; IQR = interquartile range

3536 Poster Session (Board #28), Mon, 8:00 AM-11:30 AM

Expression of amphiregulin (AREG) and response to first-line panitumumab (pmab) + FOLFIRI in metastatic colorectal cancer (mCRC). *First Author: Claus-Henning Kohne, Onkologie Klinikum Oldenburg, Oldenburg, Germany*

Background: Biomarker analyses have shown that patients (pts) with *RAS*wild-type (WT) mCRC can achieve overall survival (OS) benefits with first-line pmab plus chemotherapy. Other biomarkers may exist that could optimize pt selection. Epidermal growth factor receptor (EGFR) ligand (eg AREG) levels have been correlated with OS during anti-EGFR therapy. Here we investigate the relationship between AREG expression and treatment outcome in a single-arm first-line mCRC study of pmab + FOLFIRI. **Methods:** Qualified reverse transcription quantitative polymerase chain reaction (RT-qPCR) assays were used to measure AREG RNA expression in archival formalin-fixed, paraffin embedded tumor samples from mCRC pts in two pmab trials (STEPP and 314). The STEPP analysis was used to establish a cut-off point in AREG expression that identified the best responders. This cut-off was applied prospectively to samples previously analyzed for *RAS* in the 314 trial. Using the *RAS* MT subgroup as a non-responding comparator, Cox proportional hazards (PH) models were used to evaluate AREG expression levels as a continuous covariate. Decision curves were used to estimate the progression-free survival (PFS) hazard ratio (HR) with increasing levels of baseline AREG expression. **Results:** In the 314 trial 100 pts had evaluable AREG levels. Among 50 *RAS* WT pts, high AREG expression was associated with objective response (OR) (Table). The high AREG group had better PFS HRs (*RAS* WT/*RAS*MT: 0.30 [95% confidence intervals {CI} 0.12–0.75] compared with the low AREG group (PFS HR 0.49 [95% CI 0.21–1.1]). There was a significant biomarker-by-AREG expression interaction in the Cox PH model (p = 0.03). **Conclusions:** Treatment decision curves based on the PH model suggest that most *RAS* WT patients express AREG at levels where treatment benefit is predicted. Future analysis of samples from a *RAS* WT population may provide further insights. Clinical trial information: NCT00508404.

	RAS WT		*RAS* MT	
	High AREG (N=31)	Low AREG (N=19)	High AREG (N=14)	Low AREG (N=36)
Objective responses				
n	21	7	4	16
Rate (95% CI), %	67 (51–82)	38 (18–58)	31 (10–53)	45 (29–60)

3537 Poster Session (Board #29), Mon, 8:00 AM-11:30 AM

A phase II, randomized, double-blinded, placebo-controlled study of simtuzumab or placebo in combination with FOLFIRI for the second line treatment of metastatic KRAS mutant colorectal adenocarcinoma. *First Author: J. Randolph Hecht, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Simtuzumab (SIM) is a humanized antibody that inhibits lysyl oxidase-like molecule 2 (LOXL2), a matrix enzyme that catalyzes the cross-linking of collagen and is widely expressed across desmoplastic tumors. Inhibiting LOXL2 is expected to block formation of desmoplasia, which is thought to play an important role in tumor progression and metastasis. In Phase I, SIM was safe in patients (pts) with advanced solid tumors and showed early evidence of efficacy. Based on these results, a randomized, double-blind, placebo-controlled phase II study of SIM+5-fluorouracil, leucovorin and irinotecan (FOLFIRI) vs. placebo (pbo)+FOLFIRI as second line therapy in pts with metastatic KRAS mutant colorectal adenocarcinoma (CRC) was conducted. **Methods:** Enrolled pts had advanced KRAS mutated CRC that had progressed on first-line oxaliplatin-based chemotherapy. Pts were ECOG performance status (PS) $\leq$ 2. Subjects were randomized in a 1:1:1 ratio to receive SIM 200 mg, SIM 700 mg, or pbo in combination with FOLFIRI every 2 weeks, and the randomization was stratified according to ECOG PS (0 or $>$ 0). The primary endpoint was progression free survival (PFS) and the secondary endpoints were overall survival (OS) and objective response rate (ORR). **Results:** Between April, 2012 and December, 2014, 249 pts were randomized and treated; 85 pts (200 mg SIM/FOLFIRI), 84 pts (700 mg SIM/FOLFIRI), and 80 pts (pbo/FOLFIRI). Median PFS was 5.4 months (HR 1.45; 95% CI 1.01 to 2.06; p = 0.04 vs pbo), 5.5 months (HR 1.32; 95% CI 0.92 to 1.89; p = 0.10 vs pbo), and 5.8 months for the 200 mg SIM/FOLFIRI, 700 mg SIM/FOLFIRI, and pbo/FOLFIRI arms, respectively. Median OS was 10.5 (HR 1.50; 95% CI 0.98 to 2.30; p = 0.06 vs pbo), 11.4 (HR 1.23; 95% CI 0.80 to 1.91; p = 0.25 vs pbo), and 16.3 months, respectively. ORR was 5.9%, 11.9%, and 10%, respectively. There were no differences in the safety profile of the SIM/FOLFIRI groups versus pbo/FOLFIRI group. **Conclusions:** The addition of SIM to FOLFIRI does not improve PFS or OS in advanced KRAS mutant CRC pts. Exploratory analyses to investigate the potential prognostic factors influencing PFS or OS are being conducted. Clinical trial information: NCT01479465.

3538 Poster Session (Board #30), Mon, 8:00 AM-11:30 AM

Population-based assessment of surrogate endpoints (SE) in stage I-III colon (CCa) and rectal cancers (RCa). *First Author: Richard M. Lee-Ying, BC Cancer Agency, Vancouver, BC, Canada*

Background: In adjuvant CCa trials, 3 year disease free survival (3Y DFS) is a validated SE of 5 year overall survival (5Y OS), but this SE is less established in RCa. Effective systemic therapies introduced since 2004 may diminish the association between 3Y DFS and 5Y OS. The objective of this study was to measure SE in CCa and RCa in a population based setting, stratifying by tumor stage and era of diagnosis. **Methods:** Patients diagnosed with stage I-III CCa and RCa referred to any 1 of 5 regional cancer centers in British Columbia between 1990 and 2009 were followed by the GI Outcomes Unit. Clinical, pathological, and treatment characteristics were prospectively collected. R2 resections and early relapses were excluded. Relapses were classified as loco regional (LR) or distant. DFS and OS were measured from the date of definitive surgery until relapse or death. Correlation between DFS and OS endpoints was determined using Pearson's r coefficients. Hazard ratios (HR) were generated using multivariate Cox regression and compared between DFS and OS. 5Y OS HR was compared to calculated 5Y OS using 3Y DFS rates and the validated SE model. **Results:** Of 9147 referred patients with early stage CCa or RCa, 9031 were eligible, with 5357 CCa and 3674 RCa. The median age was 67, 55% were male, 17/34/49% had stage I/II/III disease, respectively, 51% received adjuvant chemotherapy and 87% of RCa received radiation. There were 2494 (28%) relapses of which 90% were distant. The correlation between HR for DFS and OS, 3Y DFS and 5Y OS, and 3Y LR DFS and 5Y OS were all very strong in the total population, for CCa and RCa, across stages and eras (Table 1). Predicted 5Y OS HR were similar to the observed HR where all estimates fell within the observed confidence intervals. **Conclusions:** A strong association between 3Y DFS and 5Y OS was observed in this population-based cohort, which did not differ between CCa and RCa. Correlations remained significant when stratified by tumor stage and treatment era. 3Y LR DFS was a strong surrogate of 5Y OS in RCa.

Pearson's r.

	DFS vs OS	3Y DFS vs 5Y OS	3Y LR DFS vs 5Y OS
All	0.93	0.84	0.87
CCa	0.93	0.83	0.87
RCa	0.92	0.84	0.87
Stage I	0.96	0.86	0.88
II	0.94	0.81	0.85
III	0.92	0.84	0.88
Era $\leq$ 2004	0.94	0.85	0.87
$>$ 2004	0.90	0.82	0.87

3539 Poster Session (Board #31), Mon, 8:00 AM-11:30 AM

Risk factors for interval advanced colorectal neoplasia after screening colonoscopy. *First Author: Laura W. Musselwhite, Herbert Yeargan Center for Global Health, Duke University Medical Center, Durham, NC*

Background: Knowledge of risk factors for interval colorectal neoplasia could inform screening strategies in asymptomatic individuals. Few studies have evaluated risk factors for advanced neoplasia at 5 years in individuals who have had screening colonoscopy. **Methods:** We studied 1193 participants aged 50-75 to identify factors associated with interval advanced neoplasia during a 5-year follow-up period. Participants underwent screening and 5-year colonoscopy from 1994-1997 at 13 Veterans Affairs Medical Centers. Advanced neoplasia included an adenoma $\geq$ 1cm, villous histology, high-grade dysplasia, or carcinoma. Risk factors were self-reported at baseline. We performed a multivariable logistic regression analysis of risk for interval advanced neoplasia, adjusting for age, smoking, alcohol use, BMI, colon cancer in first degree relatives, diabetes, cardiovascular disease, and prior outcome. **Results:** Participants were mostly male (97%) and white (83%). At 5 years, 392 participants (33%) had small adenomas $<$ 1cm, and 92 participants (7.7%) had advanced neoplasia. In multivariable analyses, risk for interval advanced neoplasia was associated with age in 10-year increments (OR, 2.09; 95% CI, 1.39-3.13), diabetes (OR, 1.95; 95% CI, 1.12-3.41), prior small adenomas (OR, 4.02; 95% CI, 1.65-9.80), and prior advanced neoplasia (OR, 12.41; 95% CI, 5.08-30.30). **Conclusions:** In this prospective screening study, we identified diabetes as an independent risk factor for interval advanced neoplasia. Future guidelines should consider enhanced follow up of diabetic patients.

3540 Poster Session (Board #32), Mon, 8:00 AM-11:30 AM

A phase Ib study of AUY922 and cetuximab in patients with KRAS wild-type (WT) metastatic colorectal cancer (mCRC). *First Author: Somasundaram Subramaniam, Swedish Cancer Inst, Seattle, WA*

Background: Heat shock protein-90 (HSP90) is a molecular chaperone which has an important role in EGFR stability. AUY922 inhibits ATPase activity of HSP90. Combined HSP90/EGFR inhibition is effective in pre-clinical models. In this phase IB study, we examined safety, tolerability and maximum tolerated dose of AUY922 in combination with cetuximab in patients with KRAS WT mCRC. **Methods:** This was a single-center open-label dose escalation study. Patients who had disease progression on $\geq$ 2 prior chemotherapy regimens were eligible. Treatment with prior cetuximab was allowed. Inclusion criteria: ECOG 0-1, $\geq$ 1 measurable lesion and adequate organ function. All patients received weekly treatment with cetuximab and AUY922, with dosing per table below. **Results:** Median age 54.5 (range 25 – 77), M/F: 5/11. Patients had a median of 3 prior regimens (range 2-6) and 15 patients (94%) had progressed on prior cetuximab. Median time to progression was 7.9 weeks (range 5.9 – 29.9) and median overall survival was 37.2 weeks (range 4.9 – 115.1). One patient (6%) had a partial response (PR) and 4 patients (25%) had stable disease (SD), for a disease control rate of 31.3%. For patients with disease control, median survival was 45.7 weeks (range 37.6 – 115.1). Treatment was well-tolerated without dose-limiting toxicities. Grade 3 toxicities were seen in 62.5% of patients treated including anemia(2 patients), nausea/vomiting(2), dehydration(2), fever(1), fatigue(1), anorexia(1), abdominal pain(1), headache (1), diarrhea(1) and prolonged QTc interval(1). There were no grade 4 toxicities. Pharmacokinetic studies showed AUY922 half-life of approximately 50 hours, and no interaction with co-administration of cetuximab. **Conclusions:** AUY922 can be safely administered with cetuximab in patients with mCRC. Median survival of 37.2 weeks is suggestive of clinical activity in this heavily pre-treated patient population. Further studies of this combination are warranted. Recommended Phase II dose is weekly cetuximab 250mg/m2 and AUY922 70mg/m2.

Cohort	AUY922 Dose (mg/m2)	Cetuximab Dose (mg/m2)	Number of patients	Patients with Disease Control (PR/SD)
1	40	250	3	2 (1PR, 1SD)
2	55	250	5	1 (SD)
3	70	250	4	1 (SD)
Expansion	70	250	4	1 (SD)

3541 Poster Session (Board #33), Mon, 8:00 AM-11:30 AM

PRODIGE 20: Bevacizumab + chemotherapy (BEV-CT) versus chemotherapy alone (CT) in elderly patients (pts) with untreated metastatic colorectal cancer (mCRC)—A randomized phase II trial. *First Author: Thomas Aparicio, Hôpital Avicenne, Assistance Publique Hôpitaux de Paris, Bobigny, France*

Background: AVEX study has demonstrated increased progression-free survival (PFS) with capecitabine + bevacizumab compared to capecitabine alone in pts aged over 70 with mCRC. The treatment with bevacizumab has so far not been evaluated in combination with other standard chemotherapy regimens for elderly pts. **Methods:** Pts aged 75 and over were randomly assigned in a 1:1 ratio to BEV-CT versus CT. Following regimens were authorized: LV5FU2, FOLFOX and FOLFIRI, chosen by the investigators. The primary endpoint, assessed 4 months after randomization was composite, based on efficacy: tumor control (stable disease or objective tumor response) and absence of decrease of the Spitzer QoL index and safety: absence of severe cardiovascular toxicities and unexpected hospitalization. The decision rules for the experimental arm were: if >15 pts met the efficacy criterion and if >25 pts met the safety criterion, the BEV-CT treatment is considered efficient and well tolerated. **Results:** 102 pts were randomized (51 BEV-CT and 51 CT arm), median age was 80 (range 75-91), men (55%), ECOG 0: 27%, 1: 53% and 2: 20%. CT was LV5FU2 in 53 pts (27 BEV-CT and 26 CT) and a doublet regimen in 49 pts (24 BEV-CT and 25 CT) including 23 FOLFOX and 26 FOLFIRI. Primary tumor was resected in 31 pts in BEV-CT and 30 pts in CT. Of the 46 pts evaluable in the BEV-CT arm, 23 pts (50% [90% CI: 37.1-62.9]) responded to the efficacy criterion and 28 pts (61% [90% CI: 47.7-73.0]) to the safety criterion. Multivariate analysis show that primary tumor resected and normal independent activity of daily living are predictive for the composite criterion. **Conclusions:** BEV-CT arm responded to the efficacy and safety criterion. Addition of bevacizumab to 1st line chemotherapy in pts aged over 75 years with a mCRC is efficient and well tolerated. Clinical trial information: NCT01417494.

Preliminary follow-up results.

	CT	BEV + CT
Grade 3-5 toxicities	65%	80%
Median time to autonomy failure in months (m)	5.5 [95% CI: 3.8-NA]	5.9 [95% CI: 3.8-14.8]
Median time to QoL deterioration (m)	13.6 [95% CI: 11.6-NA]	Not achieved
Median PFS (m)	7.8 [95% CI: 6.6-10.6]	10.7 [95% CI: 8.2-13.8]
Median overall survival (m)	19.7 [95% CI: 13.4-21.9]	21.7 [95% CI: 14.6-NA]

3542 Poster Session (Board #34), Mon, 8:00 AM-11:30 AM

A prospective, multi-center study of individualized, pharmacokinetically (PK)-guided dosing of 5-fluorouracil (5-FU) in metastatic colorectal cancer (mCRC) patients treated with weekly or biweekly 5-FU/oxaliplatin containing regimens. *First Author: Volker Kunzmann, Universitätsklinikum Wurzburg, Würzburg, Germany*

Background: Numerousstudies have demonstrated that body surface area (BSA)-based dosing leads to under- and overexposure in a large number of patients. PK-guided dosing of 5-FU can optimize 5-FU exposure resulting in higher overall dose intensity with reduced toxicities and improved outcomes. This study was initiated to validate use of PK-guided 5-FU dosing for mCRC patients in clinical practice. **Methods:** 75 mCRC patients from 8 academic and/or community-based medical centers located throughout Germany received up to 6 cycles of infusional 5-FU according to either the AIO (n = 16), FOLFOX6 (n = 26) or FUFOX (n = 33) regimen. Initial dosing of infusional 5-FU for all patients was based on BSA and subsequent doses were adjusted according to the previous cycle 5-FU area under the concentration-time curve (AUC) to target an AUC of 20 to 30 mg•h/L. Primary objective was to confirm that PK-guided dosing of 5-FU leads to an increased proportion of patients in the target AUC range at cycle 4 versus cycle 1. Secondary objective was to determine whether PK-guided 5-FU dose adjustment reduced treatment-related toxicities compared to historical patient groups. **Results:** Average 5-FU AUC at cycle 1 was 20 ± 15 mg•h/L, with 62%, 32% and 6% of the patients below, within or above target AUC range, respectively. By cycle 4, average 5-FU AUC was 25 ± 7 mg•h/L (p = 0.007), and a significantly higher proportion of patients were within the target 5-FU AUC range (55%, p = 0.005). Fewer 5-FU-related grade 3-4 toxicities of diarrhea (5%), nausea (3%), fatigue (0%) and mucositis (0%) were observed compared to historical data (12%, 9%, 12%, 15%, respectively). **Conclusion:** PK-guided adjustment of 5-FU dosing in routine clinical practice resulted in significantly higher 5-FU exposure, more patients achieving target exposure, and less 5-FU-related toxicities. Clinical trial information: 2011-003553-26.

3543 Poster Session (Board #35), Mon, 8:00 AM-11:30 AM

The PRIME trial: Quality-adjusted survival in patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC) receiving first-line therapy with panitumumab plus FOLFOX versus FOLFOX alone. *First Author: Jianmin Wang, RTI Health Solutions, Durham, NC*

Background: The pivotal phase III PRIME trial demonstrated that, compared with FOLFOX alone, panitumumab plus FOLFOX prolongs overall survival (OS) and progression-free survival (PFS) in patients with *RAS* WT mCRC without having a detrimental effect on overall quality of life. The objective of this analysis was to use the quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST) method to compare quality-adjusted survival between the treatment arms of PRIME. **Methods:** Patients with *RAS* WT mCRC from each treatment arm of PRIME were included in this analysis, and the area under the survival curve (AUSC) was estimated using the nonparametric Kaplan-Meier method (48 months follow-up). The AUSC was partitioned into three health states: toxicity (TOX), time without symptoms of disease progression or toxicity (TWiST, i.e., PFS minus TOX), and relapse (REL, ie, OS minus PFS). The durations of the health states were then adjusted using utility weights derived from patient-reported EuroQoL 5 measures. The null hypothesis of no difference between treatment arms was tested based on the normal approximation, with standard errors (SE) calculated by the bootstrap method. In the primary analysis, TOX consisted of grade 3 and 4 adverse events. A sensitivity analysis, with grade 2, 3, and 4 adverse events classified as TOX, was performed. **Results:** Of 1,183 patients with mCRC who were randomized, 512 patients had *RAS* WT tumors (panitumumab plus FOLFOX, n = 259; FOLFOX alone, n = 253) and were included in this analysis. Patients receiving panitumumab plus FOLFOX had a significantly longer Q-TWiST (20.5 months) than patients receiving FOLFOX alone (18.2 months) resulting in 2.3 ± 1.0 (SE) additional quality-adjusted months ($P < 0.03$). The sensitivity analysis yielded similar results, indicating that the analysis was robust. **Conclusions:** This Q-TWiST analysis showed that in a previously untreated *RAS* WT mCRC population, patients treated with panitumumab plus FOLFOX had a significantly improved duration of quality-adjusted survival compared with patients treated with FOLFOX alone. Clinical trial information: NCT00364013.

3544 Poster Session (Board #36), Mon, 8:00 AM-11:30 AM

An investigator initiated multicenter phase I/II study of TAS-102 with bevacizumab for metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE). *First Author: Yasutoshi Kuboki, Department of GI oncology, National Cancer Center Hospital East, Japan, Kashiwa, Japan*

Background: In global phase III RECOURSE trial, TAS-102 significantly improved overall survival (OS), progression-free survival (PFS) and disease control rate (DCR) over placebo for metastatic colorectal cancer (mCRC) patients (pts) refractory to standard therapies. In preclinical models, TAS-102 with bevacizumab (BEV) demonstrated enhanced activity against CRC cells compared with either drug alone. This phase I/II study was conducted to determine the recommended phase II dose (RP2D) and evaluate the efficacy, safety and pharmacokinetics of this combination in pts with mCRC refractory to standard therapies. **Methods:** Eligibility criteria were: mCRC pts who were refractory or intolerant to fluoropyrimidines, irinotecan, oxaliplatin, anti-angiogenesis therapy and anti-EGFR antibody (if *KRAS* wild-type) and had no prior regorafenib treatment. Phase I was designed to determine RP2D in the dose de-escalation design of TAS-102 (35 mg/m^2 BID on days 1–5 and 8–12 q4w for level 1 and 30 mg/m^{2}BID for level −1) with a fixed BEV dose (5 mg/kg q2w). Primary endpoint was centrally assessed PFS at 16 weeks in pts treated with RP2D. Using a single stage binomial design, this study required 21 pts, with a centrally assessed PFS rate at 16 weeks of 50% deemed promising and 25% unacceptable (alpha = 0.1; beta = 0.2). **Results:** From February to July 2014, 25 pts were enrolled. In phase I, dose-limiting toxicity was not observed in 6 pts at level 1, which was determined as the RP2D. Centrally assessed PFS rate at 16 weeks (n = 21) was 42.9% (80% C.I.: 27.8–59.0%). Median PFS and DCR by central assessment were 3.7 months and 64.0%, and by investigator assessment were 5.4 months and 72.0%, respectively (n = 25). Median OS was not reached. The most common grade 3 or worse adverse events were neutropenia (68%), febrile neutropenia (8%), thrombocytopenia (4%) and anorexia (4%) without unexpected safety signals. Drug–drug interaction was not indicated by PK analysis. **Conclusions:** The combination ofTAS-102 with BEV showed promising antitumor activity with acceptable toxicity for mCRC pts; biomarker analysis will be presented. Clinical trial information: UMIN000012883. Clinical trial information: 000012883.

3545 Poster Session (Board #37), Mon, 8:00 AM-11:30 AM

Association between c-Met expression, miR-31-3p expression and progression free survival in the New EPOC study. *First Author: Sian Alexandra Pugh, University Surgery, University of Southampton, Southampton, United Kingdom*

Background: Cetuximab in combination with chemotherapy resulted in a shorter progression free survival (PFS) when given before and after resection for colorectal liver metastases (CRLM) in the New EPOC study. MiR-31-3p expression in the primary tumor of these patients was shown to be predictive of the effect of cetuximab and other studies implicate c-Met in resistance to anti-EGFR therapy. We evaluated if c-Met expression in CRLM, in parallel with miR-31-3p, was associated with the earlier progression seen with cetuximab. **Methods:** MiR-31-3p expression was determined by qPCR and c-Met protein expression by immunohistochemistry in paired primary tumor and CRLM tissue for 94 New EPOC patients (Chemo (CT) n = 48, ChemoCetux (CTC) n = 46). c-Met expression was scored dependent on staining intensity; 0, negative; 1, weak; 2, moderate; 3, strong. Consequences of elevation or lowering of c-MET and miR-31-3p expression in paired primary tumor and CRLM on PFS were studied. **Results:** Expression of miR-31-3p and c-Met in primary tumor and matching CRLM were correlated in CT (miR-31-3p: r = 0.6 p = 0.00001, c-Met: r = 0.3 p = 0.03) but not CTC patients (miR-31-3p: r = 0.1 p = 0.47, c-Met r = 0.1 p = 0.36). In CTC, median PFS was 27.9 months for patients in whom c-Met expression was lower in the CRLM vs 14.5 months for those in whom c-Met was unchanged/elevated (HR 3.54 95%CI 1.36, 7.37 p = 0.007). This difference was not observed in CT (HR 1.01 95%CI 0.41, 2.49 p = 0.991). Patients treated with CTC (but not CT) in whom c-Met was lower and miR-31-3p was elevated in CLRM (compared to primary) had a particularly favourable PFS (median not reached) compared to the other 3 groups (log rank p = 0.002). **Conclusions:** In a trial that showed substantial detriment with EGFR inhibition a subgroup has been identified who derived significant benefit from cetuximab. The loss of correlation between primary tumors and CRLM suggests that cetuximab may modulate miR-31-3p and c-Met expression and that these may be implicated in the mechanism by which earlier progression occurred in these patients. Clinical trial information: 22944367.

3546 Poster Session (Board #38), Mon, 8:00 AM-11:30 AM

Therapy of gastrointestinal malignancies with an anti-Trop-2-SN-38 antibody drug conjugate (ADC) (sacituzumab govitecan): Phase I/II clinical experience. *First Author: Alexander Starodub, Indiana University Health, Goshen Center for Cancer Care, Goshen, IN*

Background: Sacituzumab govitecan (IMMU-132) is a conjugate of a humanized anti-Trop-2 (trophoblast cell-surface antigen) coupled site-specifically to SN-38 (7.6 moles SN-38/IgG), an active metabolite of irinotecan, using a proprietary linker. Trop-2 is widely expressed in most epithelial cancers, including gastrointestinal (GI) tumors, and therefore the safety and efficacy of this new ADC is being examined in esophageal (EAC), gastric (GC), pancreatic (PC), and colorectal cancers (CRC). **Methods:** A Phase I/II clinical trial (ClinicalTrials.gov, NCT01631552) was initiated in patients with diverse epithelial cancers, administering IMMU-132 i.v. on days 1 and 8 of 21-day treatment cycles. Treatment was continued based on tolerance or until progression. **Results:** In Phase I, 23 assessable pts were given 8, 10, 12, or 18 mg/kg. Dose-limiting neutropenia occurred at 18 mg/kg. For Phase II, enrollment was expanded to multiple cycles of 8 and 10 mg/kg. Safety data from 123 patients given 8-10 mg/kg showed neutropenia (G3, 18%; G4, 6%), febrile neutropenia (G3, 2%; G4, 2%), but only 3% G3 diarrhea (no G4). Other G3 toxicities included anemia (6%), fatigue (5%), leucopenia (2%), vomiting (2%), and asthenia (1%). No pt developed antibodies to the ADC. Among assessable patients by RECIST 1.1, of 15 EAC pts (median 3 prior therapies), 2 had PR (1 confirmed, duration 6 mo, 1 continuing; 13% ORR), and 7 (46%) SD (median time to progression (TTP) = 5.0 mo). All 3 GC pts had SD (one continuing for 11 mo). Of 14 PC pts (median 2 prior therapies), 7 (50%) had SD with a median TTP of 3.4 mo. In 26 CRC pts (median 4 prior therapies), there was 1 PR (confirmed, duration 10 mo), 14 SD (54%), and a median TTP of 5.1 mo. **Conclusions:** Repeated cycles of IMMU-132 monotherapy are well tolerated with seemingly more favorable neutropenia and diarrhea rates compared to irinotecan. Objective responses in esophageal cancer and extended stabilization in colorectal cancers are encouraging for this monotherapy. The manageable toxicity and promising disease control in these pts warrant further study in combination with other appropriate agents for GI malignancies. Clinical trial information: NCT01631552.

3547 Poster Session (Board #39), Mon, 8:00 AM-11:30 AM

Evaluation of miR 31 3p as a biomarker of prognosis and panitumumab benefit in *RAS*-wt advanced colorectal cancer (aCRC): Analysis of patients (pts) from the PICCOLO trial. *First Author: Pierre Laurent-Puig, UMR-S1147, INSERM, Paris Descartes University, Paris, France*

Background: miR 31 3p expression has previously shown correlation with outcomes in *KRAS* wild-type (wt) aCRC patients receiving EGFR-targeted therapy. We have therefore evaluated miR 31 3p in a large randomized trial of panitumumab. The *a priori* hypothesis was that pts with the lowest miR 31 3p expression would have better outcomes and increased benefit from panitumumab. **Methods:** miR 31 3p was measured in tumor from 213 pts randomized to irinotecan (Ir, n = 111) or irinotecan/panitumumab (IrPan, n = 102) in a trial of second line therapy for aCRC (PICCOLO). The analysis population comprised *RAS* wt (*KRAS* and *NRAS* wt) pts (n = 188: Ir = 101, IrPan-87). End-points were progression-free survival (PFS), overall survival (OS), complete/partial response rate (RR) and disease control rate (DCR). The predefined model divided pts into 3 tertiles with high, intermediate (int) and low miR 31 3p expression, and compared outcomes and treatment effects across these groups. Multivariate analysis was performed, adjusting for Köhne score. **Results:** In the prognostic analysis, compared with low expression pts and after adjustment for treatment arm, int and high pts had worse OS (HR 1.58, 2.03 respectively; p = 0.0012) and worse PFS (HR 1.60, 1.60 respectively; p = 0.018). In multivariate analysis, miR 31 3p and Köhne score were independently associated with OS (p = 0.0006 and p = 0.002 respectively). miR 31 3p was also significantly independently associated with RR (p = 0.015) and DCR (p = 0.074). In the predictive analysis, panitumumab produced marked PFS benefit in pts with low and int miR 31 3p expression (HR = 0.50 [p = 0.019] and HR = 0.57 [p = 0.031] respectively), but not in pts with high expression (HR 0.72, p = 0.23); however, a statistically significant treatment/expression interaction was not seen. **Conclusions:** Pts with lower miR 31 3p have significantly better OS, PFS, RR and DCR, independent of treatment. Pts with low/int miR 31 3p had significant PFS benefit from panitumumab whilst pts with high miR 31 3p did not; however this study was not powered to demonstrate a statistically significant treatment/expression interaction. miR-31-3p is a highly promising biomarker in aCRC.

3548 Poster Session (Board #40), Mon, 8:00 AM-11:30 AM

C-reactive protein and interleukin-6 as markers of systemic inflammatory response and as prognostic factors for metastatic colorectal cancer. Data from the randomized phase III NORDIC-VII study. *First Author: Maria Thomsen, Oslo University Hospital, Oslo, Norway*

Background: A systemic inflammatory response (SIR) affects prognosis and treatment outcome in metastatic colorectal cancer (mCRC). The aim of the study was to explore the prognostic significance of several SIR-derived markers and the correlation between the best marker of SIR and plasma interleukin-6 (IL- 6). **Methods:** The study was based on data from the randomized phase III NORDIC–VII study (Nordic FLOX +/- cetuximab as first line treatment of mCRC). The effect of different markers of SIR, including modified Glasgow Prognostic Score (mGPS), derived Neutrophil Lymphocyte Ratio (dNLR), levels of platelets and levels of C-reactive protein (CRP) on survival were analyzed by Kaplan-Meier plots, log-rank test, and Cox Proportional Hazards model. Further, the relationship between CRP, IL-6 and *RAS* and *BRAF* mutation status was examined. **Results:** 374 patients were eligible for the comparison of markers of SIR and 393 were eligible for the final analysis related to CRP, IL-6 and *RAF* and *BRAF* mutation status.The prognostic significance of CRP was at least as good as the other markers of SIR. CRP together with IL-6 were selected for further investigation. Log-transformed CRP and IL 6 were highly correlated (r = 0.661, p < 0.001) and an increasing level of pretreatment CRP was associated with impaired survival. Stratified by CRP level ≤ 10, 11-30, 31-60, and > 60 mg/L, the different groups showed a median overall survival (OS) of 24.3, 20.6,17.1 and 12.3 months, respectively (HR = 1.34, 95% CI 1.22-1.48, p < 0.001), and had a median progression-free survival (PFS) of 8.9, 7.6, 8.2, and 6.6 months, respectively (HR = 1.21, 95% CI 1.10-1.33, p < 0.001). Furthermore, CRP levels had a similar influence on prognosis in subgroups of patients based on *RAS* and *BRAF* mutation status. **Conclusions:** This is the largest study analyzing markers of SIR in a population of homogenously treated mCRC patients. Increasing CRP values were associated with impaired prognosis and the prognostic significance of CRP is at least equal to that of other markers of SIR. CRP values were highly correlated with IL-6 levels and may be used as a marker for plasma levels of IL-6. Clinical trial information: NCT00145314.

3549 Poster Session (Board #41), Mon, 8:00 AM-11:30 AM

Epidermal growth factor receptor mutations may confer resistance or cross-resistance to cetuximab and panitumumab and can be detected in circulating tumor DNA. *First Author: Mascha Binder, University Medical Center Hamburg, Hamburg, Germany*

Background: Acquired resistance to epidermal growth factor receptor (EGFR) targeted antibodies represents a clinical challenge in the treatment of gastrointestinal tumors such as metastatic colorectal cancer, but its molecular mechanisms are incompletely understood. **Methods:** We scanned *KRAS* exon 2/3/4, *NRAS* exon 2/3/4 and the overlapping epitopes of the EGFR antibodies cetuximab and panitumumab for mutations in pre- and post-treatment tumor tissue of 21 patients with gastrointestinal cancer treated with chemotherapy +/- EGFR antibodies by targeted next-generation sequencing ("tumor tissue" cohort). Binding, signaling and drug sensitivity studies were performed in Ba/F3 cells stably transduced with wt and mutant *EGFR*. Results were validated in circulating tumor DNA (ctDNA) of an independent "liquid biopsy" cohort of 27 patients. **Results:** We describe a novel *EGFR* exon 12 mutation acquired in tumors of 1 out of 3 patients treated with panitumumab in the "tumor tissue" cohort. This mutation introduces a positive charge within the overlap of the panitumumab and cetuximab epitopes. It abrogates antibody binding and mediates cross-resistance to both antibodies in *EGFR*-mutant transfected Ba/F3 cells. In ctDNA from the "liquid biopsy" cohort, we found this novel mutation in 1 out of 6 panitumumab-treated patients while about one third of patients show acquired *RAS* mutations. **Conclusions:** We show that acquired resistance by epitope-changing mutations also emerges during panitumumab treatment and may follow similar biochemical principles as in cetuximab resistance. Such mutations can be easily detected by next-generation sequencing of ctDNA and may perspectively help in tailoring EGFR-targeted therapies.

3550 Poster Session (Board #42), Mon, 8:00 AM-11:30 AM

***PIK3CA* mutations in colorectal and endometrial cancer with double somatic mismatch repair mutations compared to Lynch syndrome.** *First Author: Stacey Shiovitz, University of Washington, Seattle, WA*

Background: Double somatic mutations in mismatch repair (MMR) genes have recently been described in a high proportion of colorectal and endometrial cancers with microsatellite instability (MSI) not attributable to *MLH1* hypermethylation or germline mutation. We sought to define the molecular phenotype of this new tumor subtype. **Methods:** We identified patients with double somatic colorectal and endometrial tumors from two Ohio-based prospective Lynch syndrome screening studies who had abnormal tumor testing (MSI and/or by immunohistochemistry (IHC) without coexistent *MLH1* methylation), but normal germline MMR testing. We determined the frequency of *PIK3CA*, *BRAF*, *KRAS*, *NRAS*, and *PTEN* mutations in double somatic tumors by targeted next-generation sequencing and compared the mutation frequencies to tumors of other MSI sub-groups: Lynch syndrome, *MLH1* hypermethylation, and microsatellite stable (MSS) tumors. The frequencies were compared among groups with a logistic regression model. **Results:** We found that 28/35 (80%) of double somatic tumors had *PIK3CA* mutations compared to 6/21 (29%) in Lynch syndrome tumors, 4/13 (31%) in *MLH1* hypermethylated tumors, and 17/90 (19%) in MSS tumors, $p < 0.0001$. Among double somatic cases, a *PIK3CA* mutation was observed in 100% (13/13) of endometrial tumors and 68% (15/22) of colorectal tumors. These frequencies were significantly higher than all other case groups when analyzing by tumor type (colorectal $p < 0.0001$, endometrial $p = 0.02$). As expected, *BRAF* V600 mutations were frequent in *MLH1* hypermethylated tumors (8/13) and not detected in any double somatic or Lynch tumors ($p < 0.0001$). No substantive differences were observed for *KRAS*, *NRAS*, or *PTEN*. **Conclusions:** *PIK3CA* mutations are present in the majority of double somatic colorectal and endometrial cancers at frequencies significantly higher than those observed in other MSI sub-groups. *PIK3CA* mutation status may improve identification of Lynch syndrome by tumor-based screening and better define an emerging molecular entity in colorectal and endometrial cancers.

3551 Poster Session (Board #43), Mon, 8:00 AM-11:30 AM

A simplified nomogram to predict long-term survival after conversion chemotherapy followed by hepatectomy for initially unresectable colorectal liver metastases. *First Author: Katsunori Imai, Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France*

Background: Although the recent advances in surgury and chemotherapy have enabled hepatectomy in patient with initially unresectable colorectal liver metastases (CRLM), limited number of patients could actually benefit from this strategy. The aim of this study was to develop a simplified nomogram to predict long-term survival for initially unresectable CRLM treated with conversion chemotherapy followed by hepatectomy. **Methods:** From a cohort of 1275 patients who underwent hepatectomy between 1990 and 2012, 439 patients (34.4%) with initially unresectable CRLM were enrolled in this study. A nomogram to predict overall survival was developed based on the result of multivariate cox model. The predictive performance of the model was assessed by C-index, Kaplan-Meier curve, and calibration plots. **Results:** The median number of liver metastases was 5 both at diagnosis and at hepatectomy, and median tumor size was 50 mm at diagnosis and 35 mm at hepatectomy, respectively. Median number of preoperative chemotherapy courses was 10 with 136 patients (31.0%) receiving more than 1 line. Concomitant extrahepatic disease was observed in 148 patients (33.7%). Liver curative and globally curative surgery were achieved in 380 (86.6%) and 335 patients (76.3%), respectively. The 5-year overall and disease-free survival was 39.9% and 10.0%, respectively. Based on the multivariate cox model, 5 independent prognostic factors were selected into the nomogram and assigned score for each factor as follows; primary N positive: 5, tumor number at hepatectomy > 6: 7, carbohydrate antigen 19-9 at hepatectomy > 37 ng/mL: 10, disease progression during first-line chemotherapy: 9, and presence of concomitant extrahepatic disease: 3. The model achieved good discrimination and calibration, with a C-index of 0.66. The overall survival for patients with total score > 15 was significantly worse than those with £ 15 (5-year survival rate: 4.1% vs 46.3%, $P < 0.0001$). **Conclusions:** The proposed nomogram could easily stratify individual patients with initially unresectable CRLM into prognostic groups. Patients with nomogram-predicted score > 15 should be contraindicated to surgery.

3552 Poster Session (Board #44), Mon, 8:00 AM-11:30 AM

Variations in genes regulating tumor-associated macrophages (TAMs) to predict outcome of bevacizumab (bev)-based treatment in patients with metastatic colorectal cancer (mCRC): Results from TRIBE and FIRE3 trials. *First Author: Yu Sunakawa, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: TAMs with the M2-like phenotype are regulated by NF-kB pathway including TBK1, which can influence tumor progression by secretion of proangiogenic factors and tumor promoting cytokines, such as VEGF-A and CCL18. These factors drive tumor angiogenesis, migration and immunosuppression. The CCL2/CCR2 axis, histidine-rich glycoprotein (HRG), PIGF and VEGF play a critical role in the polarization of M1 and M2 phenotypes and the recruitment of TAMs to tumor microenvironment. We hypothesized that genes involved in regulating TAMs may predict outcome of bev-based therapy in patients (pts) with mCRC. **Methods:** We analyzed genomic DNA extracted from blood or tumor samples of pts receiving bev plus FOLFIRI in 2 prospective trials, using PCR-based direct sequencing. Eleven functional polymorphisms in 7 genes (*CCL2*, *CCR2*, *HRG*, *PIGF*, *NFKB1*, *TBK1* and *CCL18*) were tested for associations with clinical outcome in a discovery cohort of 228 pts (male 61%, median age 60, follow-up time 27 months [m]) enrolled in TRIBE (T) trial (NCT00719797), then validated in 244 *KRAS* exon 2 (*KRAS*) wild-type (wt) pts (male 69%, median age 64, follow-up time 39 m) enrolled in FIRE3 (F) trial (NCT00433927). 246 pts receiving cetuximab plus FOLFIRI in F served as negative control. **Results:** *TBK1* rs7486100 (A > T) was associated with response rate (RR) and overall survival (OS) in *KRAS* wt pts of T cohort (n= 95, any T vs A/A: 58 % vs 82 %, p= 0.046; 25.1 m vs 49.1 m, adjusted HR 2.39, p= 0.046, respectively). In F cohort, the association was observed for progression-free survival (any T vs A/A: 10.1 m vs 12.3 m, adjusted HR 1.42, p= 0.047) although there was no statistically association with RR and OS (23.7 m vs 28.6 m, p= 0.15). No polymorphism was established between *KRAS* mutant of T cohort and F cohort. No association was seen in control. **Conclusions:** *TBK1* rs7486100 is associated with outcome of bev-based chemotherapy in mCRC pts, suggesting that NF-kB signaling may play a critical role in tumor angiogenesis as an independent pathway. Our results also suggest that *TBK1* may be a potential biomarker to identify pts benefitting from bev-based treatment.

3553 Poster Session (Board #45), Mon, 8:00 AM-11:30 AM

Comprehensive genomic profiling of clinically advanced colorectal carcinoma to reveal frequent opportunities for targeted therapies. *First Author: Jeffrey S. Ross, Albany Medical College, Albany, NY*

Background: For patients presenting with advanced and metastatic colorectal carcinoma (CRC), standard cytotoxic therapy can provide significant benefit but patients eventually develop progressive disease. We queried whether comprehensive genomic profiling (CGP) could uncover clinically relevant genomic alterations (CRGA) that could lead to targeted therapy selection. **Methods:** DNA was extracted from 40 microns of FFPE sections from 3,117 clinically advanced CRC. CGP was performed using a hybrid-capture, adaptor ligation based next generation sequencing assay to a mean coverage depth of > 600X. The results were evaluated from each sample for all classes of genomic alterations. **Results:** There were 1746 male (56%) and 1371 female (44%) patients with all (100%) of cases either stage III or IV at the time of sequencing. The median frequency of GA per case was 5.7. The CRGA frequency was 2.1 CRGA per case. The most frequent GA were in *APC* (76%), *TP53* (75%) and *KRAS* (53%), all were higher than in TCGA (61%, 44% and 34% respectively). There was 100% concordance with the *KRAS* status determined by the CGP assay and standard hot-spot sequencing assays performed on the same tumor. The combined *KRAS* and *NRAS* mutation frequency was 56% and *BRAF* was mutated in 7%. Only 1.4% of the cases with *KRAS*, *NRAS*, or *BRAF* mutations harbored combination of any 2 out of the 3 genes. Potential CRGA that could lead to targeted therapy-based clinical trials included: *PIK3CA* (18%), *PTEN* (8%), *ERBB2* (5%), *SRC* (4%), *SMAD2* (3%), *NF1* (3%), *EGFR* (3%), *ERBB3* (2%), *MET* (1%) and *KIT* (1%). Either WNT signaling, cell cycle/apoptosis, and/or RTK/RAS signaling pathways were the altered in 83% cases. Clinical outcome case examples demonstrating efficacy of therapies targeting *BRAF*, *ERBB2*, *FGFR2*, and *MET* in CRC patients will be presented. **Conclusions:** When CRC is evaluated by CGP, a significant number of the patients harbored CRGA which have the potential to influence and personalize therapy selection. Given the limited treatment options and poor prognosis of patients with advanced chemo-refractory CRC deep genomic profiling has the potential to identify new treatment paradigms and meet an unmet clinical need for this disease.

3554 Poster Session (Board #46), Mon, 8:00 AM-11:30 AM

Genetic variant of TWEAK to predict clinical outcome in mCRC patients (pts) treated with first line FOLFIRI and Bevacizumab (FOLFIRI/BEV) in FIRE-3 and TRIBE cohorts. *First Author: Anish Parekh, Norris Comprehensive Cancer Center of USC, Los Angeles, CA*

Background: Tumor necrosis factor-like weak inducer of apoptosis (TWEAK), acting via the Fn14 cell surface receptor, is a multifunctional pro-inflammatory/pro-angiogenic cytokine that participates in wound repair and tissue regeneration in different tissues. Studies have shown that TWEAK induces embryonic fibroblast proliferation through Ras/ERK signaling pathway. TWEAK produced in the tumor microenvironment acts on vascular endothelial cells and contributes to inflammatory angiogenesis in mCRC pts. In this study, we tested whether SNPs in TWEAK (rs3803800, rs1128963) and Fn14 (rs8052002, rs13209) predict clinical outcome in mCRC pts treated with first line FOLFIRI/BEV in two independent cohorts. **Methods:** Genomic DNA was isolated from blood or tissue samples of 525 pts treated with first-line FOLFIRI/BEV in FIRE-3 arm B (n = 295) and TRIBE arm A (n = 230) trials. FIRE-3 arm B served as the training set (Median follow up: 39.6 mos; Median PFS: 11.3 mos. and OS: 25 mos). TRIBE arm A served as the validation set (Median follow up: 45.1 mos; Median PFS and OS: 10.4 and 27.3 mos. PCR-based DNA sequencing was used to determine SNPs, which were selected based on frequency and function. FIRE-3 FOLFIRI/Cet (n = 297) was control arm. **Results:** In the overall population analysis, the TWEAK rs3803800 was significantly associated with shorter PFS (9.2 mos) compared to carrying the G/G genotype (11.3 mos) in the FIRE-3 trial in both univariate (HR: 1.39 [1.03-1.86]; P = 0.026) and multivariate analyses (HR: 1.50 [1.11-2.03], P = 0.008). For KRAS mutant pts in the TRIBE trial, any A allele of TWEAK rs3803800 was associated with a similar trend toward worse PFS compared to G/G in multivariate analyses (HR: 1.64 [0.94-2.86], p = 0.079), which is confirmed in the FIRE-3 trial (8 v. 12.3 mos, logrank test P = 0.019)(HR: 2.11 [0.97-4.49], Wald test P = 0.058). No significant difference in control arm. **Conclusions:** This study provides the first evidence that TWEAKrs3803800 could be a predictive marker for PFS in mCRC pts treated with first line FOLFIRI/BEV. It also retained a significant correlation with outcomes related to KRAS mutation, which was confirmed in a validated cohort.

3555 Poster Session (Board #47), Mon, 8:00 AM-11:30 AM

Calculators for overall survival (OS) and progression-free survival (PFS) in metastatic colorectal cancer (mCRC): Construction from 19,678 ARCAD patients. *First Author: Katrin Marie Sjoquist, NHMRC Clinical Trials Centre, University of Sydney and Cancer Care Centre, St. George Hospital, Sydney, Australia*

Background: Predicting survival in mCRC is difficult; even experienced oncologists can be inaccurate. Estimation of prognosis based on readily available clinicopathologic factors has the potential to inform clinical practice and aid in risk stratification for clinical trials. We constructed prognostic calculators for OS and PFS in mCRC using the multi-trial ARCAD database. **Methods:** 19,678 mCRC pts accrued to 24 randomized phase III clinical trials since 1997 used to construct and validate Cox models for PFS and OS, stratified on treatment arm within study. Candidate variables included age, sex, BMI, performance status, colon vs. rectal cancer, prior chemotherapy, number of metastatic sites, sites of metastases (liver, lung, lymph nodes), and baseline bilirubin, albumin, white blood cell count, hemoglobin, platelets, and absolute neutrophil count. Missing data (< 11%) were imputed, continuous variables modeled with splines, and clinically relevant pairwise interactions considered if $p < 0.001$.Final models were internally validated (bootstrapping to obtain optimism-corrected calibration, discrimination C-indices) and externally validated using a 10% holdout sample from each trial. **Results:** Sex, liver, and lung metastases were not prognostic for OS; prior chemo, colon vs. rectum, liver and lymph node metastases, and sex did not predict PFS. No clinically relevant pairwise interactions were identified. Models for OS and PFS using remaining variables and were well calibrated with C-indices of 0.66 and 0.60, respectively. In external validation, concordance of predicted (> vs. < 50% probability) and actual (yes/no) 1-year OS and 6-month PFS was 71% and 67%, respectively, and median 1-year OS and 6-month PFS predictions fell within the actual 95% Kaplan-Meier intervals. Work is ongoing to include molecular markers (BRAF, KRAS mutation); calculators will be updated to include these markers by the time of presentation. **Conclusions:** The proposed calculators are well calibrated and internally and externally valid. These tools have the potential to aid prognostication and patient/physician communication, and balance risk in randomized trials in mCRC.

3556 Poster Session (Board #48), Mon, 8:00 AM-11:30 AM

Predicting individualized post-operative survival for colorectal cancer using a new mobile application derived from the National Cancer Database. *First Author: Emmanuel M. Gabriel, Roswell Park Cancer Institute, Buffalo, NY*

Background: For patients treated with surgery for colorectal cancer, prediction calculators can estimate post-operative survival and assist in the decision making process for adjuvant treatment. **Methods:** We queried the National Cancer Database (NCDB) from 1998-2006 for patients with either colon or rectal cancer who had surgical resection. Within each subset, patients were randomized to a test cohort (n_t) comprising 90% of the dataset and a validation cohort (n_v) comprising the remaining 10%. Multivariate logistic regression of n_t identified independent predictors of the 5-year overall survival (OS), which were used to build prediction models. Model performance was validated and calibrated using n_v. Correlation of observed to predicted OS using n_v was expressed as area under receiver operating characteristic curve (AUC). Prediction models were translated into a mobile application. **Results:** A total of 402,844 patients and 106,037 patients were identified from the colon and rectum datasets, respectively. Independent predictors of OS included patient specific characteristics (age, gender, race, Charlson Deyo comorbidity index, pre-operative CEA level), pathologic factors (site of tumor, size, grade, pathologic TNM stage, margin status, number of nodes examined) and treatment options (type of surgery, neoadjuvant or adjuvant chemoradiation). Length of post-operative stay and unplanned readmission rates were also associated with OS. Our prediction models showed that the predicted OS rates were accurate compared to the actual OS rates (colon AUC = 0.714, rectum AUC = 0.735). These models were translated into mobile application software for a point-of-care, user-friendly medium. **Conclusions:** We developed accurate, individualized post-operative survival calculators for colon and rectal cancer integrated into a mobile-based application platform. Unique to existing calculators, our prediction models utilize nationwide "big data", culminating in highly comprehensive and statistically robust survival calculators.

3557 Poster Session (Board #49), Mon, 8:00 AM-11:30 AM

Impact of primary tumor stage on survival following resection of metachronous liver and/or lung metastases in colorectal cancer. *First Author: Hui-Li Wong, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia*

Background: Resection of isolated liver and/or lung metastases in patients (pts) with metastatic colorectal cancer (mCRC) offers a chance at long-term survival. Multiple prognostic models have been developed to predict outcomes following resection, but the role of primary tumor stage remains controversial, contributing to a recent debate regarding the impact of stage on the value of routine pt follow-up. **Methods:** Consecutive pts with resected liver and/or lung metastases following prior therapy for an early stage CRC entered into a comprehensive, prospective database between 2000 and 2014 were identified. Cox regression analysis was performed to examine the impact of initial tumor stage on overall survival. **Results:** 867 pts with metachronous mCRC were identified; median follow-up was 40.1 months. 215 (25%) had undergone liver and/or lung resection, including 21 with initial stage I CRC, 53 with stage II colon cancer (CC), 70 with stage III CC and 71 with locally advanced rectal cancer (LARC). 5-year overall survival (OS) declined with increasing stage: 100% in stage I, 75% in stage II, 35% in stage III and 52% in LARC ($P < 0.001$). On multivariate analysis, initial stage was predictive of OS, where best outcomes were seen in pts with stage I or II disease (Table). **Conclusions:** Pts with a previous stage I primary cancer contribute only a small proportion of those undergoing resection of metachronous disease but have excellent outcomes, suggesting routine follow-up of stage I pts is worthwhile. With increasing primary tumor stage, survival outcomes deteriorate. However, the majority of 5-year survivors are pts with high-risk primaries, justifying follow-up in this pt group. Better markers of recurrence risk and of benefit from metastasectomy would be beneficial.

	Hazard ratio	95% CI	P
Primary stage	-	0.38-1.25	0.218
Stage III (Ref)	0.69	0.13-0.66	0.003
LARC	0.29		
Stage II	N/A*		
Stage I			
Age (years)	-	0.56-1.70	0.930
< 65 (Ref)	0.98		
≥ 65			
Disease-free interval (months)	-	0.32-1.04	0.069
< 12 (Ref)	0.57		
≥ 12			
Metastatic sites	-	0.55-1.73	0.924
Liver (Ref)	0.97	0.45-9.19	0.360
Lung	2.03		
Liver and lung			
No. of lesions	-	0.71-2.29	0.407
1 (Ref)	1.28		
≥ 2			
Resection margin	-	0.43-3.60	0.683
R0 (Ref)	1.25		
R1/2			

*No events

3558 Poster Session (Board #50), Mon, 8:00 AM-11:30 AM

Molecular subtypes and outcomes in regorafenib-treated patients with metastatic colorectal cancer (mCRC) enrolled in the CORRECT trial. *First Author: Michael Teufel, Bayer Pharma AG, Berlin, Germany*

Background: In the CORRECT Ph3 trial (NCT01103323), regorafenib improved overall survival (OS) and progression-free survival (PFS) vs placebo in patients with mCRC who progressed on standard therapies (Grothey 2013). Initial biomarker analyses suggested that regorafenib provides a clinical benefit in various mutational subgroups (Jeffers 2013). Here we present additional exploratory analyses to evaluate clinical benefit in CRC subgroups defined by gene expression. **Methods:** Gene expression analysis (Affymetrix ST1.0 array) was conducted on archival tumor tissue from 281 of the 760 patients (37%) enrolled in CORRECT. Next-generation sequencing (NGS) was done on 239 specimens (FoundationONE). Gene expression data were subjected to hierarchical molecular tumor classification (Marisa 2013). Cox proportional hazards models were used to identify potential prognostic or predictive biomarkers. **Results:** The distribution of the 6 different CRC subtypes characterized by gene expression clusters originally defined by Marisa and the classification of the 281 patients from CORRECT are shown in the table. The six Marisa subtypes derived a similar OS benefit from regorafenib. Although the numbers of patients in the subgroups are small, a greater PFS benefit for regorafenib was seen in patients in the 'high-risk' subgroup (C4 +C6, n = 26; HR = 0.10; 95%CI 0.02 - 0.35; p = 0.0009) than the 'low-risk' subgroup (C1+C2+C3+C5, n = 255; HR = 0.58; 95%CI 0.44 - 0.77; p = 0.002). NGS analyses suggested that the chromosomal instability group (CIN) was the predominant subgroup in CORRECT. **Conclusions:** Molecular characterization by gene expression analysis may allow the identification of CRC subgroups that correlate with regorafenib clinical benefit. Data suggest this does not depend on the presence of mutations. Additional exploratory analyses, including the use of the recently defined Consensus molecular subtypes (Dienstmann ASCO 2014), to validate these results are ongoing. Clinical trial information: NCT01103323.

Subtype	CINImmuneDown (C1)	dMMR (C2)	KRASmutant (C3)	CSC (C4)	CINWntUp (C5)	CINnormL (C6)
Marisa (2013)	21%	19%	13%	10%	27%	10%
CORRECT	36%	12%	11%	7%	32%	2%
(n)	(100)	(33)	(32)	(19)	(90)	(7)

3559 Poster Session (Board #51), Mon, 8:00 AM-11:30 AM

Two-stage hepatectomy for extensive colorectal liver metastases: How to predict the failure to complete both sequential procedures? *First Author: Katsunori Imai, Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France*

Background: Two-stage hepatectomy (TSH) has been adopted as a treatment strategy for extensive bilateral colorectal liver metastases (CRLM) unable to be resected by a single hepatectomy. However, one of the most critical problems is the risk of failure to achieve both two sequential procedures. The aims of this study were to identify the predictive factors and develop a predictive model for failure of TSH for the optimal selection of patients who could benefit from this strategy. **Methods:** Among a total of 845 patients who underwent hepatectomy for CRLM Between 2000 and 2012, 125 patients (14.8%) with extensive bilateral CRLM were scheduled to perform TSH and were enrolled in this study. Based on the result of multivariate logistic analysis, a predictive model for failure of TSH was developed. **Results:** The median number and size of liver metastases was 9 and 37 mm, respectively. Concomitant extrahepatic disease was present in 34 patients (27.2%). On an intention-to-treat basis, the 5-year overall survival (OS) rate was 33.2%. Among the 125 patients who were planned for TSH, 44 patients (35.2%) could not proceed to the second-stage mainly because of tumor progression, and their OS were significantly worse than those who completed (5-year OS: 0% and 44.2%, $P < 0.0001$). Multivariate logistic analysis revealed that carcinoembryonic antigen > 30 ng/dL (relative risk (RR) 2.73, $P = 0.034$), tumor size > 40 mm (RR: 2.89, $P = 0.036$), chemotherapy cycles > 12 (RR: 3.46, $P = 0.0098$), and tumor progression during first-line chemotherapy (RR: 6.56, $P = 0.01$) were the independent predictive factors for failure of TSH. For patients without any factors, the probability of failure was 10.5% with 5-year OS of 41.9%. The addition of subsequent factors increased the probability to 43.5% for one (5-year OS 38.8%), 72.7% for two (29.2%), 88.5% for three (0%), and 95.5% for four factors (not reached). The OS for patients with predictive score of 3-4 was significantly worth than that of 0-2 (5-year OS; 0% and 36.8%, $P < 0.0001$). **Conclusions:** TSH in patients with more than 3 risk factors should be contraindicated. Avoidance of these risk factors significantly reduces the risk of failure and is crucial for the long-term survival.

3560 Poster Session (Board #52), Mon, 8:00 AM-11:30 AM

Effects of regorafenib (REG) therapy on health-related quality of life (HRQoL) in patients with metastatic colorectal cancer (mCRC) in the phase III CONCUR trial. *First Author: Jane Chang, Bayer HealthCare Pharmaceuticals, Whippany, NJ*

Background: In the phase III CORRECT and CONCUR trials, REG significantly improved overall survival (OS) *vs* placebo (PBO) in patients with mCRC whose disease progressed on standard treatments. In CORRECT, overall HRQoL was similar between REG and PBO. This analysis reports the HRQoL effects of REG in CONCUR. **Methods:** CONCUR (NCT01584830) was an international, multicenter trial which enrolled patients in Asia (N = 204). Patients were randomized 2:1 to receive REG 160 mg (n = 136) or PBO (n = 68) once daily for weeks 1–3 of each 4-week cycle. Planned HRQoL analyses were conducted using the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) and the EuroQol-five dimension (EQ-5D) questionnaires. EORTC QLQ-C30 global health status (GHS) and the EQ-5D index and visual analogue scale (VAS) scores were expressed as least squares mean (LSM) time-adjusted area under the curve (AUC) to allow comparison of change in HRQoL across the treatment period. An exploratory *post-hoc* analysis assessed time to deterioration (TTD) of HRQoL, defined as the earliest ≥ 10-point score decline in GHS or physical functioning (PF) domain score, progression or death. **Results:** Overall changes from baseline in HRQoL scores appeared similar in the REG and PBO groups. LSM time-adjusted AUC of the EORTC QLQ-C30 GHS domain, EQ-5D index and VAS scores did not differ significantly between groups (table). TTD of HRQoL was significantly longer with REG *vs* PBO in *post-hoc* analyses (table). **Conclusions:** REG provided additional clinical benefit while maintaining HRQoL *vs* PBO in Asian patients. Clinical trial information: NCT01584830.

LSM time-adjusted AUC (95% CI)	REG (n = 131)	PBO (n = 63)
EORTC QLQ-C30 GHS	60.76 (58.81 to 62.71)	61.16 (58.48 to 63.83)
Difference from PBO	−0.40 (−3.53 to 2.72)	
EQ-5D index	0.70 (0.67 to 0.73)	0.74 (0.70 to 0.78)
Difference from PBO	−0.03 (−0.08 to 0.01)	
EQ-5D VAS	69.28 (67.48 to 71.08)	70.46 (68.01 to 72.91)
Difference from PBO	−1.18 (−4.01 to 1.66)	
Median TTD (95% CI)	REG (n = 136)	PBO (n = 68)
EORTC QLQ-C30 GHS	8.0 (7.6 to 8.0)	7.0 (5.9 to 7.4)
HR	0.54 (0.40 to 0.74; p < 0.01)	
EORTC QLQ-C30 PF	7.9 (7.3 to 8.0)	7.0 (5.0 to 7.6)
HR	0.59 (0.44 to 0.80; p < 0.01)	

3561 Poster Session (Board #53), Mon, 8:00 AM-11:30 AM

Moving foward and beyond the standard through a non-operative management in rectal cancer? Our watch and wait approach experience in Co-Recto. *First Author: Ilma Soledad Iseas, Clinical Oncology Unit, Hospital Bonorino Udaondo, Buenos Aires, Argentina*

Background: Controversies exist about the proper management of pts with clinical complete tumor regression after preoperative therapy. A non-operative management (NOM) of selected patients has achieved promising long-term outcomes in some Watch and Wait (W&W) series. Regardless of encouraging results, and in spite of being a readily accepted strategy by patients, reluctance to recommend this strategy as an affordable option still exists in rectal cancer guidelines. Our aim is to evaluate the NOM for pts with clinical complete response discussed in Co-Recto(interdisciplinary and cooperative team for the Management of rectal cancer) Argentina **Methods:** Pts with resectable rectal cancer (stage I-III) selected for neoadjuvant therapy in Co-Recto between 2008-2014 were retrospectively reviewed to determine pts with clinical complete response(cCR) selected for Non operative management. cCR was defined between digital exam, endoscopic criteria, MRI and CEA. F-up for W&W policy was performed during the first two years with MRI and EUS three-monthly and CT six-monthly. **Results:** 32pts with cCR were included. Initial staging was performed by MR (30/32, 94%) and EUS(6/32, 19%). 40.5% (12/32) were T2-T3ab N0; 59.5% (19/32 were T3c/d-T4, N+ and 49% (16/32) had CRM+. Median distance from anal verge was 30mm . Involvement into/beyond the elevator muscle: 34%(11/32) . CRT consisted of long-course RT (50.4 Gy) with capecitabine (825 mg/m2 bod for 7 d/w). Induction chemotherapy (CAPOX) was administered in 37.5% followed by CRT. Response assessment was done at 7 w (5-12w). Adjuvant therapy was administered in 18%. LR was observed in 3/32 pts (9%) within the rectal wall. 2/3 a mesorrectal nodal recurrence without endoluminal recurrence, 1/3 had endoluminal component. All feasible of salvage resection. PFS was 36 m(25-49m) Distant metastases and extrarectal pelvic recurrence weren´t observed in any case. After fup of 40 m (8-66m), no deaths occurred. **Conclusions:** a NOM with a close fup was a feasible approach, had optimal outcome avoiding surgical functional sequelae. To mitigate the remaining skepticism about W&W, collaborative randomized trials should be implemented.

3562 Poster Session (Board #54), Mon, 8:00 AM-11:30 AM

Effect of genetic variation on overall survival in a clinical trial of metastatic colorectal cancer (mCRC). *First Author: Heinz-Josef Lenz, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: TRIBE, a phase III randomized trial comparing FOLFIRI + BEV (Arm A) vs FOLFOXIRI + BEV (Arm B) as first-line treatment for mCRC, were recently published in the NEJM. No known predictive biomarkers for BEV-based chemotherapy exist. Here we assess the impact of genetic variation with overall survival (OS). **Methods:** The Illumina HumanExome array (248,538 SNPs) was genotyped on 418 genomic DNA samples from TRIBE. The analysis included 385 pts and 37,043 coding SNPs (MAF $>$ 1%) following quality control. An additive genetic model in a Cox proportional hazard framework was utilized to identify associations with OS adjusting for relevant confounders. A subgroup analysis by study arm, sex, and primary location was performed. A Bonferroni correction was applied to minimize false positives. **Results:** Arm A (N = 163) had a mean age of 59.9 years, median OS of 26.2 mos while Arm B (N = 222) had a mean age of 59.9 years, median OS of 31.0 mos. We identified 12 statistically significant associations ($P< 1.35x10^{-6}$) with OS; yielding six statistically significant subgroup interactions ($P< 4.4x10^{-4}$). In all patients group, *VEGFR2* rs10008360 is significantly associated with OS (HR = 5.76; 95%CI: 2.66-12.46; $P= 8.8x10^{-6}$); significant in Arm B (HR = 9.81; 95%CI: 3.59-26.81; $P= 8.52x10^{-6}$) and left-sided CRCs(HR = 10.48; 95%CI: 3.73-29.49; $P= 8.4x10^{-6}$), The strongest association was detected in Arm B with the missense variant rs3750025 in *DSPP* (HR = 22.7; 95%CI: 7.4-69.5; $P= 4.2x10^{-8}$), including a significant statistical interaction by study arm ($P= 2.0x10^{-5}$). The median OS in Arm B for rs3750025 AA and AG/GG genotypes were 31.0 (95%CI: 28.4-36.1) and 3.9 (1.6-7.2) mos. Among right-sided CRCs, *ZNF749* rs2240038 yielded a statistically significant association (HR = 40.3, $P= 2.27x10^{-7}$) with a median OS of 24.8 (20.5-30.9) and 4.4 (4.0-5.9) mos for the GG and GA/AA genotypes. **Conclusions:** This is the first study to identify novel biomarkers for OS among clinically relevant subgroups defined by study arm, tumor location and sex. These results demonstrate the clinical potential for novel biomarker discovery using genetic variation. Further validation of our findings in FIRE3 trial is ongoing.

3563 Poster Session (Board #55), Mon, 8:00 AM-11:30 AM

Improvement in long-term survival in patients with metastatic colorectal cancer (CRC) after liver resection with modern chemotherapy and hepatic arterial infusion (HAI). *First Author: Nancy E. Kemeny, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Hepatic resection of liver metastases from CRC is associated with 5-year (y) and 10-y overall survival (OS) of 30-50% and 20%. The aim of this study was to update OS of 5 consecutive adjuvant (adj) studies using HAI + systemic (sys) after liver resection and to determine effects of clinical factors on long-term OS. **Methods:** Patients (pts) treated on protocols with HAI FUDR/dexamethasone + sys from 1991 to 2015 with the following inclusion criteria: completely resected hepatic metastases, no extrahepatic disease, bilirubin $<$ 1.5mg/dl, platelet count $>$ 100,000/μL, and no concurrent infection. Pts on studies before 2003 were treated with HAI + sys FU/LV or irinotecan (CPT) and pts on studies after 2003 were treated with HAI + sys oxal/FU/LV or CPT/FU/LV ± molecular targeted therapies. OS was calculated from the time of liver resection until death and was estimated using the Kaplan-Meier method. Using Greenwood's formula, 95% CI at fixed time points for outcomes were calculated and compared between treatment years (before 2003 vs after 2003). **Results:** 329 pts were included with a median follow-up of 9.6 y. 5-y OS for those treated before and after 2003 was 56% [95% CI: 49%-63%] and 80% [95% CI: 71%-85%], respectively ($p < 0.01$). 10-y OS for pts treated before 2003 was 40%, while 10-y OS is not yet obtainable for pts treated after 2003. Various clinical factors and significant p-values (*p) known to influence survival are shown in the table below. **Conclusions:** Survival for pts undergoing hepatic resection and adj HAI is improving. Pts treated before 2003 with liver resection and adj HAI + sys have a 5-y OS of 56%, while pts treated after 2003 with HAI + modern sys chemotherapy have a 5-y OS of 80%.

	*p	Before 2003 n=169			After 2003 n=160	
	Before/After 2003	%	OS % 5-y	OS % 10-y	%	OS % 5-y
Age	-/-					
22 – 50		27	61	48	38	75
51 – 74		68	55	37	59	81
≥ 75		5	56	33	3	100
# Hepatic Mets	*/*					
1		39	71	57	26	87
2 – 4		46	57	35	48	85
5 – 7		11	26	16	15	67
≥ 8		5	13	0	11	52
Clinical Risk Score	*/-					
0 – 2		59	64	47	54	85
3 – 5		41	47	30	46	72
Margins (mm)	-/*					
0		6	50	10	6	40
≤ 1		50	52	37	63	78
> 1		44	66	48	31	92
Size (cm)	-/-					
< 5		69	58	42	79	81
≥ 5		31	54	35	21	72
Primary LN	*/*					
Pos		60	52	32	62	73
Neg		40	65	52	38	90
CEA Post op (ng/ml)	*/-					
< 5		68	64	44	80	83
≥ 5		32	43	30	20	65
KRAS	-/*					
WT		-	-	-	81	86
MUT					19	67

3564 Poster Session (Board #56), Mon, 8:00 AM-11:30 AM

Phase 3 RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: Geographic subgroups. *First Author: Atsushi Ohtsu, National Cancer Center Hospital East, Kashiwa, Japan*

Background: TAS-102 is comprised of an antineoplastic thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio of 1:0.5 (weight ratio, 1:0.471). The efficacy and safety of TAS-102 in patients (pts) with metastatic colorectal cancer refractory/intolerant to standard therapies were evaluated in the RECOURSE trial; enrollment criteria included ≥ 2 prior lines of standard chemotherapy. Primary results of RECOURSE demonstrated a significant improvement in overall survival (OS) and progression-free survival (PFS) with TAS-102 vs placebo (PBO) (hazard ratio [HR] = 0.68 and 0.48 for OS and PFS, respectively; both $P< 0.0001$). **Methods:** RECOURSE data were evaluated for efficacy and safety, including rate of hospitalizations, of TAS-102 vs PBO by each geographic subgroup of US, EU, and Japan (JP). **Results:** Of 768 pts, 99 US (mean age, 60 y), 403 EU (mean age, 62 y), and 266 JP (mean age, 62 y) pts were randomized to receive TAS-102 or PBO. Median OS with TAS-102 vs PBO was 6.5 mo vs 4.3 mo in US pts, 6.8 mo vs 4.9 mo in EU pts, and 7.8 mo vs 6.7 mo in JP pts. HRs for OS and PFS for US, EU, and JP pts all favored TAS-102 (Table). There were no marked differences among the US, EU, and JP subgroups with respect to overall incidence of adverse events (AEs), ≥ Grade 3 AEs, serious AEs (SAEs), or hospitalizations. **Conclusions:** Similar to the overall RECOURSE population, OS and PFS benefits were observed in each geographic subgroup randomized to TAS-102 vs PBO, with an acceptable safety profile. Clinical trial information: NCT01607957.

	US		EU		JP	
Intent to Treat	**TAS-102 (n = 64)**	**thPBO th(n = 35)**	**thTAS-102 th(n = 271)**	**thPBO th(n = 132)**	**thTAS-102 th(n = 178)**	**thPBO (n = 88)**
OS HR [95% CI]	0.56 [0.34, 0.94] $P= 0.0277$		0.62 [0.48, 0.80] $P= 0.0002$		0.75 [0.57, 1.00] $P= 0.047$	
PFS HR [95% CI]	0.43 [0.26, 0.69] $P= 0.0004$		0.41 [0.33, 0.52] $P< 0.0001$		0.58 [0.44, 0.75] $P< 0.0001$	
As Treated	**TAS-102 (n = 64)**	**PBO (n = 35)**	**TAS-102 (n = 270)**	**PBO (n = 131)**	**TAS-102 (n = 178)**	**PBO (n = 88)**
Any AE, %	96.9	100	98.5	91.6	99.4	92.0
AEs ≥ Grade 3, %	73.4	45.7	70.7	55.0	66.3	50.0
Serious AEs, %	28.1	31.4	30.4	32.1	26.4	38.6
Hospitalizations, all reasons, %	26.6	34.3	31.1	34.4	29.2	40.9

3565 Poster Session (Board #57), Mon, 8:00 AM-11:30 AM

Using mutational load in next generation sequencing (NGS) to identify mismatch repair (MMR) deficiency in colorectal cancer (CRC). *First Author: Francesca Battaglin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: NCCN guidelines recommend screening all CRC patients diagnosed at age ≤ 70 years and those > 70 who meet Bethesda Criteria with either immunohistochemistry (IHC) for MMR protein expression or PCR for microsatellite instability (MSI), and also recommend tumor sequencing for RAS/BRAF mutations in all CRC patients with metastatic disease. MMR status is also needed for management of all stage II colon cancer patients, and BRAF mutational status is useful in work up of MMR-deficient (dMMR) tumors. We hypothesized that the higher mutational burden of dMMR tumors would permit their identification on the basis of the mutation count in an NGS panel, thus allowing a single multi-gene NGS assay to reliably detect not only RAS/RAF mutations but also MMR deficiency. **Methods:** Under an IRB waiver, an institutional electronic database was queried to identify all CRC analyzed with MSK-IMPACT, our custom 341-gene NGS assay. Tumor mutational load, defined as the raw number of somatic mutations identified, was determined for each case and compared between MMR-proficient and MMR-deficient cases. **Results:** We identified 149 unique CRC patients tested with MSK-IMPACT. Of these, 93 had MMR status available, including 8 dMMR cases. 83 of 85 (98%) of MMR-proficient cases had 16 or fewer mutations, while two outliers with 158 and 250 mutations each were found to be POLE-mutant. MMR-deficient tumors had a higher mutational load with a significantly higher median number of somatic mutations (49, range 23-67) than MMR-proficient tumors (6, range 0-16), p = 0.0024. **Conclusions:** This preliminary analysis suggests that using a cut-off for mutational load, such as 20 mutations for MSK-IMPACT, may provide a highly sensitive and specific means of screening for MMR deficiency with the same assay used for tumor genotyping. If validated, the use of a single multi-gene sequencing assay to screen for both dMMR and RAS/BRAF mutations could be cost effective, particularly in metastatic CRC, but also in early stage disease, while providing additional genetic information that may be useful for research purposes. Larger numbers of known dMMR tumors are currently being analyzed with MSK-IMPACT to validate this hypothesis.

3566 Poster Session (Board #58), Mon, 8:00 AM-11:30 AM

Genomic analysis of colitis-associated cancers. *First Author: Rona D. Yaeger, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with inflammatory bowel disease (IBD) [Crohn's disease (CD) and ulcerative colitis (UC)], are at increased risk for small bowel or colorectal cancers (Colitis Associated Cancers, CAC). The genomic alterations (GA) associated with CAC have not been well-described. We hypothesized that GA associated with CAC are different than those seen with sporadic colorectal cancer (CRC). Identification of these alterations may lead to improved early detection and therapeutic options. **Methods:** We determined GA in 15 CAC cases confirmed as being associated with IBD at MSKCC including 11 UC and 4 CD, 14 primary and 1 metastasis (median age 55, range 29-77; 73% male). Primary tumor sites were ileum (2), right colon (5), and left colon (8). Histologic subtypes were moderately differentiated adenocarcinoma (4), mucinous (7), and signet ring/diffuse (4). Hybridization capture of the entire coding sequence of 405 cancer-related genes, including those associated with early onset IBD, was applied to DNA extracted from FFPE tumor specimens and sequenced to high, uniform coverage (> 500x). All classes of GA including substitution, indel, copy number alteration and rearrangement were determined. **Results:** Potentially clinically relevant GA were identified in 8/15 CAC, including *ERBB2* amplification (amp), *ERBB2* S310F, *EML4-ALK*, *FGFR2* amp, *FGFR2* amp + *FGFR2-TACC2* (same patient), *PDGFRA* T134M, and *BRAF* V600E + *TSC2* truncation (same patient). *IDH1* R132H/C were found in 2/4 CD cases (one concurrent with *FGFR2* amp/fusion). Overall, 5.7 GA per tumor were detected (range 1-12). GA in *TP53,* the most commonly altered gene, occurred in 14/15 cases (93%; 10 known hot spot mutations), compared to 52% in CRC TCGA. *KRAS* and *APC* mutations occurred in 33% and 20%, respectively, compared to 43% and 76% in CRC TCGA. Other recurrently altered genes included *SMAD4* (20%) and *RNF43* (13%). Key GA associated with early onset IBD were not identified. **Conclusions:** Comprehensive genomic profiling identified a high frequency of potentially clinically relevant GA in CAC. GA seen in CAC suggest substantial differences from those of sporadic CRC; *APC* activation is infrequent and *TP53* mutations are nearly universal including frequent possibly gain of function. Study of additional cases is ongoing.

3567 Poster Session (Board #59), Mon, 8:00 AM-11:30 AM

FOLFOX-aflibercept followed by maintenance therapy with fluoropyrimidine-aflibercept as first-line therapy in patients with metastatic colorectal cancer: A GERCOR single-arm phase II study (VELVET). *First Author: Benoist Chibaudel, Institut Hospitalier Franco-Britannique, Levallois-Perret, France*

Background: VEGF inhibition with (ziv-)aflibercept, a recombinant human fusion protein, in combination with FU/irinotecan improves patient outcomes (overall survival (OS), progression-free survival (PFS), overall response rate (ORR)) in second-line therapy of patients with metastatic colorectal cancer (MCRC) (Van Cutsem, JCO 2012). The VELVET study evaluated the efficacy and safety of the OPTIMOX-aflibercept first-line treatment strategy (EudraCT 2012-003521-25). **Methods:** Main eligibility criteria were: previously untreated, unresectable, evaluable or measurable MCRC, age ≥ 18 years, ECOG PS 0-2. Patients received mFOLFOX7-aflibercept (aflibercept 4mg/kg, folinic acid 400mg/m², oxaliplatin 100mg/m², 5FU infusion 3000mg/m²/46h) fortnightly regimen as induction therapy (6 cycles) followed by maintenance therapy with fluoropyrimidine (5FU or capecitabine) and aflibercept until disease progression or limiting toxicity. CT-scan tumor assessments using RECIST1.1 were done every 8 weeks. A Minimax Simon's two-stage design was used with a targeted improvement of 6m-PFS rate (primary endpoint) from 70% to 85%. **Results:** From May 2013 to May 2014, 49 patients were included. One patient did not receive study treatment. Thirty-seven (84.1%, se 5.5) patients were alive at 6 months without documented RECIST progression. The Kaplan-Meier 6m-PFS was 81.9% (66.8-90.6) and median PFS was 9.3 months (95%CI: 8.7-12.6). The ORR was 59.2% (N = 29/49) and 65.9% (N = 29/44) in the ITT and evaluable populations, respectively. Most common (≥ 10%) grade 3-4 adverse events reported were hypertension (23%), fatigue (12%), neuropathy (10%), neutropenia (10%). Two on treatment deaths were reported: 1 due to stroke and 1 due to neutropenic sepsis attributable to the study treatment. Circulating angiogenic biomarkers results will be presented at the meeting. **Conclusions:** OPTIMOX-aflibercept could be an active first-line treatment strategy in patients with metastatic colorectal cancer. This study warrants further investigation to confirm efficacy and safety of the combination in a randomized controlled trial. Clinical trial information: EudraCT 2012-003521-25.

3568 Poster Session (Board #60), Mon, 8:00 AM-11:30 AM

Cetuximab biweekly plus mFOLFOX6 as first-line therapy in patients (pts) with KRAS wild-type (wt) (exon 2) metastatic colorectal cancer (mCRC): Primary endpoint and subgroup analysis of the CEBIFOX trial. *First Author: Stefan Kasper, Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany*

Background: The multicenter, single-arm, phase II CEBIFOX trial (Simon's two stage minimax design) evaluated the efficacy of mFOLFOX6 + biweekly cetuximab (500 mg/m²) as 1st line therapy in *KRAS* wt (exon 2) mCRC. Final efficacy data as well as extended molecular and clinical subgroup analyses are presented. **Methods:** Primary endpoint was objective response rate (ORR) per RECIST 1.0, secondary endpoints were safety, metastasectomy rate, quality of life, progression-free (PFS) and overall survival (OS). Extended molecular profiling was performed using NGS-based panel sequencing including *NRAS* (exon 2-4), *KRAS* (exon 2-4), *BRAF* (exon 15) and *PI3KCA* (exon 10 and 21). Clinical parameters included: tumor localisation (right sided vs. left sided-LCRC), liver-limited disease (LLD), early tumor-shrinkage (ETS), depth of response (DPR), metastasectomy and inflammation markers (neutrophil/lymphocyte ratio-NLR). Differences in ORR, PFS and OS were calculated for subgroups using chi-square and logrank tests. Hazard ratios were calculated by Cox regression analysis. **Results:** Among 57 pts of the ITT, 50 pts were evaluable for response with an ORR of 72%, and a disease control rate of 90%. Median PFS and OS (ITT) were 9.5 (7.4-11.6) and 29.4 (16.7-42.0) months. Metastasectomy was achieved in 33.3%; grade 3/4 adverse events occurred in 52% of the ITT population, including leukocytopenia, rash and GI-toxicity. New *RAS* and *BRAF* mutations were detected in 17.4% and 13.3%, respectively with a negative impact on treatment efficacy. Pts with LCRC (75%), ETS (59.2%), secondary metastasectomy and LLD (49.1%) had significantly prolonged OS, whereas pts with high NLR (> 5; 28.6%) had inferior OS (all p-values < 0.05). Median DPR was -46.4%, and correlated significantly with PFS and OS (p < 0.01). **Conclusions:** This study supports the efficacy and safety of biweekly cetuximab given in combination with mFOLFOX6 in pts with mCRC. Extended mutational analyses of key oncogenes and routinely assessed clinical parameters can help to identify patients with maximum likelihood of benefit from anti-EGFR antibody-based immunochemotherapy. Clinical trial information: NCT01051167.

3569 Poster Session (Board #61), Mon, 8:00 AM-11:30 AM

Phase I study of preoperative chemoradiation with temozolomide and capecitabine in patients with locally advanced rectal cancer. *First Author: Yong Sang Hong, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Preoperative chemoradiation (CRT) with capecitabine is one of the standard treatment strategies in patients with locally advanced rectal cancer (LARC). Temozolomide improved survival of patients with glioblastoma when administered with radiotherapy (RT), especially in those with hypermethylated *MGMT* (O^6-methylguanine DNA methyltransferase). *MGMT* hypermethylation has been suggested as one of the colorectal carcinogenesis pathways. **Methods:** RT was delivered with 45 Gy/25 daily fractions with coned-down boost of 5.4 Gy/3 fractions. Concurrent chemotherapy consisted of fixed dose of capecitabine (825 mg/m^2 twice daily) and escalated dose of temozolomide (45 [level 1], 60 [level 2], and 75 mg/m^2/day [level 3]). *MGMT* hypermethylation was examined by methyl-specific PCR in the pre-treatment tumor samples. **Results:** Between May 2013 and Apr 2014, a total of 22 patients with LARC of cT3-4N0 or $cT_{any}N1$-2 were accrued. Dose-limiting toxicity did not occur among 10 patients up to dose level 3, and the dose level 3 was chosen as the recommended dose (RD). Additional 12 patients were accrued in the RD. There was no grade 4 adverse event (AE), and grade 3 AEs included leucopenia (9.1%), nausea (4.5%), and vomiting (4.5%). Pathologic complete responses (pCR) were observed in 7 patients (7/22, 31.8%). *MGMT* hypermethylation was found in 16 patients (16/22, 72.7%). The pCR rate was 37.5% (6/16) in the hypermethylated *MGMT* group and 16.7% (1/6) in the unmethylated MGMT group (p= 0.62). **Conclusions:** The RD of temozolomide was determined to 75 mg/m^2/day when added in the preoperative CRT with capecitabine. Preoperative CRT with temozolomide plus capecitabine was tolerable. There was a tendency of higher pCR rates in those with hypermethylated *MGMT*, therefore, further randomized study will be warranted. Clinical trial information: NCT01781403.

3570 Poster Session (Board #62), Mon, 8:00 AM-11:30 AM

S-1 as adjuvant chemotherapy for stage III colon cancer: Updated outcomes of ACTS-CC trial. *First Author: Yusuke Kinugasa, Division of Colon and Rectal Surgery, Shizuoka Cancer Center Hospital, Shizuoka, Japan*

Background: The ACTS-CC trial, a randomized phase III trial, demonstrated that adjuvant therapy with S-1 for stage III colon cancer was non-inferior in 3-year disease-free survival (DFS) to that of tegafur-uracil plus leucovorin (UFT/LV). We updated DFS and overall survival (OS), and performed some clinically relevant subgroup analyses. **Methods**: A total of 1,535 patients with stage III colon cancer were randomly assigned to receive S-1 (80-120 mg/day on days 1-28 every 42 days, 4 courses) or UFT/LV (UFT: 300- 600 mg/day and LV: 75 mg/day on days 1-28 every 35 days, 5 courses). Primary endpoint was DFS. Secondary endpoints were OS and safety. **Results:** A total of 1518 patients (758 in the S-1 group and 760 in the UFT/LV group) were included in the efficacy analysis. Median follow-up was 63.5 months, the mean age at enrollment was 64.5 years, wide lymph node dissection (D3) was done in 79.8%, the median number of dissected lymph nodes was 17, and stage IIIA/IIIB/IIIC were 15%/71%/14%. The hazard ratio (HR) for DFS was 0.88 (95%CI, 0.74-1.06; p = 0.177). The 5-year DFS rate was 70.2% in the S-1 group and 66.9% in the UFT/LV group. In the subgroup analysis, no significant interactions were identified between the major baseline characteristics and the DFS in S-1 and UFT/LV, except for histological type; favors S-1 in patients with poorly-differentiated adenocarcinoma. Approximately 5% of patients in the both groups experienced second cancers. Among the patients with recurrences in each group, 46.3% and 44.7% underwent surgical resection as an initial treatment for recurrence. The HR for OS was 0.92 (95%CI, 0.72-1.17; p = 0.488). The 5-year OS rates were 86.0% and 84.4% in the S-1 and UFT/LV group, respectively. **Conclusions:** Adjuvant therapy of S-1 for stage III colon cancer was confirmed to be non-inferior both in DFS and OS to those of UFT/LV after long follow-up. Favorable OS might be brought by the high resection rate of recurrent lesions. Clinical trial information: NCT00660894.

3571 Poster Session (Board #63), Mon, 8:00 AM-11:30 AM

Immunohistochemistry to initiate a complex screening cascade in the detection of Lynch syndrome. *First Author: Grainne O'Kane, St. James's Hospital, Dublin, Ireland*

Background: Lynch Syndrome (LS) accounts for 2-4% of all colorectal cancers (CRC) and is caused by germline mutations in DNA mismatch repair (MMR) genes. Increasing literature supports routine screening for LS using immunohistochemistry (IHC) to detect loss of MMR protein expression on tumour samples. We reviewed practices at 3 Irish cancer centres. The number of MMR deficient (dMMR) tumours detected was evaluated, and the subsequent number of genetic referrals and LS diagnoses determined. **Methods:** Colorectal databases at 3 Irish academic centres were reviewed from January 2005 - 2013. Centre 1 performs IHC upon physician request, centre 2 implemented reflex IHC (rIHC) in November 2008, and centre 3 has been performing rIHC since 2005. All new diagnoses of colorectal adenocarcinoma with available histology were included. Pathology reports were reviewed and genetic referrals analysed. **Results:** A total of 4,021 new CRC were diagnosed in 3,929 patients across 3 centres. The results are presented in the table below. The implementation of universal screening using rIHC in cancer centre 3 detected an increased number of dMMR tumours (11%, p<0.01), however this did not result in a similar increase in cancer genetics referrals or lynch syndrome diagnoses. A high proportion of patients underwent germline testing once referred. **Conclusions:** Increased IHC testing for MMR proteins results in more Lynch syndrome diagnoses. Adherence to protocols for cascade testing and appropriate clinical referral is required to realise the benefit of universal screening.

		Centre 1 (IHC when requested)	Centre 2 (rIHC since Nov 2008)	Centre 3 (rIHC since 2005)
Total new CRC with available histology	964	1246	1811	
Total patient number	949	1220	1760	
Median age yrs (range)	70 (17-97)	70 (16-97)	69 (27-96)	
No. (%) patients with IHC	153 (16%)	536(44%)	1760 (100%)	p<0.01
No. (%) patients with dMMR	32 (3%)	56 (5%)	202 (11%)	p<0.01
No. (%) dMMR pts. with BRAF testing	3 (9%)	4(7%)	56 (28%)	
No. dMMR pts. referred to genetics*	14	17	37	
No. (%) referrals who underwent germline testing	12(86%)	14 (82%)	33 (89%)	
No. (%) LS pts (of total pts)	7 (0.7%)	7 (0.6%**)	19 (1.1%***)	

* Numbers do not account for BRAF+ve patients who may not have been referred ** 2 results pending *** 7 results are pending

3572 Poster Session (Board #64), Mon, 8:00 AM-11:30 AM

Cost-effectiveness for extended RAS/RAF testing in metastatic colorectal cancer. *First Author: Marwan R. Al-hajeili, Karmanos Cancer Ctr, Grosse Pointe Farms, MI*

Background: Epithelial growth factor receptors (EGFR) inhibitors (Cetuximab and panitumumab) are monoclonal antibodies directed against EGFR and promote apoptosis. Douillard et al demonstrated the benefit of using EGFR inhibitors agents in wild type (WT) KRAS metastatic colorectal cancer (mCRC) and lack of benefit in mutated KRAS mCRC patients. Only WT KRAS mCRC are candidate for EGFR inhibitors, they constitute 57.6% of all mCRC patients, 27.3% of them carry other RAS/RAF mutations that preclude them from EGFR inhibitors benefits. Insurance companies are willing to pay the cost of KRAS testing and EGFR inhibitors treatment for all WT KRAS mCRC. We conducted this analysis to assess the cost-effectiveness of the extended testing for other RAS/RAF mutations for WT KRAS mCRC patients. **Methods:** A decision analysis model using (Treeage pro Software, Williamstown, MA) was developed to assess and compare treatment costs and disease outcomes associated with presence or absence of additional mutations (RAS/RAF) in a WT KRAS mCRC. . For utility estimate, Quality of life (QoL) assessment based on Skindex-16 for EGFR inhibitors side effects. The difference in median survival time was used to calculate incremental effectiveness of using EGFR inhibitors based on the extended testing or not. Costs were determined through Medicare records and direct hospital charges for extended testing, and treatment with EGFR inhibitors. For sensitivity analysis, we modify mutations probability and the extended testing cost, in both 1-way and combined 2-way sensitivity analyses. **Results:** The total expected cost was $56,306.06 vs. $42,683.75 favoring additional testing. The median overall survival was 15.8 vs.14.5 months favoring additional testing. In order to conclude extended testing is not worth it, mutation probability has to be less than 1.8%, or extended testing cost of more than 14000 $ in one way sensitivity testing. However, for two-way analysis, the mutation probability needs to be less than 17% and test cost needs to be more than $8,200. **Conclusions:** Our analysis shows that extended testing for other RAS/RAF mutations is cost-effective in WT KRAS mCRC patients before treating with EGFR inhibitors.

3573 Poster Session (Board #65), Mon, 8:00 AM-11:30 AM

Molecular classification of the invasive front in colorectal cancer. *First Author: Darragh McArt, CCRCB, Queen's University, Belfast, United Kingdom*

Background: Despite the use of 5-FU-based adjuvant therapies, a large proportion of stage III (locally advanced) colorectal cancer (CRC) patients will relapse and die of metastatic disease. Recent data from phase III trials using the anti-VEGF or the anti-EGFR mAbs have shown that, in contrast to the metastatic setting, these agents do not prolong survival in stage III CRC. Therefore, novel drugs are needed that result in further increases in overall survival in stage III CRC patients. The aim of this study was to investigate the invasive front of stage III CRC at the molecular level and correlate with clinical and pathological variables. **Methods:** mRNA was extracted from macrodissected FFPE CRC, central tumour and invasive front from 25 patients. Transcriptional analysis was performed using the CRC DSA microarray. Samples were analysed using limma for lists of differential expressed genes and using a supervised learning approach, pamr, to extract succinct gene lists between contrasts and visualised with bootstrap clustering and heatmaps. Expression of E-cadherin was measured using IHC. **Results:** IHC staining showed loss of E-cadherin expression in tumour cells at the invasive front, in keeping with an epithelial-to mesenchymal transition (EMT). Limma and pamr analysis depicted strong overlap of probes to differentiate central tumour from the invasive front. Prominent classifiers evidenced included genes with a role in inflammation and immune signalling (eg. CXCL5, C7, IL8), EMT (eg. SFRP2, WNT5A) and growth factor receptor signalling (eg. IGF1). Comparison of this expression list with the recent published gene lists, characterizing the poorest prognostic EMT/stem-cell like subgroup, showed that there is a high degree of overlap between these two signatures. **Conclusions:** Taken together, our study is the first to indicate that, in order to disseminate and metastasize, tumour cells at the invasive front develop an EMT phenotype with a molecular signature, similar to the poor prognostic stem-like molecular CRC subgroup. This data could aid in the identification of novel treatment strategies to prevent tumour recurrence/metastasis in stage III CRC.

3574 Poster Session (Board #66), Mon, 8:00 AM-11:30 AM

Zonal differences in PD-1 expression in centre of tumour versus periphery in microsatellite stable and unstable colorectal cancer. *First Author: Grainne O'Kane, The Mater Misericordiae University Hospital, Dublin, Ireland*

Background: Colorectal cancers that show evidence of microsatellite instability (MSI-H) are marked by a high tumour infiltrating lymphocyte population (TiL) which is thought to be prognostic. Programmed Death-1(PD-1) is a negative regulator of the immune system and targeting the interaction with its ligand PD-L1 offers a potential therapeutic target in many malignancies. We aimed to characterize CD8 and PD-1 expression in both the tumour centre and tumour periphery of microsatellite stable (MSS) and unstable colorectal cancers. **Methods:** Paraffin-embedded tumour blocks were cut at 5um, prepared and stained using specific antibodies for CD8 and PD-1. The tumour periphery was defined as the area within a 400x high power field (HPF) from the outline of the tumor. The tumour centre was defined as the area at least one 400x HPF apart from the tumour outline toward the centre of the tumour. Images were taken at 40x, 100x, 200x and 400x. Positive cells were averaged across 3 high power fields and classified as high or low positivity. **Results:** Forty-two specimens have been analysed to date including 28 MSI-H and 13 MSS tumours. Sixty-eight percent of MSI-H specimens were stage II and 69% of MSS were stage III. In the MSI-H group, a high CD8 count in the tumour centre and tumour periphery correlated with earlier tumour size and stage. PD-1 positivity was seen in 61% of MSI-H tumour centres compared to no positivity in the tumour centres of MSS specimens. The periphery of both MSS and MSI-H specimens showed significant PD1 expression with 71% and 85% of samples showing positivity respectively. There was no association between high or low densities of staining and stage. **Conclusions:** Zonal differences exist in the expression of CD8 and PD-1 in microsatellite stable and unstable tumours. A high proportion of MSI-H tumours show PD-1 activity in the centre of the tumour despite an improved prognosis. Further profiling of other T cell populations may help to further understand this expression which may act as a biomarker or provide a therapeutic target.

3575 Poster Session (Board #67), Mon, 8:00 AM-11:30 AM

A phase III, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of pregabalin in the prevention and reduction of oxaliplatin-induced painful neuropathy (PreOx). *First Author: Daniel Ciampi de Andrade, Instituto do Câncer de São Paulo Octavio Frias de Oliveira, São Paulo, Brazil*

Background: Patients with colorrectal cancer receiving Oxaliplatin usually develop acute and chronic painful chemotherapy-induced peripheral neuropathy (CIPN). Despite having different mechanisms, both conditions lead to central sensitization (CS). Recent data suggest that the degree of CS after acute use of Oxaliplatin increases the risk of painful CIPN. We hypothesized that preemptive use of anti-hyperalgesic drug (pregabaline) during Oxaliplatin infusions would decrease the incidence of chronic painful CIPN. **Methods:** Pain-free, chemotherapy-naïve patients (stage III/IV) receiving at least one complete cycle of modified FLOX (5-FU+leucovorin for 6 consecutive weeks+oxaliplatin 85 mg/m2 at weeks 1, 3 and 5, every 8 weeks) were randomised (1:1). Eligible patients received either pregabaline or placebo (150-600mg/d) for three days before and three days after each oxaliplatin infusion. Patients were followed for 3-6 months after the end of chemotherapy. Clinical assessments were performed at baseline, at the end of chemotherapy treatment and after the followup period. The main outcome was average pain at the last visit assessed by the visual numerical scale (0-10) item of the Brief Pain Inventory in pts with neuropathic pain according to the Douleur Neuropathique-4 score (DN4). Secondary endpoints were pain interference (BPI), pain dimensions (McGill Pain Questionnaire), score of the Neuropathic Pain Symptom Inventory (NPSI). **Results:** 206 patients (56.6±11yo, 111 female) were enrolled. Both groups presented similar baseline demographic characteristics ($p > 0.20$). The cumulative dose of oxaliplatin was similar between groups throughout the study. Data from 82 patients in the pregabaline and 84 in the placebo group were retained for analises. At the last visit, pain intensity in the pregabaline group was 0.85±2.35 and 0.88±2.40 in the placebo group ($p = 0.673$). Scores from other pain scales did not differ between groups. **Conclusions:** The preemptive use of the antihyperalgesic drug pregabaline during oxaliplatin infusions was safe, but did not decrease the incidence of chronic pain related to CIPN. Clinical trial information: NCT0145016.

3576 Poster Session (Board #68), Mon, 8:00 AM-11:30 AM

Placebo-controlled, double-blinded multi-center phase III trial of XELIRI/FOLFIRI plus simvastatin in metastatic colorectal cancer. *First Author: Sung Hee Lim, Samsung Medical Center, Seoul, Korea South*

Background: The purpose of this randomized phase III trial was to evaluate the addition of synthetic 3-hydroxy-3methyglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin to XELIRI/FOLFIRI in patients with previously treated metastatic colorectal cancer. **Methods:** We undertook a double-blind, placebo-controlled phase III trial of 269 patients with previously treated metastatic colorectal cancer, enrolled to 5 centers in South Korea. Patients were randomly assigned (1:1) to receive irinotecan 180 mg/m^2 as a 90-min infusion followed by leucovorin 200mg/m^2 in a 2-h infusion, and then 5-FU 400mg/m^2 bolus injection followed by 2400mg/m^2 as a 46-h continuous infusion (FOLFIRI) or irinotecan 250mg/m2 as a 90-min infusion with capecitabine 1000mg/m^2 twice daily for 14days (XELIRI) plus simvastatin (134 patients) or XELIRI/FOLFIRI plus placebo (135 patients). The primary end point was progression-free survival (PFS) and secondary end points included response rate, duration of response, overall survival (OS), time to progression (TTP) and toxicity. **Results:** Between April 2010 and July 2013, 269 patients were enrolled and assigned to treatment groups (134 simvastatin, 135 placebo). The median progression-free survival (PFS) was 5.9 months (95% CI, 4.5-7.3) in XELIRI/FOLFIRI plus simvastatin group and 7.0 months (95% CI, 5.4-8.6) for XELIRI/FOLFIRI plus placebo group ($P = 0.937$). There was no significant difference in overall survival (median, 15.9 months (simvastatin) vs. 19.9 months (placebo), $P = 0.826$). Grade 3 or higher grade nausea and anorexia were noted slightly more in patients with simvastatin arm compared to placebo arm (4.5 vs 0.7%, 3.0 vs 0% respectively). **Conclusions:** These results show that the addition of 40mg simvastatin to XELIRI/FOLFIRI did not improve PFS in previously treated metastatic colorectal cancer although it does not increase toxicity. Clinical trial information: NCT01238094.

3577 Poster Session (Board #69), Mon, 8:00 AM-11:30 AM

A randomized controlled trial to evaluate laparoscopic versus open with Japanese D3 dissection for stage II,III colorectal cancer (CRC): First efficacy results from Japan Clinical Oncology Group Study JCOG0404. *First Author: Tomonori Akagi, Oita University Faculty of Medicine, Department of Gastroenterological and Pediatric Surgery, Oita, Japan*

Background: The benefits of laparoscopic surgery (LAP) compared with open surgery (OP) have been suggested; however, the long-term survival of LAP for advanced CRC requiring Japanese D3 dissection is still unclear. We conducted a trial to confirm the non-inferiority of LAP to OP in terms of overall survival (OS). Favorable short-term complications and clinical benefits of LAP have already been demonstrated. Overall survival, the primary endpoint, and late post-operative complications are presented here. **Methods:** Only accredited surgeons from 30 Japanese institutions participated. Eligibility criteria included histologically proven CRC; tumor located in the cecum, ascending, sigmoid or rectosigmoid colon; T3 or deeper lesion without involvement of other organs; N0-2 and M0; tumor size = < 8 cm; age 20-75 years. Patients with pathological stage III received adjuvant chemotherapy with fluorouracil plus leucovorin. The planned sample size was 1050 patients with a power of 80%, a one-sided alpha of 5% and the non-inferiority margin of the hazard ratio (HR) as 1.366. **Results:** A total of 1057 patients were randomized (OP 528, LAP 529) between October 2004 and March 2009. Conversion to OP was needed for 29 patients in LAP arm. 5-year OS was 90.4% (95%CI: 87.5-92.6%) in OP, and 91.8% (89.1-93.8%) in LAP. The non-inferiority of laparoscopic D3 in OS was not demonstrated (HR: 1.06 [90%CI: 0.79-1.41(> 1.366)], p = 0.073). 5-year RFS was 79.7% (76.0-82.9) in OP and 79.3% (75.6-82.6) in LAP (HR: 1.07 [95%CI: 0.82-1.38]). Proportion of grade (G) 2-4 late complications was 22.6% (OP 12.5%, LAP 10.1%). Late complications (G2-G4) included constipations (OP 6.0%, LAP 4.4%), diarrhea (OP 2.9%, LAP 2.7%), paralytic ileus (OP 1.2%, LAP 1.7%), and bowel obstruction of small intestine (OP 3.1%, LAP 2.1%). **Conclusions:** The non-inferiority of laparoscopic D3 in OS was not demonstrated for stage II,III CRC. However, since OS of both arms are almost identical and better than expected, laparoscopic D3 is acceptable as a treatment option for stage II,III CRC. Clinical trial information: NCT00147134.

3578 Poster Session (Board #70), Mon, 8:00 AM-11:30 AM

Effect of Sym004 on acquired resistance to cetuximab in colorectal cancer (CRC) in a novel mouse avatar model. *First Author: Deepak B. Vangala, Department of Medicine, Knappschaftskrankenhaus, Ruhr-University Bochum, Bochum, Germany*

Background: Monoclonal antibodies against EGFR have shown improved survival for mCRC-patients in clinical trials. Unfortunately, virtually all patients acquire resistance to these agents during the course of treatment. Preclinical models of acquired resistance with close resemblance to the patient tumor are lacking. Sym004, a novel monoclonal anti EGFR antibody mixture has shown to overcome cetuximab (c-mab) resistance in HNSCC cell lines. **Methods:** Samples of 100 CRC patients undergoing surgery were implanted subcutaneously in nude mice. Treatment cohorts of 10 wildtype (WT for KRAS, BRAF, NRAS, PI3K) tumors and 3 tumors with either KRAS, BRAF or PI3K mutation respectively were generated for i.p. treatment with Sym004, c-mab (25mg/kg biw) or control. Primary observational period was 29 days. In case of response, treatment was continued until acquired resistance – defined as tumor doubling after primary observational period – arose. **Results:** Tumors with KRAS, BRAF or PI3K mutations were resistant to c-mab. All but two tumors with WT-status responded to c-mab and Sym004 during primary observational period (stable disease or tumor regression). Sym004 showed a significantly deeper response in 4 cases at day 29. Acquired resistance for c-mab developed in 4 tumors at days 33, 48, 60 and 71, respectively. In two of these cases tumor volume was stable with Sym004 and in the other two cases acquired resistance developed with substantial delay (d60 vs d33, d105 vs d60). Complete remission with c-mab and Sym004 occurred in two cases, one of which faster with Sym004 and lasting 100 days beyond end of treatment (c-mab: 10 days). **Conclusions:** Here, we present the first preclinical patient derived xenograft model of acquired resistance to anti-EGFR targeted therapy in CRC. We show that Sym004 is able to generate a deeper and prolonged response in 5 of 10 tested WT CRC patient derived tumors. This superior response rate of Sym004 suggests that clinical trials of Sym004 in CRC are warranted. Lastly, our successful proof of principle experiments for *in vivo* modeling of secondary resistance in CRC indicate that this strategy can serve as a testing platform for treatment optimization of targeted therapy addressing secondary resistance.

3579 Poster Session (Board #72), Mon, 8:00 AM-11:30 AM

Long-term outcome after R1 resection for colorectal liver metastases: Is a cure possible? *First Author: Isamu Hosokawa, Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France*

Background: Increasingly efficient chemotherapy regimens have improved the outcomes after R1 resection (tumor-free margin < 1 mm) for colorectal liver metastases (CLM). However the long-term survival benefit and the potential of cure after R1 resection are not clearly demonstrated. The aim of this study was to evaluate long-term outcomes after R1 resection using an aggressive strategy consisting of modern perioperative chemotherapy and repeated surgeries, and to define factors predictive of cure after R1 resection. **Methods**: All resected CLM patients at our institution from 2000 to 2009 were prospectively evaluated. Exclusion criteria were: presence of extrahepatic disease, use of ablative treatment modalities, and incomplete macroscopic (R2) resection. Cure was defined as a disease-free interval ≥ 5 years from last hepatic or extrahepatic resection to last follow-up. **Results**: Of 639 patients consecutively resected for CLM, 384 (60%) were eligible for the study, 193 (30%) of whom underwent R0 resection (tumor-free margin ≥ 1 mm), and 191 (30%) underwent R1 resection. The 5-year overall survival rates (OS) for patients with R0 resection and R1 resection were 65% and 56%, respectively (P = 0.15). Of the 191 patients who underwent R1 resection, 121 patients had a more than 5 years follow-up. Of these, 23 patients (19%) were considered "cured" and 88 patients (73%) were considered "non-cured". For the included 111 patients, after a mean follow-up of 57 months, 5- and 10-year OS were 47% and 32%, respectively, and disease-free survival rates were 15% and 14% at 5 and 10 years, respectively. Although there were no significant differences in the number or maximum size of metastases at diagnosis between the two groups, cured patients more often responded to first-line chemotherapy (P = 0.02) with fewer cycles (P = 0.002). Independent predictive factors of cure included: ≤ 10 total cycles of preoperative chemotherapy and objective response following preoperative chemotherapy. **Conclusions:** In the era of modern chemotherapy, cure can be achieved overall in 19% of patients after R1 resection for CLM. The best conditions to achieve cure after R1 resection rely on a good response to an efficient and relatively short first-line chemotherapy.

3580 Poster Session (Board #73), Mon, 8:00 AM-11:30 AM

Continuing single-agent capecitabin as maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of metastatic colorectal cancer. *First Author: Rui-hua Xu, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Colorectal cancer (CRC) is one of the most common malignant tumors. All advanced CRC will progress after first-line treatment. Therefore, it is emergent to seek an efficient and low toxic maintaining regimen to prolong progression free survival (PFS). Some clinical researches demonstrated that maintaining treatment followed first-line treating could extend PFS. Our previous non-randomized small sample study indicated that patients receiving first-line treatment of XELOX followed by capecitabine as maintaining therapy had significantly prolonged median time to progression (TTP). Therefore, we plan to initiate the first randomized study to evaluate the efficacy and safety of maintenance therapy with capecitabine following induction of (XELOX) or (FOLFOX) versus observation until progression in first-line therapy in metastatic CRC. **Methods:** This is a multi-center, randomized phase III study. Patients who received 18-22 weeks chemotherapy with XELOX or FOLFOX and achieved objective response or stable disease were randomized 1:1 to received maintenance therapy of capecitabine (1,000 mg/m^2 twice a day from days 1–14, every 3 weeks) or only observation until disease progression. The primary endpoint was PFS, which was defined as the interval between initial treatment and the first documentation of disease progression or death. **Results:** The intent-to-treat population comprised 275 patients (capecitabine maintenance, n= 136; observation, n=139); there were no significant differences in baseline characteristics. The median follow-up was 29.0 months (range, 0–62.5 months). Median PFS in capecitabine maintenance group was significantly longer than the observation group (11.0 months [95% confidence interval (CI) 9.45 to 12.5m] versus. 8.0months, [95%CI 7.2m to 8.8m]; p < 0.001). The most common grade 3 or 4 toxicities in capecitabine maintenance versus observation were neutropenia, hand–foot syndrome, and mucositis. **Conclusions:** Maintenance therapy with capecitabine single agent following induction of XELOX or FOLFOX improved the outcome in patients with mCRC, as compared with the observation group. Clinical trial information: NCT02027363.

3581 Poster Session (Board #74), Mon, 8:00 AM-11:30 AM

Baseline carcinoembryonic antigen (CEA) serum levels to predict bevacizumab-based treatment response in patients with KRAS exon wild-type metastatic colorectal cancer (mCRC) receiving 1st-line therapy with FOLFIRI plus cetuximab or bevacizumab (AIO KRK0306, FIRE3 trial). *First Author: Marlies Michl, Department of Hematology and Medical Oncology and Comprehensive Cancer Center, University Hospital Grosshadern, LMU Munich, Munich, Germany*

Background: Recently, Prager et al. proposed the hypothesis that carcinoembryonic antigen (CEA) is involved in tumor angiogenesis and therefore might predict bevacizumab-based treatment response in metastatic colorectal cancer (mCRC) (Cancer Research, 2013; Cancer Science, 2014). The present study aimed to evaluate this hypothesis in the FIRE-3 trial where patients (pts) with KRAS exon 2 wild-type mCRC were randomized to receive first-line chemotherapy with either FOLFIRI + cetuximab (cet) or FOLFIRI + bevacizumab (bev). **Methods:** Baseline CEA levels were analyzed either as continuous variable (ln) or categorized in two groups ($\leq$ / $>$ 25% quartile; $\leq$ / $>$ 6.2ng/ml) with regard to their predictive impact on PFS and OS in the two different treatment arms. Correlations relied on Cox regression analysis. Survival was estimated by Kaplan-Meier. **Results:** For analysis of CEA, 522/592 pts (cet: 257 pts; bev: 265 pts) were eligible. When CEA baseline level was evaluated as a continuous variable, CEA (ln) was inversely correlated with PFS (p= 0.02) and OS (p= 0.001) in the bev arm, but not in the cet arm. Using the 25% quartile of CEA as a cut-off, only in the bev arm an effect on OS (24.2 mo vs. 33.3 mo; HR 0.60; CI95%:0.41-0.88; p= 0.009) and PFS (10.4 mo vs. 11.7 mo; HR 0.67; CI95%:0.48-0.94; p= 0.02) was observed, but not in the cet arm. Pts with high CEA baseline levels ($>$ 6.2ng/ml) showed a shorter OS in the bev arm compared to the cet arm (bev: 24.2 mo vs. cet: 30.0 mo; HR 1.52; CI95%:1.16-2.00; p= 0.002). In pts with low CEA baseline level ($\leq$ 6.2ng/ml) no significant survival difference was observed between arms (HR 0.92; CI95%:0.58-1.44; p= 0.70). Univariate analysis identified CEA as an independent predictor of OS in the bev arm, but not in the cet arm. **Conclusions:** The present analysis supports the hypothesis that CEA acts as a predictor of bev activity, while outcome parameters in the cet arm are not affected by baseline CEA. Patients with elevated CEA baseline levels appeared to benefit from anti-EGFR directed therapy, while anti-VEGF based treatment was inferior.

3582 Poster Session (Board #75), Mon, 8:00 AM-11:30 AM

A phase III multicenter trial comparing two different sequences of second/third line therapy (irinotecan/cetuximab followed by FOLFOX-4 vs. FOLFOX-4 followed by irinotecan/cetuximab in K-RAS wt metastatic colorectal cancer (mCC) patients refractory to FOLFIRI/Bevacizumab. *First Author: Stefano Cascinu, Clinica di Oncologia Medica, Università Politecnica delle Marche, AO Ospedali Riuniti, Ancona, Italy*

Background: Improvements in survival have been reported in mCC with the addition of bevacizumab or cetuximab to chemotherapy. However, their efficacy in different therapy lines and the optimal sequence are still controversial. While bevacizumab seems to lose its efficacy along the course of treatment lines, cetuximab is active even in 2° and 3° line therapy. We designed a randomised, phase III study to compare efficacy and safety of two different sequences of Cetuximab or FOLFOX to optimize the treatment of mCC pts refractory to FOLFIRI/bevacizumab. **Methods:** Pts were randomised in a 1:1 ratio to receive as 2° or 3° line cetuximab/irinotecan followed by FOLFOX-4 (Arm A) or FOLFOX-4 followed by cetuximab/irinotecan (Arm B). Primary end point was progression free survival (PFS); secondary end points were overall survival and toxicity. **Results:** 109 mCC pts were enrolled and 108 were evaluable for analysis. 63 patients were males and 45 females, with a median age of 61 years. Efficacy results are reported in the table. Treatments were well tolerated with a low number of serious adverse reactions in both arms (8 and 4, respectively), even if grade 3-4 toxicity was overall higher in cetuximab treatment. **Conclusions**: While the primary end point was not met (PFS was not statistically different), FOLFOX seems to be more effective than cetuximab (overall survival: 18.6 months vs 12.4 months) as 2° line treatment in patients receiving bevacizumab/FOLFIRI. This seems to confirm preclinical and clinical (FIRE-3) data suggesting that a prior anti-VEGF therapy may determine a lower sensitivity to a subsequent anti-EGFR treatment. Clinical trial information: NCT01030042.

Evaluable patients	Arm A (54 patients)	Arm B (54 patients)	Hazard Ratio (Arm B vs. Arm A) (95% confidence interval)
ORR			
II line	**15/52 (29%)**	**21/52 (40%)**	
III line	**7/30 (23%)**	**8/38 (21%)**	
PFS (median) (months)	9.9	11.3	HR = 0.85 (0.56-1.28); p = 0.42
OS (median) (months)	12.4	18.6	HR = 0.79 (0.52-1.22); p = 0.28
Treatment compliance			
Completed			
II line	66.7%	70.3%	
III line	80%	71%	

Arm A: CETUXIMAB followed by FOLFOX; **Arm B**: FOLFOX followed by CETUXIMAB

3583 Poster Session (Board #76), Mon, 8:00 AM-11:30 AM

HER3 as a biomarker of prognosis and panitumumab (Pan) benefit in *RAS*-wt advanced colorectal cancer (aCRC). *First Author: Jenny F. Seligmann, University of Leeds, Leeds, United Kingdom*

Background: EGFR pathway activation is important in aCRC, but EGFR expression is not predictive for anti-EGFR drug efficacy. Signalling occurs across ErbB receptors and EGFR may mediate oncogenesis by dimerization with other receptors, including HER3. Therefore, we here explore HER3 mRNA expression as a biomarker of prognosis and predictor of Pan benefit in a randomized trial in aCRC. **Methods:** HER3 expression, *KRAS*, *NRAS* and *BRAF* mutations were assessed in tumor from 308 patients (pts) randomized to 2nd-line irinotecan (Ir) or IrPan (PICCOLO, *Lancet Onc* 14:749-59). Prognostic analysis was in all Ir alone pts. Predictive analysis, in the 208 *RAS*-wt pts, compared baseline values with outcomes using Cox proportional hazards models. HER3 was treated first as a continuous variable; an exploratory binary model of high *vs* low expression was also tested. **Results:** Higher HER3 was significantly prognostic for OS (HR [per 2-fold change] = 0.91 [0.83-0.99], p = 0.04), but not PFS (HR = 0.93 [0.83-1.05], p = 0.25). Higher HER3 was associated with PFS benefit in IrPan-treated pts (HR = 0.71 [0.61-0.82], p $<$ 0.001), but not Ir-treated pts (HR = 0.96 [0.82-1.13], p = 0.65). There was a strong biomarker/treatment interaction (p = 0.001), which remained after adjustment for *BRAF* status and primary tumor location; this was also seen for OS (interaction p = 0.004). HER3 status (above/below 66th centile) was not prognostic for OS (p = 0.35) or PFS (p = 0.86). However, it was predictive of Pan benefit: in *RAS*-wt pts with high HER3, median PFS was 8.2 mo (IrPan) vs 4.4 mo (Ir) (HR = 0.33 [0.19-0.58], p $<$ 0.001); but pts with low HER3 had no benefit: 3.3 mo (IrPan) vs 4.3 mo (Ir) (HR = 0.96 [0.67-1.38], p = 0.84); interaction p = 0.002. A predictive effect was also seen for OS (interaction p = 0.01). **Conclusions:** Among *RAS*-wt pts, HER3 hold promise as a predictive biomarker for Pan benefit. High HER3 identified 1/3rd who gained markedly from Pan, *vs* 2/3^{rds} who did not benefit, with statistically significant biomarker/treatment interactions for PFS and OS. This finding is of potential clinical utility, and deserves further study to confirm.

3584 Poster Session (Board #77), Mon, 8:00 AM-11:30 AM

DYPD genotyping to predict toxicity in patients with stage III colon cancer treated with 5-fluorouracil-based adjuvant chemotherapy in the PETACC-8 phase III trial. *First Author: Valérie Boige, Service de Gastro-Enterologie, Institut Gustave Roussy, Villejuif, France*

Background: Previous pharmacogenetic studies have shown the prognostic impact of several rare dihydropyrimidine dehydrogenase gene (DPYD) variants on 5-FU-related toxicity. However, conflicting results highlight the need for prospective validation in large homogeneous patient populations uniformly treated with current standard combination therapies used in colon cancer (CC). **Methods:** We genotyped 1545 patients with resected stage III CC treated in the PETACC-8 randomized phase III trial with adjuvant FOLFOX-4 alone or combined with cetuximab, and tested the individual associations between 25 DPYD variants and 5FU-related adverse events (5FUAEs). Logistic regressions were used to assess univariate and multivariable associations. **Results:** The incidence of grade $\geq$ 3 5FUAEs in D949V and V732I (DPYD*6) carriers were 18/21 (85.7%) and 121/199 (60.8%), respectively. After adjusting for multiple variables, statistically significant associations were identified between grade $\geq$ 3 5FU-AEs and both D949V (OR = 6.3; 95% CI = 0.037-0.49; p = 0.0007) and V732I variants (OR = 6.3; 95% CI = 0.037-0.49; p = 0.0004). Both SNPs were significantly associated with grade $\geq$ 3 overall hematologic toxicity (p = 0.0006 and 0.00002, respectively), and V732I with grade $\geq$ 3 neutropenia (0.0002). The association for D949V and V732I with the occurrence of grade $\geq$ 3 hematologic toxicity was validated in an independent cohort of 339 patients with metastatic colorectal cancer receiving FOLFOX in the FFCD2000-05 phase III trial (p = 0.02 and p = 0.001, respectively). **Conclusions:** In this large phase III study, statistically significant associations were found between DPYD variants (D949V and V732I) and increased incidence of grade 3 or greater 5FU-AEs in patients treated with adjuvant 5-FU-based combination chemotherapy.

3585 Poster Session (Board #78), Mon, 8:00 AM-11:30 AM

Outcomes for FOLFIRI plus bevacizumab (BEV) or cetuximab (CET) in patients previously treated with oxaliplatin-based adjuvant therapy: A combined analysis of data from FIRE-3 and CALGB 80405. *First Author: Volker Heinemann, Department of Internal Medicine III and Comprehensive Cancer Center, Klinikum Grosshadern, Ludwig-Maximilians University of Munich, Munich, Germany*

Background: mCRC previously treated with adjuvant therapy may differ biologically from untreated mCRC. This study examines outcomes for BEV vs. CET in the patients on FIRE-3 and C80405 who previously received adjuvant oxaliplatin (OX). **Methods:** In both studies, pts with KRAS wt (codons 12 and 13) mCRC and performance status 0-1 were treated with standard chemotherapy and randomized to either CET 400 mg/m2 X 1, then 250 mg/m2 qw or BEV 5 mg/kg q2w. Rx continued until progression, death, unacceptable toxicity, or surgery with curative intent. Patients previously treated with adjuvant oxaliplatin ($<$ 12 months prior to enrollment in 80405, $<$ 6 months prior for FIRE-3) were identified for this analysis. **Results:** 125 patients received adjuvant OX (67 from 80405 and 58 from FIRE-3); 56 were randomized to BEV and 69 to CET. Baseline demographics were similar for both treatment groups and similar between patients enrolled in FIRE-3 vs. 80405. All received FOLFIRI as the chemotherapy regimen. In the combined analysis, CR + PR in the CET arm vs. BEV was 58% vs 42%, respectively (chi square p = 0.08). PFS was 11.3 mos for BEV and 10.2 mos for CET (HR 1.2, p = 0.24) with 117 PFS events. Median OS for BEV was 41.0 mo vs. 28.5 mo for CET (HR 1.4, p = 0.18) with 79 OS events. **Conclusions:** No significant difference in OS by biologic was found in this unplanned subset analysis. Patients with prior OX exposure had very good overall outcomes with both biologics.

3586 Poster Session (Board #79), Mon, 8:00 AM-11:30 AM

Final results from ASPECCT: Randomized phase 3 non-inferiority study of panitumumab (pmab) vs cetuximab (cmab) in chemorefractory wild-type (WT) *KRAS* exon 2 metastatic colorectal cancer (mCRC). *First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Adelaide, Australia*

Background: The primary analysis of ASPECCT demonstrated that pmab was non-inferior to cmab for overall survival (OS) in chemorefractory WT *KRAS*mCRC. Here, we report the final analysis of ASPECCT. **Methods:** In ASPECCT, patients (pts) had WT *KRAS*mCRC, ECOG performance status (PS) $\leq$2, prior irinotecan, oxaliplatin, and fluorouracil treatment, and no prior anti-EGFR therapy. Pts were stratified by geographic region (North America/Western Europe/Australia vs rest of world) and ECOG PS (0-1 vs 2) and randomized 1:1 to receive pmab 6 mg/kg q2w or cmab 400 mg/m2 followed by 250 mg/m2 qw. The primary endpoint was OS assessed for non-inferiority (retention of $\geq$50% of the cmab effect vs best supportive care [BSC]; HR=0.55 [95% CI: 0.41 - 0.74] based on NCIC CTG C0.17). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. All pts were followed for survival for up to 2 years after the last pt was randomized and a final analysis of efficacy and safety was conducted. No formal hypothesis testing was performed. **Results:** 999 pts were randomized and treated: 499 pmab and 500 cmab. 90% of pts had died at the time of this analysis (78% in the previously reported primary analysis). Baseline demographics and disease characteristics were similar between arms. Non-inferiority results for OS are shown (Table). Overall, any grade and grade 3-4 adverse events (AEs) were similar between arms. AEs of interest were (pmab vs cmab): grade 3-4 skin toxicity 13% vs 10%, grade 3-4 infusion reactions 0.5% vs 2%, and grade 3-4 hypomagnesemia 7% vs 3%. **Conclusions:** Consistent with the primary analysis, the final analysis of ASPECCT showed that pmab was non-inferior to cmab for OS in chemorefractory WT *KRAS*mCRC. Safety profiles were as expected for pmab and cmab. Clinical trial information: NCT01001377.

	Pmab N = 499	Cmab N = 500
Median OS, mos (95% CI)	10.2 (9.4-11.4)	9.9 (9.0-10.8)
HR (95% CI)	0.94 (0.82-1.07)	
***P* value**	0.0002	
OS retention rate*	1.11 (0.88-1.33)	
Median PFS, mos (95% CI)	4.2 (3.2-4.8)	4.4 (3.2-4.8)
HR (95% CI)	0.98 (0.87-1.12)	
ORR,% (95% CI)	21.6 (18.1-25.5)	19.2 (15.8-22.9)

*Rate of cmab OS benefit (cmab:BSC) retained by pmab.

3587 Poster Session (Board #80), Mon, 8:00 AM-11:30 AM

Randomized phase 3 study of panitumumab (pmab) vs cetuximab (cmab) in chemorefractory wild-type (WT) *KRAS* exon 2 metastatic colorectal cancer (mCRC): outcomes by hypomagnesemia (hypomag) in ASPECCT. *First Author: Marc Peeters, Antwerp University Hospital and University of Antwerp, Edegem, Belgium*

Background: ASPECCT met its primary endpoint of non-inferiority of overall survival (OS) of pmab vs cmab. We evaluate outcomes by hypomag, an on-treatment, anti-EGFR related adverse event that develops due to the inhibition of EGFR function. Conflicting reports have suggested hypomag is associated with survival. **Methods:** Patients (pts) with previously treated WT *KRAS* exon 2 mCRC were randomized 1:1 to receive pmab or cmab. The primary endpoint was non-inferiority of OS. Progression-free survival (PFS) and objective response rate (ORR) were secondary endpoints. Pts were categorized $\pm$ any grade hypomag during the study and data from the primary analysis was evaluated by treatment arm. Analysis of Mg supplementation during hypomag was not conducted. **Results:** 999 pts were randomized and treated: 499 pmab, 500 cmab. Any grade hypomag was 28.8% and grade $\geq$3 was 7.3% in the pmab arm vs 18.9% and 2.6% in the cmab arm, respectively. Median time to first hypomag onset was 82 days in the pmab arm and 57 days in the cmab arm. In the pmab arm, 1.0% of pts discontinued treatment and 5% of pts had dose modifications due to hypomag vs $<$0.5% and 3% in the cmab arm, respectively. Results are shown (Table). **Conclusions:** In ASPECCT, rates of hypomag were higher in the pmab vs the cmab arm. Pts who developed any grade hypomag with pmab or cmab had higher ORR, PFS, and OS compared with those pts who did not. Clinical trial information: NCT01001377.

Pmab Arm	Hypomag – Yes (n = 143)	Hypomag – No (n = 353)	HR (95% CI)
Median OS - mos (95% CI)	13.8 (11.6 – 15.5)	8.7 (8.1 – 9.8)	0.61 (0.48 – 0.77)
Median PFS - mos (95% CI)	6.7 (5.2 – 6.8)	3.0 (2.8 – 3.1)	0.46 (0.37 – 0.56)
ORR[a] - % (95% CI)	34.5 (26.7 – 42.9)	16.9 (13.1 – 21.2)	
Odds Ratio (95% CI)	2.71 (1.67 – 4.34)		
Median duration of treatment - wks (range)	28.0 (6.3 – 88.0)		11.7 (2.0 – 130.0)
Cmab Arm	**Hypomag – Yes (n = 95)**	**Hypomag – No (n = 408)**	**HR(95% CI)**
Median OS - mos (95% CI)	12.5 (10.0 – 14.8)	9.4 (8.3 – 10.5)	0.70 (0.55 – 0.91)
Median PFS - mos (95% CI)	6.6 (5.0 – 6.8)	3.2 (3.0 – 4.0)	0.53 (0.42 – 0.68)
ORR[a] - % (95% CI)	28.0 (19.1 – 38.2)	17.9 (14.2 – 22.0)	
Odds Ratio (95% CI)	1.81 (1.02 – 3.15)		
Median duration of treatment - wks (range)	27.0 (4.0 – 94.3)		14.0 (1.0 – 69.9)

[a]Evaluable pts per modified RECIST.

3588 Poster Session (Board #81), Mon, 8:00 AM-11:30 AM

A single arm phase II study of neoadjuvant transarterial regional therapy (TACE) using preloaded Irinotecan Beads in patients with resectable colorectal liver metastases (CRLM). *First Author: Robert Peter Jones, University of Liverpool, Liverpool, United Kingdom*

Background: Perioperative chemotherapy confers 3-year progression free survival advantage following CRLM resection. Good pathologic response is associated with improved overall survival. Chemoembolisation using DEBIRI gives sustained delivery of drug directly to tumor, thereby maximising response and reducing systemic exposure. This study examined the safety and feasibility of neoadjuvant DEBIRI before CRLM resection and subsequent early disease free survival (DFS). **Methods:** Patients with resectable CRLM received segmental DEBIRI (median dose 100 mg Irinotecan, range 25-200) 1 month before surgery, with radiological endpoint of near stasis during the procedure. Primary study end-point: tumor resectability. Secondary end-points: safety; radiologic response (RECIST); pathologic tumor response; disease-free survival. **Results:** 40 patients received DEBIRI-TACE. All proceeded to surgery, 38 underwent hepatectomy (2 peritoneal disease, resectability rate 95%). 30-day post-operative mortality 5% (n = 2), neither death TACE related (1 intraoperative pneumomediastinum, 1 aspiration pneumonia). 66 lesions (median 2 per patient) resected. RECIST at 1 month demonstrated 60% stable disease/partial response (24/40). Histologic major or complete pathologic response in 77.3% of targeted lesions (51/66). Correlation between radiologic and histologic response was poor. At 12-month follow-up, 18/40 (45.0%) of patients had disease recurrence (56% intrahepatic, 44% extrahepatic) (55% 1 year DFS). 2 patients died of recurrent disease (95% 1 year overall survival). **Conclusions:** Resection after neoadjuvant DEBIRI-TACE for CRLM is feasible and safe. Single treatment with DEBIRI-TACE resulted in tumor pathologic response and 1 year DFS similar to that seen after neoadjuvant systemic chemotherapy. RECIST at 1 month did not correlate with pathologic response or 1 year DFS. Clinical trial information: NCT00844233.

3589 Poster Session (Board #82), Mon, 8:00 AM-11:30 AM

Treatment until progression: Data of the "on-treatment" population of the FIRE-3 (AIO KRK-0306) study. *First Author: Sebastian Stintzing, Department of Hematology and Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, University Hospital Grosshadern, LMU Munich, Munich, Germany*

Background: The FIRE-3 study (AIO KRK-0306) was designed as a randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab (cet) to FOLFIRI plus bevacizumab (bev) as first-line treatment in KRAS WT mCRC patients. FOLFIRI plus cet as first-line treatment of KRAS WT mCRC patients resulted in comparable overall response rates (ORR) and progression free survival (PFS) when compared to FOLFIRI plus bev. Overall survival (OS) was significantly longer in the FOLFIRI plus cet arm. **Methods:** In this exploratory analysis outcome parameters were calculated in dependence of progression during antibody treatment. As reported before by Saltz et al. (ASCO GI 2007) an "on study treatment" population was defined using all RAS wild-type pts that were treated until progression or death occurred. To exclude early progressing patients the analysis was also performed in patients with a PFS >6 months. **Results:** See Table. **Conclusions:** In general, patients progressing during 1st-line treatment had a shorter PFS and OS than patients that had progressed after stop of treatment for any cause. Patients that discontinued treatment for other reasons than progression had a significantly longer median OS when treated with FOLFIRI plus cetuximab in first-line when compared to FOLFIRI plus bevacizumab. This effect was also seen after exclusion of early progressors (PFS <6 mo).

All patients		Median PFS (95% CI)	p	Median OS (95% CI)	p
PFS event during treatment	FOLFIRI + Cet (n= 72)	7.6 (6.1-9.7)	0.94	22.6 (17.3-27.9)	0.50
	FOLFIRI + Bev (n= 74)	7.4 (6.0-9.0)		20.8 (15.5-23.7)	
PFS event after treatment	FOLFIRI + Cet (n= 106)	10.8 (10.0-13.3)	0.59	38.3 (27.1-45.0)	0.01
	FOLFIRI + Bev (n= 111)	11.7 (10.3-13.1)		28.2 (24.8-33.3)	
Patients PFS >6months		**Median PFS (95% CI)**	**p**	**Median OS (95% CI)**	**p**
PFS event during treatment	FOLFIRI + Cet (n= 46)	11.0 (8.8-12.2)	0.85	27.9 (23.6-33.8)	0.85
	FOLFIRI + Bev (n= 46)	9.9 (9.0-11.7)		26.1 (23.1-31.5)	
PFS event after treatment	FOLFIRI + Cet (n= 91)	12.4 (10.5-14.1)	0.35	38.7 (36.4-49.8)	0.002
	FOLFIRI + Bev (n= 100)	12.4 (11.1-13.4)		28.8 (25.6-35.0)	

3590 Poster Session (Board #83), Mon, 8:00 AM-11:30 AM

Influence of molecular alterations on site-specific (ss) time to recurrence (TTR) following adjuvant therapy in resected colon cancer (CC) (Alliance Trial N0147). *First Author: Ryan Eldredge Wilcox, Mayo Clinic, Rochester, MN*

Background: Influence of tumor molecular alterations on ssTTR after resection of stage 3 CC has not been well studied. Phase 3 trial N0147 (adjuvant FOLFOX +/- cetuximab) provided an opportunity to assess possible correlations. **Methods:** 3098 stage 3 CC pts were enrolled and sites of all recurrences were reviewed centrally: liver, lung, peritoneal, local (< 5 cm of anastomosis), regional, and other metastatic. Genetic markers include MMR, mutations (mut) in *KRAS* exon 2 (codons 12, 13), *BRAF* V600E exon 15. Cumulative incidence rate (CIR) was estimated for ss recurrences. Associations between biomarkers and TTR across sites (interaction) were assessed by a frailty Cox model. Association between biomarker and ssTTR were evaluated by multivariable Cox model when the site-biomarker interaction effect presents, adjusting for age, T/N stage, type of surgery, tumor sidedness, and treatment. **Results:** Most common recur sites were liver, regional, peritoneal, and lung, with 3 yr CIR of 8.4%, 8.3%, 5.5% and 5.4%, respectively, with no difference between treatment arms (p = 0.9). Interactions between sites of recurrence and *BRAF* (p = .006) or MMR (p = .018) status were significant and marginal for combined *KRAS/BRAF (p = .10)*. Compared to wild type (wt) pts, *BRAF* mut pts had shorter TTR for peritoneal HR2.14; 95% CI, 1.36-3.37; p_{adj}= .001] and metastatic sites [HR, 1.19; 95 CI, 1.07-3.42; p_{adj}= .033], but not for liver or lung. *KRAS* mut/*BRAF* wt pts had shorter TTR for liver (HR, 1.55; 95% CI, 1.19-2.03) and lung (HR, 1.81, 95% CI, 1.32-2.50), and *KRAS* wt/*BRAF* mut pts had shorter TTR for peritoneal (HR, 2.14; 95% CI, 1.36-3.37) compared to double wt pts. dMMR pts had longer TTR for liver (HR, 0.44; 95% CI, 0.25-0.78; p_{adj}= .002) and peritoneal (HR, 0.46; 95% CI, 0.25-0.82; p_{adj}= .004) compared to pMMR pts. **Conclusions:** Status of MMR and *BRAF*, but not *KRAS* (alone), influences site of recurrence and TTR. Accordingly, these biomarkers may assist in treatment and follow-up approaches. Clinical trial information: NCT00079274.

3591 Poster Session (Board #84), Mon, 8:00 AM-11:30 AM

Patients' and physicians' risk-benefit trade-off preferences for metastatic colorectacl cancer treatments. *First Author: Juan Marcos Gonzalez, RTI Health Solutions, Durham, NC*

Background: Preferences for treatment-related benefits and risks associated with metastatic colorectal cancer (mCRC) therapies may vary between patients and physicians. **Methods:** A literature review and clinician interviews were carried out to develop risk-benefit profiles. PFS and probabilistic adverse outcomes were described in an online discrete-choice experiment completed by patients and physicians. Participants assessed a series of 10 choices between pairs of hypothetical medication profiles . Each profile included attributes within a pre-determined range: PFS (12 months, 8 months, 6 months), severe papulopustular rash (PR) (0%, 5%, 10%, 25%), serious hemorrhage (0%, 2%, 10%, 35%), cardiopulmonary arrest (0%, 2%, 10%, 20%), and gastrointestinal perforations (0%, 2%, 10%, 20%). Choice questions were based on an experimental design with known statistical properties. Random-parameter choice models produced preference weights indicating the strength of trade-off. These weights were used to calculate the maximum acceptable risk of different adverse events associated with various mCRC therapies. **Results:** A total of 127 patients and 150 physicians completed the discrete-choice survey. The mean maximum level of treatment-related risk patients were willing to accept for a 4-month increase in PFS from 8 to 12 months was 16.7% (0.0%-82.9%) for PR, 13.8% (4.6%-23.2%) for gastrointestinal perforation, 10.3% (3.3%-17.1%) for serious hemorrhage and 5.1% (1.7%-8.7%) for cardiopulmonary arrest. For the same PFS improvement, physicians were willing to accept a risk of severe PR that exceeded 25% and more than 20% risk for gastrointestinal perforation, which were the maximum levels shown in the survey for each of these treatment-related adverse events. Physicians were also willing to accept 18.9% (12.3%-24.5%) risk for serious hemorrhage and 7.0% (3.0%-10.8%) for cardiopulmonary arrest for the same 4-month PFS improvement. **Conclusions:** The benefit-risk tradeoff data obtained in this study show potential risk-tolerance differences between patients and oncologists, highlighting the importance of understanding preferences from the patient's perspective when making treatment decisions.

3592 Poster Session (Board #85), Mon, 8:00 AM-11:30 AM

Phase II trial of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: 5-year clinical outcomes of a trial of the ECOG-ACRIN Cancer Research Group (E3204). *First Author: Jerome Carl Landry, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: As previously reported, the regimen of preoperative capecitabine, oxaliplatin, and bevacizumab with radiation therapy (RT) followed by surgery and postoperative 5-FU, leucovorin, oxaliplatin (FOLFOX) andbevacizumabfor locally advanced rectal cancer did not improve pathologic complete response (path CR) rates. However, the effect of an intensified adjuvant regimen is not reflected in path CR. The purpose of this report is to describe the 5-year oncologic outcomes of this regimen. **Methods:** Fifty-seven patients (pts) with resectable T3/T4 rectal adenocarcinoma were enrolled. Preoperative treatment: capecitabine (825 mg/m² bid M-F), oxaliplatin (50 mg/m² weekly), bevacizumab (5 mg/kg D1,15,29), and RT (50.4 Gy). Surgery was performed by 8 weeks after neoadjuvant therapy. Beginning 8 – 12 weeks after surgery, patients received FOLFOX plus bevacizumab (5 mg/kg) Q2 weeks for 12 cycles. **Results:** Fifty-three of 57 enrolled pts were eligible and included in the analysis. Most patients were clinical (c)T3 (92%) and cN positive (64%). Of the 48 patients who underwent curative surgery, 26 (54%) began adjuvant chemotherapy. After a median follow-up period of 41 months, the 5-year overall survival (OS) rate for all patients was 80% (90% confidence interval (CI) [67%, 92%]). Only 2 patients experienced cancer recurrence, 1 distant and 1 locoregional, respectively. The 5-year recurrence free survival rate (RFS) was 81% (90% CI [68%, 94%]). **Conclusions:** Despite the path CR primary endpoint of this trial not being reached, the 5-year OS and RFS rates were excellent. However, as previously reported, the neoadjuvant and surgical toxicity of this regimen was significant and was the primary reason for the low compliance with adjuvant systemic therapy. Due to the lack of an improvement in the path CR rate, the substantial associated toxicity, and negative phase III trials of adjuvant bevacizumab in colon cancer, this regimen cannot be recommended for further study. Clinical trial information: NCT00321685.

3593 Poster Session (Board #86), Mon, 8:00 AM-11:30 AM

Time-dependent patterns of recurrence and death in resected colon cancer (CC): Pooled analysis of 12,223 patients from modern trials in the ACCENT database containing oxaliplatin. *First Author: Lindsay A. Renfro, Mayo Clinic, Rochester, MN*

Background: A 2009 analysis of 20,898 CC patients from 18 randomized studies of adjuvant therapy (AT) in the ACCENT database showed that treatment with AT (versus surgery alone) lowers the risk of recurrence and death at all time points, especially in stage III (versus stage II) disease. However, this analysis evaluated only FU/LV therapies and excluded modern oxaliplatin-based (OX) therapies. **Methods:** With mature follow-up now available (median 6 years), 12,233 patients from ACCENT enrolled to C-07, C-08, N0147, MOSAIC, and XELOXA (18% stage II, 82% stage III) were pooled to examine the impact of OX and tumor specific factors (tumor stage, nodal stage, tumor location, and tumor grade) on the time course of recurrence and death from all causes. For each endpoint, continuous-time risk was modeled over 8 years post-treatment in (1) OX-treated patients from all trials and (2) patients concurrently randomized to OX versus 5FU/LV, where the latter set of analyses supported time-dependent treatment comparisons. **Results:** Addition of OX reduced the risk of recurrence and death at all time points and in all disease subgroups, with no differences in the timing of outcomes between treatment groups (i.e., OX did not simply postpone recurrence or death compared to 5FU/LV alone; see Table). OX significantly reduced recurrence risk during the first 4 years, and significantly reduced risk of death from 2 to 6 years post-treatment. Recurrence risk peaked near 14 months for both treatment groups, with 83% of patients treated with OX (80% of patients treated with 5FU/LV) who recurred within 8 years doing so by 3 years post-treatment. Risk of recurrence and death increased with increased tumor and nodal burden. **Conclusions:** These analyses support the addition of oxaliplatin to fluoropyrimidines as a curative therapy in the adjuvant setting and strongly underscore the need for adequate surveillance of CC patients, especially during the first 3 years after adjuvant therapy.

		Year 1	Year 2	Year 3	Year 4	Year 5
Recur	5FU	11.0%	10.5%	5.2%	3.4%	2.0%
	OX	8.6%	8.8%	4.7%	2.2%	1.9%
Death	5FU	2.9%	5.4%	5.4%	4.9%	3.8%
	OX	2.8%	5.3%	4.3%	4.5%	3.2%

3594 Poster Session (Board #87), Mon, 8:00 AM-11:30 AM

Monitoring minimal residual disease (MRD) by *KRAS* mutation burden in urinary or plasma circulating tumor (ct) DNA in colorectal cancer (CRC) patients with resectable liver metastases. *First Author: Cecile Rose T. Vibat, Trovagene, San Diego, CA*

Background: Over half of patients with CRC will develop liver metastases. Surgical resection greatly improves outcomes in these patients. Non-invasive markers are needed to better monitor treatment responses and guide complex treatment decisions. This study evaluated the utility of quantifying *KRAS* mutation burden in urine and plasma ctDNA for monitoring MRD in surgical CRC patients with liver metastases. **Methods:** A blinded retrospective ctDNA analysis was conducted in 20 Stage I-IV CRC patients with *KRAS* positive primary tumor, 16 of whom had undergone curative or palliative intent surgical resection of primary tumor or liver metastases in combination with various systemic therapies. Urine and plasma specimens were collected prior, during, immediately after surgery, and at additional time points post-surgery. 193 matched urine and plasma specimens (archived 3-5 years) were tested using a novel, NGS-based method for quantitative detection of *KRAS* mutations in ctDNA. **Results:** In a blinded analysis, a *KRAS* mutation that correlated with *KRAS* mutation in tissue was identified in 95% of evaluable baseline plasmas (19 of 20) and 92% of evaluable baseline urines (11 of 12). 12 of 12 (100%) matched urine and plasma pairs at baseline were concordant (11 KRAS positive and 1 KRAS negative). Analysis of 193 archival longitudinal urine and plasma samples demonstrated a clear correlation and highly comparable fold change between plasma and urinary ctDNA *KRAS* levels on treatment. Significantly, in 5 of 5 patients with curative intent surgery, urine or plasma ctDNA *KRAS* levels were undetectable at 7 days post-surgery. In contrast, ctDNA *KRAS* remained detectable or increased after surgery in 10 of 11 patients with incomplete, palliative surgery. **Conclusions:** We demonstrate for the first time a clear correlation between the dynamics of urine and plasma *KRAS* ctDNA changes, and clinical applicability of ctDNA for assessing post-surgery MRD in CRC patients. A prognostic significance of post-surgical *KRAS* levels and the overall survival in Stage IV CRC patients with liver metastases is being evaluated in a larger cohort. Supported by IGA MZ Grant 13660.

3595 Poster Session (Board #88), Mon, 8:00 AM-11:30 AM

TAS-102 vs placebo (PBO) in patients (pts) ≥65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis of the RECOURSE trial. *First Author: Eric Van Cutsem, University Hospitals Leuven, Leuven, Belgium*

Background: TAS-102 is comprised of an antineoplastic thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio of 1:0.5 (weight ratio, 1:0.471). Efficacy and safety of TAS-102 in pts with mCRC refractory to standard therapies were evaluated in the RECOURSE trial; enrollment criteria included ≥ 2 prior lines of standard chemotherapy. Primary results of RECOURSE demonstrated a significant improvement in overall survival (OS) (TAS-102 7.1 mo vs PBO 5.3 mo; HR=0.68; $P<0.0001$) and progression-free survival (PFS) (HR=0.48; $P<0.0001$). **Methods:** This prespecified analysis compared the efficacy and safety of TAS-102 vs PBO in pts ≥ 65 y and < 65 y with mCRC. A retrospective analysis of pts ≥ 75 y was also performed. **Results:** Of 800 randomized pts, 352 (44.0%) were ≥ 65 y and 60 (7.5%) were ≥ 75 y. Median OS in pts ≥ 65 y was 7.0 mo with TAS-102 vs 4.6 mo with PBO (HR=0.62, 95% CI: 0.48-0.80, $P=0.0002$). PFS HR was 0.41 (95% CI: 0.32-0.52, $P<0.0001$) for pts ≥ 65 y, also favoring TAS-102. In pts ≥ 65 y, disease control rate (complete or partial response or stable disease) was 48.7% with TAS-102 vs 15.5% with PBO. An age-related difference in overall incidence of adverse events (AEs) was not observed in either treatment arm. Treatment-related AEs, ≥ Grade 3 AEs, and severe AEs were generally more common in pts ≥ 65 y than in pts < 65 y (Table). Mean drug exposure was similar among pts ≥ 65 y and ≥ 75 y, as was overall safety profile. **Conclusions:** Significant improvements in OS and PFS were observed in pts ≥ 65 y who received TAS-102 vs PBO, with a mild increase in toxicity. Pts ≥ 65 y and < 65 y showed a generally favorable safety profile. A significant increase in toxicity in pts ≥ 75 y was not apparent vs the overall ≥ 65 y population. Clinical trial information: NCT01607957.

	TAS-102, < 65 y (n=299)	TAS-102, ≥ 65 y (n=234)	TAS-102, ≥ 75 y (n=36)
Overall AEs, %	98.0	98.7	100
Treatment-related AEs, %	83.6	88.5	91.7
≥ Grade 3 AEs, %	65.2	74.8	75.0
Severe AEs, %	28.8	30.8	33.3
Anemia, %*	23.4	41.9	44.4
Neutropenia, %*	25.8	32.5	33.3
Decreased platelets, %*	9.0	21.4	11.1
Decreased appetite, %*	23.7	29.9	22.2

*Treatment-related.

3596 Poster Session (Board #89), Mon, 8:00 AM-11:30 AM

Phase I study of ganetespib (G), capecitabine (C), and radiation (RT) in rectal cancer. *First Author: Bassel F. El-Rayes, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Ganetespib (G) is a heat shock protein 90 inhibitor . Preclinical data show that G is a potent radiosensitizer for rectal cancer. The aim of this study is to determine the recommended phase II dose of G when combined with capecitabine (C) and radiation (RT) in resectable rectal cancer. **Methods:** Patients (pts) with stage II or III rectal adenocarcinoma with distal border within 12 cm of anal verge, no prior therapy, and adequate organ functions, were eligible. A 3+3 dose escalation design was used. Pts received 2 weeks of G at 150 mg/m^2 I.V. on days -14, -11, -7, and -4. Pre and post-treatment tumor biopsies were obtained. C (825 mg/m^2) and RT (50.4Gy) were administered 5 days per week for 5.5 to 6 weeks starting day 1. G was administered on days 1, 8, 15, 29 and 36. G dose levels were 60, 80, 100, and 120 mg/m^2. Pharmacokinetic sampling for C and G were performed on days 1, 2, 15, and 16. Dose limiting toxicities (DLT) were defined as the occurrence of any treatment related: grade (gr) 4 hematologic or gr 3 or higher non-hematologic toxicities, gr 3 nausea, vomiting or diarrhea lasting > 4 days, any interruption of RT > 10 days, more than 2 interruptions in RT, delay in completion of RT for > 14 days, or inability to deliver more than 85% of planned RT dose. **Results:** 16 pts were enrolled in the study; 1 pt received only day-14 and was not .evaluable for toxicity. Evaluable pts had a median age of 61 yrs, 7 females, and endoscopic stage: T3N0 (6 pts), T3N1 (6), T3N2 (2), T4N1 (1); 3 pts were treated on each dose level, 2 pts on dose level 4 required dose reduction, so we enrolled 3 additional pts on level 3 (100 mg/m^2). One DLT was observed (gr 3 diarrhea for more than 4 days). Other toxicities on the study were: diarrhea gr 3 (3 pts), gr 2 (6), gr 1 (2), radiation dermatitis gr 2 (9), gr 1 (3), fatigue gr 2 (5), gr 1 (4), hand foot syndrome gr 2 (1), mucositis gr 1 (2), and nausea/vomiting gr 2 (2), gr 1 (8). 12 pts have completed surgical resection (2 APR and 10 LAR). Pathologic complete response (pCR) rate was 25% (3/12) and 2 pts had residual tumors less than 1 cm (pT1N0). Six of 9 (67%) pts had clearing of lymph nodes disease on pathologic specimen. **Conclusions:** G can be safely combined with standard C and RT in the neoadjuvant setting in rectal cancer. Preliminary data on activity appear promising. Clinical trial information: 01554969.

3597 Poster Session (Board #90), Mon, 8:00 AM-11:30 AM

Therapeutic biomarker differences between MSI-H and MSS colorectal cancers. *First Author: Zoran Gatalica, Caris Life Sciences, Phoenix, AZ*

Background: Approximately 15% of colorectal cancers (CRC) display high level of microsatellite instability (MSI-H) due to either hereditary predisposition (Lynch syndrome, LS) or somatic hypermethylation of MLH1. They carry a significantly different prognosis and responses to treatments compared with microsatellite stable (MSS) or low microsatellite instability (MSI-L) CRC. We investigated therapeutically important biomarkers, which may underlie different treatment options for CRC. **Methods:** Sixty-four MSI-H (including 20 confirmed LS cases), 9 MSI-L and 558 MSS cases were profiled at Caris Life Sciences (Phoenix, AZ) using immunohistochemistry and sequencing (NextGen and Sanger). **Results:** Compared with non-MSI-H, MSI-H tumors had significantly higher expression of Thymidylate Synthase (TS) (85% vs. 31%), PTEN (71% vs. 48%) expressions and significantly higher mutation rates of *BRAF* (35% vs. 5%), *CTNNB1* (10% vs. 0.7%), *HNF1A* (32% vs. 0.2%), *BRCA1* (19% vs. 5%) and *BRCA2* (50% vs. 14%). MSI-H cancers were also significantly more often infiltrated with PD-1+ lymphocytes (71% vs. 43%). Features found specific to sporadic MSI-H tumors (defined as MSI-H and *BRAF V600E*) in comparison with non-MSI-H tumors included higher mutation rates on select genes within the PI3K/AKT/mTOR pathway, including *FBXW7* (31% vs. 7%), *PTEN* (19% vs. 3%) and *STK11* (18% vs. 1%). 20 confirmed LS cases also exhibited significantly higher TS (100%) expression, *CTNNB1* (10%) and *HNF1A* (40%) mutations than non-MSI-H and lower *FBXW7* (10% vs. 31%), *PTEN* (10% vs. 19%) and *STK11* (0% vs. 18%) mutation rates than sporadic MSI-H tumors (all $p < 0.02$). **Conclusions:** Significantly higher TS expression is a characteristic of both sporadic MSI-H and Lynch tumors, potentially explaining the observed reduced clinical benefit from 5-FU. Higher PD-1+ TIL, *BRCA1/2* and *CTNNB1* mutations suggest MSI-H as a more promising group for targeted immunotherapy, PARP and Wnt pathway inhibitors. Different molecular features of sporadic MSI-H and Lynch subgroups including PI3K/AKT/mTOR offer insight into targeted therapies for these subgroups of CRC.

3598 Poster Session (Board #91), Mon, 8:00 AM-11:30 AM

Measuring the impact of Next Generation Sequencing (NGS) technique implementation in metastatic colorectal cancer (mCRC) drug development program. *First Author: Carolina Ortiz, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Molecular screening and biomarker enrichment strategies in mCRC trials may impact patient (pt)´s outcome. The introduction of NGS technologies in clinical investigation may enhance pt inclusion through the discovery of a wider set of mutations (mt) in oncogenes and tumor suppressor genes. **Methods:** From March/2012 to December/2014 411 pts with chemorefractory mCRC underwent genetic tumor profiling as part of the molecular enhancement strategy in our early drug development program. Base extension chemistry followed by mass detection (MassARRAY, Sequenom) (SQ) was used including 268 frequent hotspots in 25 oncogenes with a sensitivity of 10% of mutant alleles. Since June/2014, Amplicon sequencing (NGS) was implemented assessing mt in 59 oncogenes and tumor suppressors with a sensitivity of 3% mutant alleles. **Results:** From March/2012 to Jun/2014 324 pts were screened using SQ, 261 mt were detected: 0.80 mt per patient. A total of 117 pts (36%) resulted wild-type (wt) after the test. Frequency of mt were: 48.77% *KRAS*, 16.67% *PI3KCA,* 7.41% *NRAS*, 7.41% *BRAF*, along with minor events: 2 mt in *AKT1* and 1 mt in *PDGFRA*, *GNAS* and *ERBB2* allowing a total of 89 inclusions on matched targeted therapies (27.47% inclusion rate per total samples). From Jun/2014 to Dec/2014 78 pts were screened with NGS, 5 pts (6%) were wt. A total of 160 mt were detected (1.83 mt per patient): 44.83% *KRAS*, 4.6% *NRAS*, 51.72% *TP53*, 43.68% *APC*, 5.75% *BRAF*, 5% *PI3KCA*, 4.6% *SMAD4*, 3.45% *PTEN* and 1mt in *GNAS*, *AKT2*, *MET*, *STK11*, *FBXW7, JAK3, FGFR1, NOTCH1, MSH6, RNF43, RET* and *NF2* providing 21 inclusions to treatment with targeted therapy (26.4% inclusions per total samples). **Conclusions:** Our results show that NGS techniques allow the identification of a wider spectrum of mts per patient compared to prior generation genomic tests, although this has failed to be translated yet into higher inclusion rates in clinical trials with targeted agents. An enhanced discovery of mutations in tumor suppressor genes, thus far out of therapeutic reach and other factors like recent implementation of NGS and the increasing search for more specific molecular populations can contribute to this fact.

3599 Poster Session (Board #92), Mon, 8:00 AM-11:30 AM

A genome-wide association study (GWAS) of overall survival (OS) in 609 metastatic colorectal cancer (mCRC) patients treated with chemotherapy and biologics in CALGB 80405. *First Author: Federico Innocenti, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Support: U10CA180821, U10CA180882, CA31946, Bristol-Myers Squibb, Genentech, Pfizer **Background:** Irinotecan/5-FU (FOLFIRI) or oxaliplatin/5-FU (FOLFOX), combined with bevacizumab or cetuximab, are first-line treatments for mCRC. We aimed to identify germline variants associated with survival in mCRC patients treated with these regimens. **Methods:** In CALGB 80405, patients with wild-type *KRAS* (codons 12 and 13) mCRC received either FOLFOX (> 80% of patients) or FOLFIRI and were randomized to either cetuximab or bevacizumab. The primary endpoint of the study was OS.DNA was extracted from peripheral blood and genotyped for ~700,000 single-nucleotide polymorphisms (SNPs). The association between SNPs and OS in 609 patients (both arms combined) of European genetic ancestry was tested by a Cox proportional hazards model. **Results:** Median OS in genotyped patients was 29.6 months, and was comparable to that of the parent study (Venook et al., ASCO 2014). The three most significant SNPs associated with OS were in the genes *RDH14* (hazard ratio, HR 1.63, $p < 1.12 \times 10^{-6}$), *TMEM16J* (HR 1.52, $p < 2.03 \times 10^{-6}$), and *AXIN1* (HR 1.40, $p < 4.26 \times 10^{-6}$). Among these genes, the most compelling evidence for a link to the biology of CRC is for *AXIN1*. The AXIN1 protein functions as a negative regulator of WNT signaling by interacting with APC in CRC (Li et al., Cell 2012). In the present GWAS, rs11644916 (G to A) in *AXIN1* is a common germline intronic variant (30% allele frequency). Median OS for patients with the AA, AG or GG genotypes of rs11644916 was 18.4 (95% CI 14.2-27.6), 25.6 (23.6-30.4) or 36.6 (32.9-41.1) months, respectively. Testing of arm and extended RAS analysis as covariates did not alter the association with the rs11644916 in *AXIN1*. **Conclusions:** This is the first, large GWAS ever conducted in mCRC patients treated with standard of care in a randomized phase III trial. A common SNP in the *AXIN1* gene confers worse OS. This study selects *AXIN1* as a new putative determinant of CRC progression. Further replication in additional patient cohorts and functional studies in CRC experimental models are required. Clinical trial information: NCT00265850.

3600 Poster Session (Board #93), Mon, 8:00 AM-11:30 AM

Modified FOLFIRI (Irinotecan 150 mg/m2) compared to FOLFIRI (Irinotecan 180 mg/m2) in Korean patients with gastrointestinal cancer. *First Author: Kyu-Pyo Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: The aim of this study was to investigate the association between initial irinotecan dose and UGT1A1 genotype, dose intensity, response rate, neutropenia and survival in advanced colorectal and gastric patients. **Methods:** This is an update of a prospective pragmatic trial performed UGT1A1 *6 and *28 genotyping in colorectal and gastric cancer patients who received FOLFIRI as 1st or 2nd line palliative chemotherapy. Patients were grouped as "defective" if the patient had a mut/mut genotype for either UGT1A1*6 or *28; and the others (wt/wt, wt/mut) were grouped as "control". Initially safety including Gr ¾ neutropenia, febrile neutropenia and diarrhea was evaluated for the first cycle of FOLFIRI treatment. Patients were comprised of colorectal cancer (1st line, 602; 2nd line, 332) and gastric cancer (1st line, 216; 2nd line, 395). We updated the efficacy analysis which included response rate, progression free survival and overall survival. **Results:** A total of 1,575 patients were enrolled. The initial dose of irinotecan was 180 mg/m^2 and 150 mg/m^2 in 63.9% and 32.5% of the patients. Grade ¾ neutropenia, febrile neutropenia and diarrhea were observed in 28.3%, 2.2% and 1.4% at the 1st cycle and 55.6%, 3.6% and 3.8% during all cycles of FOLFIRI. Although multivariate analysis revealed defective genotype and female gender to be significant associated with Gr ¾ neutropenia ($P < 0.0001$, $P = 0.0125$, $P = 0.0011$), these factors did not have an effect on the PFS (HR 0.988 [0.831-1.174], 1.013 [0.905-1.134]) and OS (HR 0.925 [0.742-1.155], 1.031 [0.899-1.184]). However, when initial dose was compared, HR favored 180 mg/m^2 over 150 mg/m^2 after adjusting for UGT1A1 genotypes, sex and dose intensity of irinotecan for PFS (HR 0.640 [0.559-0.733]) and OS (HR 0.619 [0.522-0.734]). In a subset analysis, colorectal cancer patients who received 1st line FOLFIRI showed a significant benefit for initial usage of 180 mg/m^2 over 150 mg/m^2 in PFS ($P < 0.001$)and OS($P < 0.001$). **Conclusions:** Our findings indicate that lowering the starting dose of irinotecan may be associated with inferior efficacy of FOLFIRI. Clinical trial information: NCT01271582.

3601 Poster Session (Board #94), Mon, 8:00 AM-11:30 AM

Clinical utility of a circulating cell-free DNA assay for clinical trial enrollment in refractory metastatic colorectal cancer patients. *First Author: Van Karlyle Morris, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Circulating cell-free DNA (cfDNA) isolated from the plasma of cancer patients has been shown to accurately reflect the genomic mutation profile of the tumor, and assays are now available for clinical use. However, physician and patient assessment of clinical utility of these assays in patients has not been previously evaluated. **Methods:** Patients (pts) were prospectively consented as part of the Assessment of Targeted Therapies Against Colorectal Cancer (ATTACC) protocol, with collection of 20mL of blood for cfDNA extraction and sequencing on a 54-gene panel in a CLIA-certified lab (Guardant360, Guardant Health). FFPE tissue from prior resections or biopsies underwent 50-gene sequencing (Ion Torrent, Life Technology). Results from both assays were returned to the treating physicians for patient care and clinical trial selection. Follow up surveys and chart reviews assessed clinical utility. **Results:** 120 mCRC pts were enrolled between 6/1/2014 and 1/7/2015, with a median of 3 prior lines of therapy. With cfDNA sequencing, 83% (99/120) of samples had a detectable genomic alteration (including 26% with detectable amplifications in EGFR, MET, or ERBB2), with an average of 4.2 mutations/pt. Sequencing of tissue provided detectable mutations in 88% of cases (106/120), with an average of 2.9 mutations /pt. cfDNA testing provided results within a median of 11 days, 14-days faster than tissue testing. 54% of cfDNA cases had potentially actionable alterations, and 66% of cases could be genomically matched to at least one clinical trial in the institution. 52% of these pts were able to be enrolled in the identified trial, with the remainder limited by eligibility criteria (9%), lack of patient interest (22%), or no current trial openings (17%). Physicians felt that the cfDNA testing improved the quality of care they were able to provide in 75% of the cases, and improved patient satisfaction with the efforts to personalize experimental options in 92% of cases. **Conclusions:** cfDNA sequencing can provide timely information on potentially actionable mutations and amplifications, thereby facilitating clinical trial enrollment and improving the perceived quality of care.

3602 Poster Session (Board #95), Mon, 8:00 AM-11:30 AM

Outcome evolution of matched molecular targeted agents (MTAs) in metastatic colorectal cancer (CRC) patients (pts): VHIO experience. *First Author: Guillem Argilés, Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain*

Background: Biomarker-driven selection of new MTAs has not been widely successful in CRC as we reported in 2012. New screening platforms and drugs have reached early drug development. We aimed to evaluate outcome evolution between 2012 and 2014 **Methods:** MTAs given to CRC pts based on molecular tumor profiling (MTP) from Jan/2012 to Dec/2014 were compared to the reported in 2012. MTP included mutations (mt) detected by Sequenom (Sq), VHIO-Card Amplicon panel, cMET amplifications (amp), PTEN and PDL1 expression. Benefit was calculated comparing treatment failure of prior line (TTF1) to the MTAs' one (TTF2). TTF2/TTF1≥1.3 supposed MTAs benefit. Relevant MTAs-biomarker pairs were analyzed. **Results:** A total of 174 MTAs were given. Pairs biomarker-MTAs were: *KRAS*mt: MEK inhibitors (i)+PI3Ki or MEKi + anti-receptor tyrosine kinase (RTK) mAbs; *PIK3CA*mt or PTEN loss: PI3Ki, MTORi, dual PI3K-MTORi, MTORi + anti-RTK mAbs; cMET path activation: METi [mAbs or RTKi]; *BRAF V600*mt: BRAFi, BRAFi + MEKi +/- CDK4i, BRAFi + anti-EGFR mAbs +/- PI3Ki; *RAS* wild-type (wt): 2nd generation anti-EGFR mAbs. Median (m)TTF1 was 21.9 weeks (w) (18.9-24.8), mTTF2 8.3w (7.7-8.9), with 17.2% of pts benefiting from MTA (i.e. TTF2/TTF1≥1.3). Derived benefit was not higher to the reported in 2012 mTTF1 16.3w (14-18.5), mTTF2 7.9w (7.2-8.5) with 14.3% pts benefiting from MTAs (p=0.47). *BRAF V600E* mt pts receiving BRAFi combos was the group with more benefit from MTAs (30%) **Conclusions:** Recent evolution with MTAs in CRC does not widely correlate with better outcome in overall population. However, significant benefit is observed when there is a mechanistic rationale for MTA (*BRAF V600E*). Further CRC molecular subtyping is needed to improve outcomes.

MatchedMTAs	pts	mTTF1 w	mTTF2 w	% clinical benefit
*BRAF V600E*mt(BRAFi combos)	23	21.8 (12-31.7)	10.9 (7.3-14.4)	30.4%
*RAS*mt(MEKi + PI3Ki)	51	18.1 (11.4-24.9)	7.9 (7.1-8.6)	11.8%
*RAS*mt (MEKi + anti-RTKsmAbs)	22	25.4 (21.5-29.4)	6 (4.2-7.8)	18.2%
*RAS*wt (2nd generation anti-EGFR mAbs)	38	21.6 (14.8-28.3)	12.6 (7-18.2)	21.1%
*PIK3CA*mt/PTEN loss (s/a PI3K-path i)	40	15 (10.8-19.3)	8.4 (7.5-9.3)	20%
*PIK3CA*mt/PTEN loss (combos PI3K-path i)	24	24.4 (9.8-39.9)	8 (7.9-8.1)	17.2%

3603 Poster Session (Board #96), Mon, 8:00 AM-11:30 AM

Retrospective study of patients (pts) who were managed with Watch and Wait strategy (W&W) after neoadjuvant chemoradiation (NCRT) for Locally Advanced Rectal Cancer (LARC). *First Author: Sina Vatandoust, Flinders Medical Centre and Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, Australia*

Background: The management of LARC involves NCRT followed by resection +/- adjuvant chemotherapy. Rectal resection has associated short and long-term morbidity and functional compromise. Complete Response (CR) is observed in ~ 20% of cases after NCRT and resection may be avoidable in these pts. We retrospectively report a cohort of pts who received NCRT and have been followed up with 'W&W'. **Methods:** All patients with LARC who had CR to NCRT, and did not proceed to surgery but instead were managed by a surveillance strategy, were identified from clinical records. All pts had received long course NCRT as suggested by multidisciplinary team meeting. CR was defined as the absence of any residual viable cancer, proven through examination, colonoscopy (+ biopsy if indicated) and imaging (including MRI). Pts with metastatic rectal cancer were excluded. Data on demographics, management and outcomes were extracted from records. Follow up included regular 3 monthly physical examination, sigmoidoscopy/colonoscopy (+ biopsy if indicated) and MRI scans. Follow up times were calculated from date of diagnosis of rectal cancer. **Results:** 22 pts achieved a CR and were managed by 'W&W', without surgery. Median follow up 19 (9-49) months (mo), 50% (n = 11) male, median age 62 (34-78), Stage at diagnosis: T2N0 4.5% (n = 1), T2N1 27.3% (n = 6), T3N0 13.6% (n = 3), T3N1 22.7% (n = 5) and T3N2 31.8% (n = 7). 2 pts had other concurrent cancers (1 with metastatic small cell carcinoma and 1 with breast cancer). 2 pts (9.1 %) developed salvageable local recurrences: 1 had local recurrence 11 mo after primary diagnosis and underwent ultra-low anterior resection; the other had recurrence 8 mo after the primary diagnosis and underwent low anterior resection, both with clear margins. Both were detected on follow-up reviews (evident at sigmoidoscopy). Another pt developed metastatic disease 10 mo after the original diagnosis. All 22 pts are alive at the time of this report. **Conclusions:** In this cohort of pts with LARC who had achieved CR to NCRT, W&W did not lead to unsalvageable local recurrence. Prospective study design and longer follow up is needed to confirm the utility of this approach.

3604 Poster Session (Board #97), Mon, 8:00 AM-11:30 AM

Predictors of clonal evolution in metastatic colorectal cancer patients. *First Author: M. Pia Morelli, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Concordance of somatic mutations between primary and metastatic colorectal tumors is high in colorectal cancer (CRC), circulating cell-free DNA (cfDNA) accurately reflects the mutation status of metastatic disease. Intervening treatment and metastatic dissemination may result in clonal evolution from pre-existing intratumoral heterogeneity, with the resulting discordance in minor clones.**Methods:** Patients (pts) were prospectively consented for collection of cfDNA from plasma samples for sequencing on a 54-gene platform optimized for very low allele frequencies (Guardant360), with concurrent sequencing of clinically available and macrodissected historic FFPE tissue (50-gene Ion-Torrent panel), both performed in CLIA-compliant labs. Eligible cases had plasma and tissue sequencing where the modal mutation was present with ≥ 1% and ≥ 5% allele frequencies, respectively. Minor clones were defined as those with an allele frequency < 10% of the highest detected allele frequency in the sample.**Results:** 61 pts were enrolled after a median of two prior lines of therapy for metastatic disease, with plasma collected a median of 12.6 months after FFPE tissue (18 metastatic/44 primary tumor tissue). 213 mutations were detected on both tissue DNA and cfDNA, with at least one mutation detected in all cases; 54% of the mutations were present in both samples, with 32% of the mutations uniquely present in the plasma. Microsatellite instability (P = 0.025), intervening treatment with oxaliplatin (P = 0.04) or cetuximab/panitumumab (P < 0.001), but not irinotecan or bevacizumab, were associated with the detection of new minor clones. There was no association with reference tissue source, time from tissue collection, location nor number of metastatic sites.Minor clones represented 30% of the detected mutations and were concordant for only 11%, in contrast to 84% concordance for major clones (P < 0.0001). .**Conclusions:** Intervening chemotherapy and microsatellite instability results in the appearance of new minor clones in potentially clinically relevant genes in more than half of metastatic CRC pts. Based on this small data set, development of minor clones may be dependent on exposure to specific cytotoxic or molecular drugs.

3605 Poster Session (Board #98), Mon, 8:00 AM-11:30 AM

Prognostic and predictive value of tumour budding in stage II colorectal carcinoma. *First Author: Bojana Mitrovic, Mount Sinai Hospital, Department of Pathology and Laboratory Medicine, Toronto, ON, Canada*

Background: High-grade tumor budding (HGTB) is reported to be an independent adverse prognostic factor in colorectal cancer (CRC). Its presence is not routinely assessed by pathologists due to uncertainties about its clinical value, risk group thresholds, and the reproducibility of its assessment. Moreover, the benefit of chemotherapy in stage II CRC with HGTB remains to be demonstrated. This study aimed to (1) confirm the prognostic significance of HGTB in stage II CRC (2) determine the optimum threshold for HGTB reporting and (3) determine the responsiveness of stage II CRC with HGTB to chemotherapy. **Methods:** Whole slide images from CRC resections of 979 QUASAR trial patients (majority stage II) were evaluated for tumor budding as per the method of Ueno (2002). A tumor bud was defined as a single cell or a cluster of < 5 cells on a hematoxylin and eosin stained section. The highest tumor bud count per 1.23 mm^2field was recorded. The optimal cutoff for HGTB was determined by maximal likelihood methods. Influence of risk group on recurrence and all-cause mortality was investigated in stratified logrank analyses in 'training' ($n = 501$) and then 'test' ($n = 478$) data sets. **Results:** The optimal cut-off for HGTB was determined to be 10+ buds/1.23 mm^2field. Defined as such, HGTB was associated with significantly worse outcome: 10-year recurrence 35% vs 22% (risk ratio [RR] = 1.93 [95%CI 1.48–2.51], $2p < 0.00001$) and mortality 51% vs 36% (RR = 1.73 [1.38–2.16], $2p < 0.00001$), which was largely independent of other factors, including N and T-stage, grade, MMR, KRAS and BRAF status. There was a non-significant trend towards increasing chemotherapy efficacy with increasing bud counts ($p = 0.12$). **Conclusions:** HGTB is a strong independent predictor of disease recurrence and survival in stage II CRC. The proportional reductions in recurrence with chemotherapy in patients with higher bud counts appear at least equivalent to those with low counts, hence the absolute reductions in recurrence with chemotherapy should be about twice as large in patients with 10+ than < 10 tumor bud counts.

3606 Poster Session (Board #99), Mon, 8:00 AM-11:30 AM

Risk of colorectal cancer after diagnosis of prostate cancer: A population-based study. *First Author: Danielle Nicole Desautels, University of Manitoba, Winnipeg, MB, Canada*

Background: Prior studies on risk of colorectal cancer (CRC) among survivors of prostate cancer (PC) have not controlled for important confounding factors such as competing risk of death and other cancers, and comorbidities. We assessed the risk of CRC (overall, sub-site- and treatment-specific) among PC survivors. **Methods**: A historical cohort study was performed by linking the Manitoba Cancer Registry and the Manitoba Health administrative databases. Each subject diagnosed with PC as his first cancer between 1987 and 2009 was age-matched with up to five men with no history of invasive cancer on the index date (date of PC diagnosis). All subjects were followed up to the date of diagnosis of CRC or another cancer, death, migration from the province, or study end-point (December 31, 2009). Competing-risk proportional hazard models were used to compare the CRC incidence rates with adjustment for age, history of lower gastrointestinal endoscopy, intensity of health care visits, diabetes and socio-economic status. There were three mutually exclusive (and competing) outcomes: CRC, another primary cancer, and death. Time dependent analysis was performed to assess effect of radiation treatment. **Results**: 14,164 men with PC and 69,051 controls were followed for a total of 559,081 person-years. Men diagnosed with PC had an increased risk of subsequently being diagnosed with CRC (all CRC: hazard ratio (HR) 1.14; 95% confidence interval (CI): 1.02-1.27; rectal cancer: HR 1.36; 95%CI: 1.09-1.71). Among men with PC, treatment with radiation was associated with increased risk for rectal/rectosigmoid cancer (HR 2.06; 95%CI: 1.42-2.99) compared to men with PC not treated with radiation, with the majority of excess cases being diagnosed within 5 years from PC diagnosis. **Conclusions**: Following a diagnosis of PC, the probability of diagnosing a CRC is increased, in particular rectal cancer among those treated with radiation. CRC screening soon after PC diagnosis should be considered.

3607 Poster Session (Board #100), Mon, 8:00 AM-11:30 AM

A phase II study of 5-fluorouracil (5-FU), ziv-aflibercept, and radiation for the preoperative and adjuvant treatment of patients (pts) with stage II/III rectal cancer. *First Author: Peter Acs, Florida Cancer Specialists/SCRI, Ft. Myers, FL*

Background: Radiation exposure upregulates VEGF expression which protects endothelial cells from the effects of radiation therapy. Combining an angiogenesis inhibitor with radiation therapy may help to suppress VEGF expression and enhance antitumor activity. Aflibercept is an antiangiogenic agent that binds to VEGF-A, VEGF-B and placental growth factor. This phase II, non-randomized study combined ziv-aflibercept (aflibercept outside the US) with chemoradiation as preoperative treatment for pts with stage II/III rectal cancer, followed by 4 months of mFOLFOX6 plus ziv-aflibercept. **Methods:** Pts with stage II/III adenocarcinoma of the rectum received preoperative 5-FU (225 mg/m^2 IVCI, days 1-42), radiation (50.4 Gy, Mon.-Fri., weeks 1-6), and ziv-aflibercept (4 mg/kg IV, days 1-15) each 28 day cycle for 6 weeks. Six weeks from last dose of ziv-aflibercept, pts underwent surgical resection. Treatment with mFOLFOX6 plus ziv-aflibercept began 8 weeks after surgery for 4 cycles. The primary objective was to evaluate the pathologic complete response (pCR) rate. Secondary objectives included overall survival (OS), disease-free survival (DFS), sphincter preservation (SP) rate, and safety. **Results:** Thirty-nine pts were treated: median age 60 yrs (range, 36-89), 64% male, 82% ECOG 0, 69% stage III. Ninety-five percent of pts received preoperative treatment, 82% underwent resection, and 54% received postoperative treatment. The most common treatment-related toxicities (% G1/2; % G3/4) included diarrhea (51%; 21%), fatigue (59%; 5%), mucositis (38%; 15%), nausea (46%; 0), and hypertension (13%; 21%). Three postoperative complications of G3 pelvic abscess (2) and G3 GI fistula (1) were seen. Of the 32 pts resected, 8 pts (25%) achieved pCR, and pathologic partial response was seen in 24 pts (75%: 9 macroscopic, 15 microscopic). The SP rate was 72%; 31 pts (97%) had R0 resection. Median OS/DFS have not yet been reached. **Conclusions:** The 5-FU-based chemoradiation therapy combined with ziv-aflibercept in localized rectal cancer pts was well tolerated and showed a pCR rate in range with historical data. Median DFS is pending. Clinical trial information: NCT01749956.

3608 Poster Session (Board #101), Mon, 8:00 AM-11:30 AM

Prospective evaluation of a 409-gene next generation sequencing platform to facilitate genotype-matched clinical trial enrollment. *First Author: Scott Kopetz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We initiated a prospective, institution-wide study to determine whether genomic testing with a 409-gene panel in solid tumors can identify new actionable genomic information (beyond that identified by smaller hot-spot panels) and lead to enrollment in genotype matched trials using agents relevant to the alteration(s) identified. **Methods:** Eligible patients (pts) had no remaining standard of care therapy anticipated to extend life by more than 3 months, ECOG performance status of ≤ 1, and a willingness to consider clinical trial enrollment. The pts' tumors were initially sequenced using a hotspot panel (predominantly a 50-gene panel, Ion Torrent, Life Technology), and if no actionable alterations were found, then tumor and paired germline were sequenced with a 409-full-length gene panel (Ion Proton). Actionable genes were defined as those for which a matched genotype selected trial exists in the institution. **Results:** 200 pts across more than 30 tumor types were consented and underwent 409-gene testing. Novel alterations in an actionable gene not found on a previous hot-spot panel were found in 39.5% of pts. Of these 79 pts, the specific somatic gene variant was of known activity based on existing literature in only 23%; for 77% the somatic variant was of unknown significance. Of the 79 pts, 20 pts (25%) were enrolled in a genotype matched trial, with 8 (10%) anticipated to enroll in the next line of therapy. Reasons for non-enrollment were the treating physician's opinion that there was insufficient evidence for the functional significance of the variant (23, 29%), exclusion criteria or lack of available slots (16, 20%), or other reasons including pt choice (12, 15%). **Conclusions:** A significant population of pts with variants in potentially actionable cancer genes not evaluated in a traditional hot-spot cancer gene panel can be identified using a 409-gene targeted gene panel. The high number of somatic variants of unknown significance represents a knowledge gap of clinical importance. While many factors contribute to bottlenecks in utilizing the expanded sequencing results, expanded genomic testing combined with robust decision support can facilitate trial enrollment.

3609 Poster Session (Board #102), Mon, 8:00 AM-11:30 AM

A phase II single arm feasibility trial of neoadjuvant chemotherapy (NAC) with oxaliplatin/fluorouracil (OxMdG) then short-course preoperative radiotherapy (SCPRT) then immediate surgery in operable rectal cancer (ORC): COPERNICUS (NCT01263171). *First Author: Simon Gollins, North Wales Cancer Treatment Centre, Bodelwyddan, United Kingdom*

Background: Feasibility was assessed of giving NAC prior to SCPRT then immediate surgery in ORC at high risk of metastatic relapse. **Methods:** Patients (pts) had non-metastatic rectal adenocarcinoma. Pre-treatment pelvic MRI showed resection margin was not at risk (disease > 1mm from mesorectal fascia) but adverse risk factors were present (disease > T3b or node positive or extramural vascular invasion). Pts received 4x2-weekly cycles of oxaliplatin 85mg/m^2 + levofolinic acid 175 mg, fluorouracil (FU) 400 mg/m^2 (bolus), then FU 2400 mg/m^2 (continuous IV in 46 hr). Within 14 days pts had pelvic SCPRT to 25 Gy in 5 daily fractions. Definitive surgery then occurred within a week. Post surgery pts received 16 weeks of OxMdG or oxaliplatin/capecitabine. The primary endpoint was the proportion of pts completing protocol treatment including surgery. **Results:** 60 UK pts were recruited May 2012-June 2014. At baseline: male 44 (73%), median age 63 (IQR: 56.5-70), WHO PS 0/1 55/5. On pre-treatment MRI tumour was T2/3x/3a/3b/3c/3d/4 in 2/2/16/24/12/1/3 and N0/1/2 in 7/40/13 pts. All pts commenced OxMdG with 57(95%) receiving all 4 cycles. 20 pts (33%) needed a dose reduction and 22 (37%) a dose delay. 58 pts commenced SCPRT (all received full dose) and 57 underwent surgery: anterior resection in 43 (75%), abdominoperineal resection in 11 (19%), Hartmanns in 3 (5%). Three pts withdrew prior to surgery: one lost to follow up after SCPRT, one pt choice and one due to cardiospasm during NAC. Median gap between OxMdG and starting SCPRT was 10 days (IQR: 5-15) and between completing SCPRT and surgery 10 days (IQR: 5-13). Postoperative histology was T0/1/2/3a/3b/3c/4a in 7/3/19/8/9/10/1 pts, N0/1/2 in 39/13/5 pts and ypT0ypN0 in 7/57 pts (12%). All 57 resected pts had a clear (R0) resection margin with no 30 day postoperative mortality. **Conclusions:** This is the first trial to report on giving NAC prior to SCPRT then surgery within a short time interval in ORC, which proved feasible with good compliance and promising efficacy. The UK NCRI intend to include a similar regimen in a future phase III trial. Clinical trial information: NCT01263171.

3610 Poster Session (Board #103), Mon, 8:00 AM-11:30 AM

Characterization of the immune microenvironment of synchronous primary tumor and liver colorectal metastases. *First Author: Marc Van Den Eynde, Institut Roi Albert II, Cliniques universitaires St-Luc, UCL, Brussels, Belgium*

Background: The adaptive Th1 immune response (CD3, CD8, CD45RO T cells) observed in resected primary colorectal tumor (PCT) and liver colorectal metastases (LCM) is an important prognostic factor. Preoperative treatment modifies the LCM immune microenvironment with a significant association between pathological response and increase of T (CD3, CD8) and B cells (CD20) and downregulated T regulatory cells (FoxP3). We investigated the impact of different preoperative treatments on the quality and density of the immune infiltrates in synchronous resected PCT and LCM. **Methods:** Metastatic colorectal patients (n = 107) undergoing curative liver surgery for all resected LCM (n = 338) were investigated. 28 patients have been operated concomitantly for synchronous LCM (n = 102) and PCT (n = 23 available) after surgery alone (S), chemotherapy (Cht) alone, Cht + anti-VEGF and Cht + anti-EGFR. The density of CD3 (T cells), CD8 (cytotoxic), CD45RO (memory), CD20 (B cells) and FoxP3 (regulatory) in the core (CT) and invasive margin (IM) of all synchronous LCM and PCT was quantified on immunostained slides. The mean density value (CT, IM) was calculated for each marker with a dedicated image analysis software on whole-slide imaging. Comparisons were made using the Wilcoxon-Mann-Whitney test. **Results:** Global analysis of immune cell density in LCM and corresponding PCT showed no significant correlation even when further subcategorizing by treatment (preoperative or S), metastasic burden or subdividing by the least, the mean or the highest infiltrated LCM for patients with multiple LCM.Compared to PCT, LCM were more frequently associated with a high immune infiltrate for CD3 and CD45RO in the IM ($p < 0.001$) and CD8 in CT and IM ($p < 0.001$). Conversely, high CD20 and FoxP3 density were higher in the CT of PCT ($p < 0.005$). When comparing preoperative treatment to S, only Cht+anti-EGFR significantly increases CD3 and CD8 in CT of LCM but not PCT ($p < 0.001$). **Conclusions:** Cytotoxic/memory T cells and B/regulatory T cell densities were significantly higher in LCM and PCT, respectively. Only anti-EGFR treatment increases T cells densities in the CT of the LCM but not in the PCT, suggesting a specific treatment effect in this tumor region.

3611 Poster Session (Board #104), Mon, 8:00 AM-11:30 AM

Reduced PD-1/PD-L1 expression in KRAS-mutant versus wild-type microsatellite instable (MSI-H) colorectal cancer (CRC) and association of wnt pathway corepressor TLE-3. *First Author: Namrata Vijayvergia, Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA*

Background: MSI-H CRC comprises ~15% of CRC & has higher PD-1 & PD-L1 (P(+)) expression in CD4+ lymphocytes & tumor cells, respectively, compared to non-MSI-H CRC. Immune-checkpoint inhibitor therapy is being tested in clinical trials for MSI-H CRC (NCT02060188, NCT01876511). Human homologue of Groucho, Transducin-like-Enhancer of Split orthologue (TLE-3), inhibits Wnt signaling by competition with b-catenin for LEF/TCF binding. We investigated different biomarkers that may characterize P(+) MSI-H CRC. **Methods:** 55 MSI-H (including 13 Lynch Syndrome cases) CRCs were profiled at Caris Life Sciences (Phoenix, AZ). Immunohistochemistry (IHC) & mutation analysis was performed to compare P(+) & P(-) MSI-H CRC. PD-1 expression was measured on Tumor Infiltrating Lymphocytes (TIL) with the cutoff of 1+, 1% (1/HPF); PD-L1 expression was measured on tumor cells with the cutoff of 2+, 5%. IHC assays underwent a stringent validation process meeting CLIA/CAP criteria. Fisher's exact test was used to compare categorical variables. **Results**: Analysis of 55 MSI-H tumors revealed 39 (71%) were P(+) (39 PD-1(+); 1 also PD-L1(+)) & 16 (29%) were P(-). The P(+) group expressed TOPO-1/2 (43%/93%), EGF-R (88%), TS (90%), RRM1 (77%), PTEN (77%), c-MET (50%), and MGMT (53%) by IHC, and the expression was not significantly different compared to the P(-) group. TLE-3 protein expression, however, was 43% in P(+) and only 8% in P(-) MSI-H tumors ($P = 0.04$). Only 9 (27%) of P(+) tumors harbored a KRAS mutation, while 10 (62%) had KRAS mutation in P(-) tumors ($P = 0.04$). **Conclusions:** PD-1/PD-L1 protein expression is inversely associated with KRAS mutation status in MSI-H CRC. This is relevant to clinical trials testing immune checkpoint inhibitors in MSI-H CRC. The signaling between KRAS mutation & low or absent PD-1/PD-L1 should be further investigated. TLE-3 expression may dampen b-catenin signaling in P(+) tumors.

3612 Poster Session (Board #105), Mon, 8:00 AM-11:30 AM

Proteomic signatures of colorectal cancer to identify distinct and reproducible subgroups and to reflect prognosis. *First Author: Michael Sangmin Lee, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: While colorectal cancer (CRC) has classically been categorized by gene expression, proteomic analysis directly elucidates the functional state of protein signaling, which may better reflect cellular behavior. We performed an antibody-based proteomic analysis (reverse-phase protein array; RPPA) of a large cohort of MD Anderson (MDACC) and The Cancer Genome Atlas (TCGA) samples to determine patterns of protein expression in CRC. **Methods:** Protein was extracted from 725 archived CRC tumor samples (263 MDACC discovery set, and 462 TCGA validation set), and RPPA was performed to determine the expression levels of 127 cellular proteins. Upon unsupervised hierarchical clustering, samples dichotomized with distinct patterns of protein expression. The proteins with highest discriminatory utility were identified by LIMMA in the discovery set and confirmed in the validation set. Clinical variables and DNA sequencing results were available for correlation. **Results:** Among the top 40 discriminant proteins for the dichotomized groups in each dataset, 24 were common to both and correlated with each other. One group was notable for high EMT/reactive stroma (high fibronectin, low E-cadherin), while the other group was notable for high TSC/MTOR (high MTOR, phospho-MTOR, Tuberin), and high RTK pathway components (high BRAF, HER2, HER3). This latter group also was notable for elevated beta-catenin and elevated phospho-AMPK. In the MDACC and TCGA cohorts, the high RTK group was more likely to have lymphovascular invasion ($p = 0.023$ in MDACC, $p = 0.017$ in TCGA) and less likely to have BRAF mutation ($p = 0.011$ in MDACC, $p = 0.002$ in TCGA). On multivariate Cox regression analysis of relapse-free survival of 171/233 Stage II-III MD Anderson patients with complete data, stage (HR 3.121, 95% CI 1.373-7.093, $p = 0.007$) and proteomic grouping (HR 2.105, 95% CI 1.037-4.274, $p = 0.039$) were significantly associated with inferior relapse-free survival, while age, BRAF mutation status, and lymphatic invasion status were not significant. **Conclusions:** CRCs appear to have distinct subsets defined by proteomic features. These findings reflect distinct differences in cellular function that have prognostic implications.

3613 Poster Session (Board #106), Mon, 8:00 AM-11:30 AM

Genetic variants of kinases suppressors of Ras (KSR) to predict tumor response to first-line cetuximab in patients with mCRC: Prospective analysis in the FIRE 3 trial. *First Author: Leonor Benhaim, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Activation of EGFR pathway in RAS-BRAF wild-type models can be modulated by scaffold proteins kinase suppressor of ras (KSRs) that binds RAS promoting ERK activation. We previously showed in patients with KRAS-BRAF wild-type tumor treated with FOLFIRI-cetuximab that KSR2 rs11068551 TT was associated to significantly longer PFS. On the other hand, among female patients treated with FOLFIRI-bevacizumab the KSR1 rs2241906 CC genotype was associated to significantly shorter PFS. We aimed at validate our finding by investigating the correlation between KSR variants and clinical outcomes in patients enrolled in the FIRE 3 trial. **Methods:** Genomic DNA was isolated from tissue samples of 592 patients with KRAS exon 2 wild-type enrolled in the randomized phase III, FIRE 3 trial that was designed to compared the efficacy of two targeted agents when associated to FOLFIRI regimen. Patients were randomly assigned to first-line FOLFIRI associated with either bevacizumab (n = 295) or cetuximab (n = 297) (NCT00433927). In both arms, DNA was amplified by PCR and KSR variants were detected by direct sequencing. **Results:** We confirmed prospectively that KSR2 rs11068551 could predict outcomes in patients receiving cetuximab. 1/Patients with the TT genotype (n = 40) demonstrated a significant lower response rate than patients carrying C (n = 133) in the cetuximab arm (55% vs. 77%, p= 0.008). 2/ Patients with left-sided tumors and TT genotype (n = 32) showed a significant longer PFS (12.9 vs. 10.2 months, log rank p = 0.049) than patients harboring any of the C allele (n = 128) in the cetuximab arm. 3/ No association between KSR2 rs11068551 and outcomes was seen in the bevacizumab arm. We did not confirm the relation between KSR1 rs2241906 and outcomes (response rate, PFS or OS) even when adjusted with gender and location. **Conclusions:** We prospectively validated the predictive value of KSR2 rs11068551 mCRC pts treated with first-line cetuximab-containing therapy. This predictive value may dependent on tumor location. We could not confirm the predictive value of KSR1 rs2241906 in patients receiving bevacizumab-containing treatment.

3614 Poster Session (Board #107), Mon, 8:00 AM-11:30 AM

Phase II trial of autophagy inhibition using hydroxychloroquine (HCQ) with FOLFOX/bevacizumab in the first-line treatment of advanced colorectal cancer. *First Author: Arturo Loaiza-Bonilla, University of Pennsylvania, Philadelphia, PA*

Background: We have shown that autophagy, the regulated dissolution of cellular elements to maintain survival in adverse environmental conditions, is a determinant of resistance to chemotherapy in colorectal cancer models, and is reversed by chloroquine (Selvakumaran M, et al. Clin Cancer Res, 2013). A Phase I run-in demonstrated that full doses of mFOLFOX6/ bevacizumab were tolerated with HCQ 600mg PO twice daily. **Methods:** We report a Phase II trial in previously-untreated patients with metastatic colorectal cancer. Patients were treated every two weeks with 5-FU (400mg/m2 bolus, then 2400 mg/m2 over 46h) together with leucovorin 200mg/m2, oxaliplatin 85mg/m2, bevacizumab 5mg/kg, all IV, repeated every two weeks, with HCQ as above. After 12 cycles, oxaliplatin was omitted and patients were continued on 5-FU, bevacizumab, and HCQ. Imaging was performed every 8 weeks. **Results:** Twenty-four patients (pts) have been accrued, of whom 23 are eligible: 10 female/13 Male; 19 Caucasian/3 Black/1 East-Asian. Toxicity has been generally tolerable. Grade 3 effects included neutropenia 9/23), diarrhea (1/23), and anorexia (1/23). There were two episodes of myocardial infarction, one fatal, one of atrial arrhythmia, and two of pulmonary embolism in the course of the trial. 20/23 patients were able to maintain full dose of HCQ. Patients evaluable for response include 19 (4 pts too early). There were 1 complete response (5%), 9 partial responses (47%), and 7 stable disease (37%). Four patients went off study for resection of metastatic disease after 3-25 months. Median progression-free and overall survival have not been reached. Autophagy biomarkers in peripheral mononuclear cells show autophagy inhibition in the majority of patients. Six of thirteen patients with genomic testing available had a TP53 mutation. Four of these six patients had a major response (1CR, 3 PR). **Conclusions:** The combination of FOLFOX/ bevacizumab with HCQ is an active regimen in unselected patients with colorectal cancer. A randomized Phase II trial of the combination is in development. Clinical trial information: NCT01206530.

3615 Poster Session (Board #108), Mon, 8:00 AM-11:30 AM

Phase 1 extension study of BBI503, a first-in-class cancer stemness kinase inhibitor, in patients with advanced colorectal cancer. *First Author: Derek J. Jonker, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

Background: Targeting cancer stem cells (CSC) has shown pre-clinical efficacy and holds therapeutic promise. BBI503 is a first-in-class cancer stemness kinase inhibitor with potent in vitro and in vivo activity against CSC. BBI503 works through inhibition of stemness pathways, including Nanog. High Nanog expression in patients with colorectal cancer (CRC) predicts poor prognosis. Patients with advanced CRC who had failed all standard treatments were enrolled in a phase I and disease-specific cohort expansion study. **Methods:** BBI503 was given orally and continuously in 28-day cycles until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Eligible patients with CRC received BBI503 monotherapy at 20 mg to 500 mg total daily. Archival tissue was evaluated by IHC for Nanog expression. **Results:** 47 patients with heavily pre-treated CRC were enrolled (median 4 prior lines standard therapy). Bevacizumab was used in 80%, anti-EGFR AB in 60%, and regorafenib in 23%. Most (N = 35, 75%) received BBI503 at RP2D, 300 mg once daily. Median treatment duration was 8 weeks (range < 1 to 46+). Common adverse events (AE) considered related to therapy were grade 1 to 2 diarrhea, abdominal pain, fatigue, and nausea/vomiting/anorexia. At RP2D, Grade 3 AE were diarrhea (N = 3), fatigue (N = 3), nausea (N = 2), and weight loss (N = 1). Archival tissue was available from 39 patients (83%). DCR (CR+PR+SD) in evaluated patients with high Nanog expression (biomarker positive) was 56%, while DCR in biomarker negative patients was 13% (p = 0.040). Median overall survival (mOS) in biomarker positive patients (ITT) was 38 weeks, while mOS in biomarker negative patients (ITT) was 16 weeks (p = 0.089 Log-Rank). **Conclusions:** BBI503, a first-in-class cancer stemness kinase inhibitor, demonstrated tolerability at the RP2D administered to patients with pre-treated mCRC. Disease control and prolonged overall survival were observed in CRC patients with positive Nanog expression in tumor tissues. Further clinical evaluation of BBI503 alone or in combination with standard chemotherapeutic agents in CRC is warranted. Clinical trial information: NCT01781455.

3616 Poster Session (Board #109), Mon, 8:00 AM-11:30 AM

A phase Ib study of BBI608 in combination with FOLFIRI with and without bevacizumab in patients (pts) with advanced colorectal cancer (CRC). *First Author: Joleen Marie Hubbard, Mayo Clinic, Rochester, MN*

Background: BBI608 is an oral first-in-class cancer stemness inhibitor of Stat3. Potent anti-tumor activity was observed *in vitro* and *in vivo*,in mono- and combination therapy. In a phase I study, BBI608 monotherapy was generally well tolerated at 500 mg BID with encouraging signs of anti-tumor activity. **Methods:** A phase Ib open label, multi-center study in pts with advanced CRC was performed to determine RP2D, safety, tolerability, and preliminary anti-cancer activity of BBI608 in combination with FOLFIRI with or without bevacizumab. BBI608 was administered at 240 mg BID in combination with FOLFIRI (5-FU 400 mg/m^2 bolus with 2400 mg/m^2, irinotecan 180 mg/m^2, and leucovorin 400 mg/m^{2}infusion) with or without bevacizumab 5 mg/kg, administered bi-weekly until progression of disease, unacceptable toxicity, or other discontinuation criterion was met. **Results:** 9 pts were enrolled with 4 pts receiving FOLFIRI and 5 pts receiving FOLFIRI with bevacizumab in combination with BBI608. All pts were pretreated with ≥ 1 line and 67% (6/9) of pts with ≥ 4 prior lines of therapy. Combination treatment was well tolerated with no dose-limiting toxicity and safety profile similar to that of each regimen individually, with no difference in safety observed with addition of bevacizumab. Most common adverse events included grade 1 and 2 diarrhea, abdominal cramps, nausea, vomiting and anorexia. Grade 3 diarrhea was observed in 2 pts, and resolved with a brief BBI608 dose holiday or dose reduction to 160 mg BID and anti-diarrheal medications, respectively. Additionally, self-resolving grade 3 fatigue lasting 4-8 days was observed in 2 pts. No significant pharmacokinetic interactions were observed. Disease control (PR+SD) was observed in 9 of 9 evaluable pts (100%) with 1 PR (44% regression) and 8 SD with tumor size reduction (25%, 23%, 17%, 16%, 14%, 14%, 4% and 2%, respectively). The median progression free survival was 23.7 weeks with SD of ≥ 6 months in (33.3%) 3/9 pts. **Conclusions:** This phase Ib study demonstrated that BBI608 at 240 mg BID can be safely combined with FOLFIRI with and without bevacizumab. Encouraging anti-tumor activity was observed in pts with advanced and heavily pretreated CRC. Clinical trial information: NCT02024607.

3617 Poster Session (Board #110), Mon, 8:00 AM-11:30 AM

A phase Ib/II study of cancer stem cell inhibitor BBI608 administered with panitumumab in KRAS wild-type (wt) patients (pts) with metastatic colorectal cancer (mCRC) following progression on anti-EGFR therapy. *First Author: Kristen Keon Ciombor, Ohio State University Wexner Medical Center, Columbus, OH*

Background: BBI608 is an oral first-in-class cancer stemness inhibitor that works by targeting Stat3. Potent preclinical anti-tumor activity was observed *in vitro* and *in vivo*, in mono- and combination therapy. In a phase I study, BBI608 was well tolerated with encouraging signs of activity and a RP2D of 500 mg BID with additional ongoing studies showing that BBI608 can be safely combined with multiple chemotherapeutics. **Methods:** A phase Ib/II open-label, multi-center study in pts with advanced *K-Ras*wt mCRC was performed to determine safety and preliminary activity of BBI608 administered orally at 480-500 mg BID with panitumumab (6 mg/kg bi-weekly) until disease progression, unacceptable toxicity, or other discontinuation criterion was met. Following clearance of the DLT period in 6 pts, 18 more pts were enrolled. **Results:** All of the 24 pts enrolled were pre-treated with ≥2 lines of therapy and 12/24 with ≥3 lines of therapy. An MTD was not determined and BBI608 could be given in combination with full dose panitumumab. The safety profile was consistent with that of each agent as monotherapy and most common adverse events included grade 1-2 diarrhea, abdominal cramps, nausea and vomiting. Grade 3 hypokalemia and dehydration occurred in 2 pts. No significant pharmacokinetic interactions were observed. Disease control (SD+PR) was observed in 4 of 9 (44.4%) anti-EGFR naïve pts. Of those, 2 of 9 (22%) had PR (35.5% and 33.3% regressions), and 2 had SD. Disease control (only SD) was observed in 8/15 (53.3%) pts who had failed anti-EGFR (cetuximab) therapy, 2 of which had SD with regression (12.9% and 6.8%). The median progression free survival was 9 and 16.4 weeks in anti-EGFR naive and previously exposed pts, respectively. **Conclusions:** This phase Ib/II study demonstrated that BBI608 and bi-weekly panitumumab can be safely combined at full dose. The response rate in anti-EGFR naïve pts was notably greater than that of anti-EGFR monotherapy. Moreover, encouraging preliminary activity was observed in K-*Ras* wt mCRC regardless of prior anti-EGFR exposure, suggesting that BBI608 may sensitize pts to repeat anti-EGFR therapy. Clinical trial information: NCT01776307.

3618 Poster Session (Board #111), Mon, 8:00 AM-11:30 AM

Phase I/II study of everolimus (E) with irinotecan (Iri) and cetuximab (C) in 2nd line metastatic colorectal cancer (mCRC): Hoosier Cancer Research Network GI05-102. *First Author: E. Gabriela Chiorean, University of Washington, Seattle, WA*

Background: Preclinically, mTOR and EGFR inhibitors are synergistic. We hypothesized that the mTOR inhibitor E would enhance clinical efficacy when added to C. The Phase I portion determined the safety, and maximum tolerated dose (MTD), and the Phase II evaluated the response and survival rates with this combination. Preliminary results of the Phase I study (ASCO 2011, Shahda et al) determined the MTD as E 5 mg po daily (qd) combined with Iri and C. Here we report overall safety and efficacy results of the Phase I/II study. **Methods:** Patients (pts) were treated with Iri 125 mg/m^2 weekly (qw) x 2 every 3 wks, C 400 mg/m^2 loading, then 250 mg/m^2 qw, and escalating doses of E: 5 mg qod, 5 mg qd and 10 mg qd in 21-day cycles (Phase I), and 5 mg qd (Phase II). Eligibility allowed KRAS mutated (MUT) mCRC. During phase II, KRAS wild-type (WT) pts were randomized to Iri+C+E vs Iri+C, and all KRAS MUT pts received Iri+C+E. Archival tumors were analyzed for biomarkers of EGFR and mTOR pathways activation. The study was discontinued early due to funding termination by Novartis. **Results:** 43 pts were enrolled, median age 60 y (25-77), 24 male. 30 pts enrolled in phase I (KRAS WT n = 15, KRAS MUT n = 13, KRAS unknown n = 2), and 13 pts in phase II (KRAS WT: n = 5 Iri+C+E, n = 2 Iri+C; KRAS MUT n = 6 Iri+C+E). The most common gr 3/4 AEs were diarrhea (35%), neutropenia (23%), fatigue (21%), mucositis (21%), and rash (19%). Among KRAS WT pts (n = 22) there were 1 CR, 3 PR (RR 18%), 12 SD (54%), and among KRAS MUT pts (n = 19) there were 1 PR (5%) and 11SD (52%). Median progression-free survival (PFS) and overall survival (OS) rates were 6 and 16 mos, respectively for all KRAS WT pts treated with Iri+C+E (n = 20), and 8.3 and 21.6 mos, respectively for KRAS WT pts treated at MTD (n = 11). Median PFS and OS were 4.3 and 12.3 mos, respectively for KRAS MUT pts. Only 2 KRAS WT pts were randomized to Iri+C before study closure. PD markers will be presented. **Conclusions:** The combination of Iri+C+E has an expected toxicity profile, and was clinically active as second-line treatment for KRAS WT mCRC pts. Further studies should assess the CRC pts most likely to benefit from mTOR inhibitors in addition to EGFR blockade. (NCT00522665) Clinical trial information: NCT00522665.

3619 Poster Session (Board #112), Mon, 8:00 AM-11:30 AM

Programmed death-ligand 1 (PD-L1) expression in small bowel adenocarcinomas (SBA). *First Author: Katrina Pedersen, Mayo School of Graduate MedcI Education, Rochester, MN*

Background: SBAs are rare, resulting in a paucity of data on effective treatments. Highly active immune surveillance within all parts of the intestine may explain the rarity. In such an environment, tumor cells may express PD-L1 to inhibit immune-mediated cytotoxicity. We hypothesized that SBAs would have a high prevalence of PD-L1 IHC positive cells, which could be a marker for future immunotherapeutic efficacy. **Methods:** Forty-five archived SBA primary tumor samples were selected for IHC staining with the PD-L1 (anti-B7-H1 clone 5H1) antibody. Patient records were reviewed for clinical data outcomes including overall survival (OS), gender, primary site, and known microsatellite instability (MSI) status. **Results:** By site, we examined 25 (56%) duodenal, 14 (31%) jejunal, and five (11%) ileal tumors. 53% of tumors (24/45) demonstrated strong PD-L1 staining, with 4/45 (9%) in a cellular pattern and 21/45 (47%) in the intratumoral stroma, morphologically consisting of a mononuclear cell infiltration. Stratified by disease location, 11/25 (44%) of the duodenal tumors (9/11 stromal pattern, 1/11 cellular pattern, 1/11 positive for both), 9/14 (64%) of the jejunal tumors (8/9 stromal, 1/9 cellular), and 3/5 (60%) of the ileal tumors (2/3 stromal, 1/3 cellular) are PD-L1 positive by IHC. One site-unclassified tumor had positive stromal staining. An unadjusted survival analysis shows that PD-L1 staining within tumor cells is associated with poorer median OS (10 months vs. 5.5 years, p = 0.0009 by Log-Rank). Stromal PD-L1 staining does not exhibit a statistically significant difference in OS (median 66.9 months, vs 34.5 months p = 0.51). Of five tumors known to be MSI-H, 1/5 (20%, stromal pattern) has concomitant PD-L1 expression. **Conclusions:** To our knowledge, this is the first report of PD-L1 expression in SBA, with 53% staining positive. Given reported activity of anti-PD1 therapy in gastric cancer and MSI-H colon cancer, this indicates a potential role for immunotherapy in SBA. Those expressing PD-L1 intracellularly may have worse outcomes. Further studies to address prognostic and therapeutic implications PD-L1 expression are indicated.

TPS3620 Poster Session (Board #113a), Mon, 8:00 AM-11:30 AM

A phase III study of the impact of a physical activity program on disease-free survival in patients with high-risk stage II or stage III colon cancer: A randomized controlled trial (NCIC CTG CO.21). *First Author: Christopher M. Booth, Division of Cancer Care & Epidemiology, Cancer Research Institute, Queen's University, Kingston, ON, Canada*

Background: Observational studies indicate that physical activity (PA) is associated with colon-cancer specific survival. The NCIC Clinical Trials Group CO.21 (CHALLENGE) trial is designed to determine the effects of a structured physical activity (PA) intervention on disease-free survival in high-risk stage II or III colon cancer survivors who have completed adjuvant chemotherapy within the previous 2-6 months. **Methods:** Phase III randomized controlled trial. Target sample size of 962 patients is powered to detect a Hazard Ratio of 0.75 for disease-free survival (DFS). Trial participants are stratified by centre, disease stage, body mass index, and performance prior to randomization to a structured PA intervention or general health education materials. The PA intervention consists of a behavioural support program and supervised PA sessions delivered over a three-year period, beginning with regular face-to-face sessions and tapering to less frequent face-to-face or telephone sessions. The goal of the PA program is to increase weekly PA by 10 MET-hours/week. The PA program is delivered by physical activity consultants trained in exercise physiology and behavior change. **Outcomes:** The primary endpoint is DFS. Main secondary endpoints include multiple patient-reported outcomes (including those that measure fatigue), objective physical functioning, biologic correlative markers (including assessment of the insulin pathway), and an economic analysis. Data are also being collected on motivational outcomes and behavior change that will inform program delivery. **Current Enrollment:** The study is open at 21 centers in Canada and 26 centers in Australia with recent expansion into the United States, Israel, and Korea. As of January 1, 2015 341 patients are randomized. The new international partnerships will accelerate accrual. **Summary:** Cancer survivors and cancer care professionals are interested in the potential role of PA to improve disease-free survival and quality of life. A randomized controlled trial is needed to provide compelling evidence to justify changes in health care policies and practice. Clinical trial information: NCT00819208.

TPS3621 Poster Session (Board #113b), Mon, 8:00 AM-11:30 AM

Genotype-directed phase II study of irinotecan dosing in metastatic colorectal cancer (mCRC) patients receiving FOLFIRI + bevacizumab: The GENIC study. *First Author: Grant Richard Williams, UNC Chapel Hill, Chapel Hill, NC*

Background: Infusional fluorouracil/leucovorin plus irinotecan with bevacizumab (FOLFIRI-bev) is a standard first-line option for mCRC. The active metabolite of irinotecan, SN-38, is inactivated via glucuronidation by UGT1A1. Common germline variants of UGT1A1 are well known to alter the rate of glucuronidation and exposure to SN-38. UGT1A1*28 decreases UGT1A1 expression such that *28/*28 homozygotes have greater SN-38 exposure and increased risk of neutropenia. Despite the well-described association of genotype and SN-38 exposure, irinotecan doses have been established independent of genotype. Dose-limiting toxicity in the ~10% of patients homozygous for *28/*28 may have led to under-dosing of patients with other genotypes. In phase I genotype-directed dose-finding studies of FOLFIRI +/- bev, *1/*1 and *1/*28 patients were able to tolerate significantly higher doses of irinotecan (Sharma GI ASCO 2014, Marcuello BJC 2011, Toffoli JCO 2010) with a promising efficacy signal. We hypothesize that genotype-guided irinotecan dosing—in which *1/*28 and *1/*1 genotypes receive higher doses of irinotecan—will increase the overall benefit of FOLFIRI-bev for patients with mCRC with tolerable toxicity. GENIC is a phase II multicenter, single arm trial designed to estimate the progression-free survival (PFS) of genotype-guided irinotecan dosing in patients receiving first-line FOLFIRI-bev for mCRC (NCT02138617). **Methods:** Patients with unresectable mCRC eligible for FOLFIRI-bev will be assigned irinotecan dose based on UGT1A1 genotype: *1/*1 = 310mg/m^2; *1/*28 = 260mg/m^2; or *28/*28 = 180mg/m^2. Fluorouracil, leucovorin, and bevacizumab are given at standard doses. The primary objective is to estimate PFS compared with recently reported PFS from FIRE-3 and 80405. 100 patients are planned to ensure 86 are evaluable, giving 80% power to detect a 3.5 month improvement in PFS. Secondary objectives will evaluate toxicity, response rate, and overall survival. Efficacy by genotype will be explored. The Patient Reported Outcomes (PRO) version of the CTCAE will evaluate patient reported tolerance and the concordance between patient and clinician assessment. Clinical trial information: NCT02138617.

TPS3622 Poster Session (Board #114a), Mon, 8:00 AM-11:30 AM

Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases: The randomized phase III CAIRO5 study of the Dutch Colorectal Cancer Group. *First Author: Joost Huiskens, Academic Medical Centre, Amsterdam, Netherlands*

Background: Colorectal cancer patients with unresectable liver-only metastases may be cured after downsizing of metastases by neoadjuvant systemic therapy. However, the optimal neoadjuvant induction regimen has not been defined, and the lack of consensus on criteria for (un)resectability complicates the interpretation of published results. **Methods:** CAIRO5 is a multicenter, randomized, phase III clinical study. Colorectal cancer patients with initially unresectable liver-only metastases are eligible, and will not be selected for potential resectability to avoid selection bias. The unresectability status is prospectively assessed by a central panel consisting of at least one radiologist and three liver surgeons, and defined as no radical resection possible in one session with resection only. Tumors of included patients will be tested for *RAS* and *BRAF* (for stratification purpose) mutation status. Patients with *RAS* wild type tumors are treated with doublet chemotherapy (FOLFOX/FOLFIRI, choice of investigator) and randomized between the addition of either bevacizumab or panitumumab, patients with *RAS* mutant tumors are randomized between doublet chemotherapy (FOLFOX/FOLFIRI) or triple chemotherapy (FOLFOXIRI), both with bevacizumab. Resectability status will be re-evaluated every two months. The primary study endpoint is median progression-free survival. Secondary endpoints include the R0/1 resection rate, and median overall survival. **Conclusion** CAIRO5 is a prospective multicenter trial that investigates the optimal systemic therapy for patients with initially unresectable, liver-only colorectal cancer metastases. **Discussion** The unique aspects of CAIRO5 concern the prospective phase III randomized comparison of neoadjuvant treatment regimens in this population with the use of uniform and transparent criteria for unresectability by an expert panel. This CAIRO5 panel may contribute to a consensus on criteria for unresectability and to awareness of secondary resections in these patients. Clinical trial information: NCT02162563.

TPS3623 Poster Session (Board #114b), Mon, 8:00 AM-11:30 AM

Phase II study of ruxolitinib with regorafenib for relapsed/refractory (r/r) metastatic colorectal cancer (mCRC). *First Author: David R. Fogelman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Therapeutic options are limited after patients (pts) with mCRC progress following treatment with current standards of care. As with pancreatic cancer (PC), CRC induces a systemic inflammatory response, possibly from inflammatory cytokine production by colorectal tumor cells themselves or by the local inflammatory milieu. Elevated levels of inflammatory cytokines are associated with more advanced disease and reduced survival. In the phase II RECAP study, treatment with the JAK1/JAK2 inhibitor ruxolitinib + capecitabine showed improved overall survival (OS) relative to placebo + capecitabine in pts with metastatic PC who had evidence of systemic inflammation as demonstrated by elevated C-reactive protein levels (Hurwitz et al. ASCO 2014. abs 4000). Given the evidence supporting a role for the JAK-STAT pathway in the systemic inflammatory response in CRC, ruxolitinib may be an effective therapeutic strategy in pts with r/r mCRC. **Methods:** Eligible pts are aged ≥ 18 years with histologically or cytologically confirmed adenocarcinoma of the colon or rectum that is metastatic; have an ECOG performance status of 0–2; have received fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF therapy (if no contraindication) and an anti-EGFR therapy (if *KRAS* wild-type and no contraindication). Exclusion criteria are prior regorafenib treatment; active GI disease interfering with absorption; known central nervous system metastases; hepatitis B virus (HBV) or hepatitis C virus viremia or at risk for HBV reactivation. The study consists of 2 parts. Part 1 is open label and dose finding and will assess the safety and tolerability of ruxolitinib in combination with regorafenib. In Part 2, pts are randomized 1:1 to receive 28-day cycles of ruxolitinib 15 mg twice daily + regorafenib 160 mg once daily (days 1–21) or placebo + regorafenib. The primary endpoint of part 2 is OS. Secondary endpoints include progression free survival, overall response rate, duration of response, and disease control. Treatment will continue as long as tolerated and discontinuation criteria are not met. Enrollment in this study was initiated in March 2014 and is ongoing. The planned enrollment is 373 pts. Clinical trial information: NCT02119676.

TPS3624 Poster Session (Board #115a), Mon, 8:00 AM-11:30 AM

FOLFOXIRI with or without bevacizumab as first-line treatment for unresectable liver-only metastatic colorectal cancer patients with RAS mutation-type. *First Author: Yanhong Deng, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: For liver limited metastatic colorectal cancers, complete resection of liver metastases is the only potentially curative treatment and can significantly improve overall survival. The current goal of medical treatment for colorectal cancer with initially unresectable liver metastases is to maximize the rate of secondary resection. This phase II study is to explore whether FOLFOXIRI plus bevacizumab compared with FOLFOXIRI alone as first-line treatment could improve radical resectability in patients with RAS mutaion-type, unresectable liver-only metastatic colorectal cancer. **Methods:** The primary endpoint is the conversion rate of liver metastases, which is defined as the proportion of patients who had a curative liver treatment following protocol treatment, i.e., liver metastases that can be radical resected with or without ablation with no postoperative evidence of residual malignant disease. Secondary endpoints include safety, objective response rate, overall survival, progression free survival, quality of life and an assessment of predictive molecular markers of response. 160 cases of patients meet inclusion criteria and are enrolled in the trial will be randomized to two therapy groups: experimental arm A (FOLFOXIRI plus bevacizumab) or control arm B (FOLFOXIRI alone) in a 1:1 allocation ratio, stratifying for centers, ECOG status, synchronous or metachronous metastases, and a risk score derived from Nordlinger. All patients will receive the study treatment regimen every 2 weeks, and a total of the maximum of 12 cycles. CT scan or MRI of the abdomen will be performed after 2 or 3 cycles of therapy to assess clinical response and resectability of liver metastases by multidisciplinary team including hepatic surgeon. If liver metastases are not deemed to be resectable at this assessment, but tumor assessment demonstrates stable disease or partial response, therapy will continue with re-assessment for clinical response and resectability after the next cycle. Clinical trial information: NCT02350530.

TPS3625 Poster Session (Board #115b), Mon, 8:00 AM-11:30 AM

LUME-Colon 1: A double-blind, randomized phase III study of nintedanib plus best supportive care (BSC) versus placebo plus BSC in patients with colorectal cancer (CRC) refractory to standard therapies. *First Author: Heinz-Josef Lenz, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Clinical studies with anti-VEGF agents, such as regorafenib (R), demonstrate that angiogenesis is critical to CRC tumor growth and metastasis. R has provided proof of principle in patients (pts) with refractory CRC, but is associated with a specific safety profile; there is a need for effective alternative treatments with different safety profiles. Nintedanib (N) is a triple angiokinase inhibitor of VEGF, PDGF and FGF signaling. N is approved in the European Union for the treatment of pts with advanced adenocarcinoma NSCLC after 1st-line chemotherapy and has shown clinical benefit in trials in several tumor types. In a phase I study of N in CRC, a clinically relevant anti-angiogenic effect was observed in 67% of pts. These findings and a manageable safety profile provide a rationale to examine N in refractory CRC. The objective of this study (NCT02149108; 1199.52) is to evaluate the efficacy and safety of N in pts with refractory CRC after failure with standard chemotherapy and biologic agents. **Methods:** 764 pts worldwide (including 10 US sites) – age ≥ 18 years, ECOG-PS 0–1, and histologically/cytologically confirmed CRC adenocarcinoma not amenable to surgery and/or radiotherapy – will be randomized 1:1 to receive either N (200 mg bid) + BSC or placebo (bid) + BSC in 21-day courses until disease progression or undue toxicity. The study is powered to distinguish a clinically meaningful effect in the co-primary endpoints PFS and OS. Secondary endpoints are objective tumor response and disease control. Pts will be stratified at randomization based on previous R treatment, time from onset of metastatic disease to randomization and region. PFS and OS will be evaluated by the log-rank test to determine the effect of N independently at the two-sided alpha level of 0.05. Other assessments include frequency and severity of adverse events and changes in laboratory parameters to measure safety; health-related quality of life; and biomarker analyses focusing on exploring predictive biomarkers and drug resistance mechanisms. As of Jan 7, 2015, 180 pts were randomized and recruitment is ongoing. Results are expected in 2016. Clinical trial information: NCT02149108.

TPS3626 Poster Session (Board #116a), Mon, 8:00 AM-11:30 AM

Induction mFOLFOX6 with or without aflibercept followed by chemoradiation (CRT) and surgery in high risk rectal cancer: Phase II randomized, multicenter, openlabel trial—The GEMCAD RIA study. *First Author: Carlos Fernandez-Martos, Instituto Valenciano de Oncologia, Valencia, Spain*

Background: Induction chemotherapy (CT) before CRT and surgery is now considered a new treatment alternative for patients with locally advanced rectal (LAR) cancer. Willet et al. (Nat Rev 2004) demonstrated that Induction treatment with anti VEGF therapy bevacizumab (BEV) before CRT, decreased tumor interstitial fluid pressure and blood flow, suggesting normalization of the tumor vasculature. The AVCROSS phase II trial (Nogue, The Oncologist 2011) showed that BEV combined with induction CT followed by BEV combined with CRT and surgery produced high pCR rates (36%) but with an unacceptable rate of surgical reoperations. Aflibercept (Afli) (ziv-aflibercept in the US) is a novel anti-angiogenic agent that acts as a soluble receptor that binds to human VEGF-A, VEGF-B, PlGF. We hypothesized that administering induction Afli/FOLFOX followed by CRT will improve pCR rate without compromise wound healing. **Methods:** We will conduct a multicenter phase II randomized trial, stratified by mrT stage and institution, with 2:1 allocation, comparing preoperative induction mFOLFOX6 with or without Afli prior to standard CRT (capecitabine with 50.4 Gy) and surgery. Primary endpoint: pathological complete response (pCR). 180 patients (p) will be recruited (120 p for mFOLFOX6 + Aflibercept group and 60 p for mFOLFOX6). Assumptions: 10% of dropouts, 0.10% one-sided type-I error, 80% power to detect a 15% difference in pCR. 2 interim analyses for safety, efficacy/futility (Lan de Mets, O'brien-Fleming). Major eligibility criteria: High-risk rectal cancer with 1 of the following criteria on high resolution MRI: Extramural vascular invasion or extramural extension > 5 mms into perirectal fat or mesorectal fascia threatened or involved in middle T3 tumors. mrT3 distal and mrT4 or N2 middle or distal tumors. Enrollment began in January 2015. ClinicalTrials.gov Identifier: NCT02340949 Clinical trial information: 02340949.

TPS3627 Poster Session (Board #116b), Mon, 8:00 AM-11:30 AM

SWOG S0820/PACES (Preventing Adenomas of the Colon with Eflornithine and Sulindac): A randomized, double-blind, placebo-controlled phase III clinical trial. *First Author: Jason A. Zell, UC Irvine Health, Chao Family Comprehensive Cancer Center, Orange, CA*

Background: After standard treatment for stage 0-III colorectal cancer (CRC), patients remain at increased risk for metachronous high-risk adenomas (HRAs) and 2ndprimary CRCs. Polyamines, in excess, are implicated in CRC carcinogenesis. In prior CRC chemoprevention clinical trials, low doses of polyamine-inhibitory agents eflornithine (E) and sulindac (S) demonstrated impressive efficacy. In the prior phase III clinical trial of colorectal adenoma (CRA) patients the combination E+S vs. placebo for 3-years resulted in > 92% reduction in risk of HRAs. Utility of these agents in colon cancer survivors, however, is unknown. **Methods: Eligibility:**Patients age > 18 with colon or rectosigmoid adenocarcinoma, stage 0, I, II, or III are eligible. Patients with major cardiovascular risk factors (MI, CVA) are excluded, as are patients with hearing loss > 30dB at 4K Hz and below. Daily low dose aspirin is allowed. **Study Design:** Patients are enrolled 9-15 months postoperatively for a 3-year duration in the randomized, double-blind, placebo-controlled Phase III trial. The intervention consists of eflornithine 250mg or matching placebo 2 tablets daily and sulindac 150mg or matching placebo one tablet daily. Baseline and end-of-study audiograms are required. Using a 2x2 factorial design, we will conduct 3 formal comparisons, each at the 2-sided, alpha = .0167 level with > 80% power. We tested the marginal effects of E &S, and the combined effect of E+S compared to placebo only. 1488 patients will be accrued over 5 years. Optional study components include pharmacogenetic, pharmacokinetic, & diet/lifestyle studies. The DSMC last met in October of 2014 and suggested that the trial continue as planned. **Endpoints:** The primary objective is to assess whether eflornithine 500 mg or sulindac 150mg are effective in reducing the 3-year event rate, defined as HRA or 2nd primary CRC, in Stage 0- III colon cancer patients. **Hypothesis:** In stage 0-III colon cancer patients during postoperative year 1-4, one or both of the single active agents will produce a 35% decrease in the rate of HRAs + 2nd primary CRCs; combination E+S will result in a 58% decrease compared to placebo alone. Clinical trial information: NCT01349881.

TPS3628 Poster Session (Board #117a), Mon, 8:00 AM-11:30 AM

Multi-center, randomized, controlled, open-label effectiveness study of primary tumor resection or not in asymptomatic colorectal cancer with unresectable metastatic disease. *First Author: Gong Chen, Sun Yat-Sen Univ Cancer Ctr, Guangzhou, China*

Background: It is still unclear whether asymptomatic colorectal cancer patients with unresectable metastatic disease can benefit from palliative resection of primary tumor. Retrospective studies showed a controversial result that some patients who received the resection of the primary tumor would prolong their overall survival time for 6 months. We plan to initiate the first randomized study to evaluate the efficacy of the resection of primary tumor in asymptomatic metastatic colorectal cancer patients who respond to initial chemotherapy. **Methods:** This is a multi-center, randomized, controlled, open label, phase III study. The primary endpoint of the study was overall survival (OS) based on independent assessment. Secondary end-points include progress free survival (PFS), health-related quality of life (HRQoL) and toxicity profiles. The study was designed to have 80% power to detect a 0.71 HR of OS in surgery arm (from 15 month to 21 month). Results from a one-sided log rank test at 0.025 significance level will be presented. Based on these assumptions, a total of 480 patients are needed to observe 320 events. All asymptomatic colorectal cancer patients with unresectable metastatic disease who agree to join this study will receive screening chemotherapy (any useful first line chemotherapy can be used here, except -becacizumab-which may affect the safety of surgery) for 6 months. Those who respond to chemotherapy or stable will be randomly assigned (1:1) to receive surgical resection of the primary tumor or continue chemotherapy. The patients in surgery group will receive chemotherapy after recover from surgery. Recruitment will begin in March 2015. The duration of the trial will be 72 months (36 months recruitment and 36 months follow-up). Clinical trial information: NCT02149784.

TPS3629 Poster Session (Board #117b), Mon, 8:00 AM-11:30 AM

Phase IB/II study of neoadjuvant chemoradiotherapy with CRLX101 and capecitabine for locally advanced rectal cancer. *First Author: Andrew Wang, UNC Chapel Hill, Chapel Hill, NC*

Background: There is strong interest in the development of novel agents and strategies to further improve the therapeutic ratio of neoadjuvant chemoradiotherapy for rectal cancer. One innovative approach is to incorporate nanoparticle (NP) therapeutics, which are designed to preferentially accumulate in tumors. CRLX101 is an investigational nanoparticle-drug conjugate with a camptothecin payload. Preclinically, CRLX101 has been shown to be a potent radiosensitizer in colorectal cancer. The purpose of this Phase IB/II study is to assess tolerability and to evaluate whether the addition of CRLX101 to capecitabine and radiotherapy can improve pathologic complete response (pCR) and clinical outcomes for rectal cancer. **Methods:** This ongoing open label, single-arm multicenter Phase Ib/II study is designed to evaluate the addition of CRLX101 to a standard 5FU-based chemoradiotherapy regimen in patients with locally advanced rectal carcinoma (stage cT3-4N0 or cT1-4N+). Phase Ib employed a 3+3 dose escalation design with starting dose of 12 mg/m^2. Dose level +1 was 15 mg/m^2, the MTD for single agent CRLX101. 8 patients have completed treatment without DLT (3 in cohort 1 and 5 in cohort 2) and 1 patient is undergoing treatment at the 15mg/m^2 dose level. We have identified 15mg/m2 as the MTD /RP2D. The Phase II portion of the study is ongoing and will evaluate the efficacy of this MTD/RP2D and further characterize the safety of CRLX101 combined with CRT. Patients in the Phase Ib portion with resectable disease and who were treated at the RP2D will be included in the Phase II study population for efficacy analysis. Target accrual is 53 evaluable patients in the Phase II trial and a primary endpoint of pCR rate will be evaluated using a Simon two-stage design. Secondary objectives include evaluation of pathological response, disease free survival (DFS) and overall survival (OS). We hypothesize that our proposed regimen will improve the rate of pCR compared to 15-20% historical benchmarks. If results are consistent with a pCR rate of at least 35%, the treatment regimen will be considered worthy of further investigation. Clinical trial information: NCT02010567. Clinical trial information: NCT02010567.

TPS3630 Poster Session (Board #118a), Mon, 8:00 AM-11:30 AM

The CAIRO4 study: The role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer—A randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *First Author: Jorine 't Lam - Boer, Radboud University Medical Center, Nijmegen, Netherlands*

Background: There is no consensus regarding resection of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastatic colorectal cancer. A potential benefit of resection of the primary tumour is to prevent complications of the primary tumour in later stages of the disease. Retrospective studies also show a potential survival benefit for patients undergoing resection. However, surgery can cause severe morbidity and mortality in this patient group. We hereby propose a randomized trial in order to demonstrate that resection of the primary tumour improves overall survival. **Methods:** The CAIRO4 study is a multicentre, randomized, phase III study of the Dutch Colorectal Cancer Group (DCCG). Patients with synchronous unresectable metastases of colorectal cancer and few or absent symptoms of the primary tumour are randomized 1:1 between systemic therapy only, and resection of the primary tumour followed by systemic therapy. Patients will be stratified according to location of the primary tumour (colon versus rectum), WHO performance status (0-1 versus 2), hospital of inclusion, serum LDH (normal versus abnormal) and number of metastatic sites (single versus multiple). To demonstrate a survival benefit of 6 months in the experimental arm, a total of 218 events are needed (80% power, significance lever 0.05). Accounting for accrual time and follow-up, we need a total of 360 patients (180 patients per arm). Systemic therapy will consist of fluoropyrimidine-based chemotherapy in combination with bevacizumab. The primary objective of this study is to determine the clinical benefit in terms of overall survival of initial resection of the primary tumour. Secondary endpoints include progression free survival, surgical morbidity, quality of life and the number of patients requiring resection of the primary tumour in the control arm. Accrual has started in September 2012. As of January 2015, 64 centres in the Netherlands and Denmark are participating in the CAIRO4 study. Clinical trial information: NCT01606098.

TPS3631 Poster Session (Board #118b), Mon, 8:00 AM-11:30 AM

The ORCHESTRA trial: A phase III trial of adding tumor debulking to systemic therapy versus systemic therapy alone in (mCRC) multi-organ metastatic colorectal cancer. *First Author: Elske C. Gootjes, Department of Medical Oncology, VU University Medical Center, Amsterdam, Netherlands*

Background: In the current multidisciplinary approach of mCRC, local treatment of oligometastases is common practice. Results of large case series of selected patients treated with complete surgical resection of metastatic lesions suggest that this approach substantially improves survival rates to around 30-60%. Other techniques such as radiofrequency or microwave ablation (RFA, MWA), transarterial chemoembolization (TACE) or stereotactic ablative radiotherapy (SABR) can also be applied in local treatment. Curative treatment options are generally not available for patients with extensive hepatic and/or extrahepatic mCRC. These patients primarily receive palliative systemic treatment consisting of combination chemotherapy as well as targeted agents. So far, reports on the benefit of local treatment for metastases in multi-organ mCRC have major limitations, including being small, non-randomized, single-center and retrospective. The benefit from local treatment of metastases for these patients should be established to allow for interruption of the standard systemic therapy and exposure to possible adverse events from local treatment. **Methods:** The 'ORCHESTRA' trial is a randomized multicenter clinical trial for patients with multi-organ mCRC, comparing the combination of chemotherapy and maximal tumor debulking versuschemotherapy alone (NCT01792934). We will examine the interplay of both efficacy and toxicity for the combination of systemic chemotherapy and locoregional therapy. Our study design incorporates systemic as well as local therapy in the experimental arm and combines local treatment modalities to pursue maximal tumor debulking. We aim to improve overall survival of patients with multi-organ mCRC by maximal tumor debulking after induction chemotherapy with at least six months. A total of 478 patients will be included to meet the primary endpoint (power 80%, type I error rate 5%). We define local treatments feasible when they can be performed within a 3-month time period to prevent extensive delay of systemic therapy. Currently, 34 patients are included in 19 participating Dutch hospitals. Clinical trial information: NCT01792934.

TPS3632 Poster Session (Board #119a), Mon, 8:00 AM-11:30 AM

MErCuRIC1: A Phase I study of MEK1/2 inhibitor PD-0325901 with cMET inhibitor crizotinib in *RAS*MT and *RAS*WT (with aberrant c-MET) metastatic colorectal cancer (mCRC) patients. *First Author: Sandra Van Schaeybroeck, Queen's University Belfast Centre for Cancer Research and Cell Biology, Belfast, United Kingdom*

Background: *RAS* is mutated (*RAS*MT) in ~55% of mCRC, and phase III studies have shown that patients harbouring *RAS* mutations do not benefit from anti-EGFR MoAbs. In addition, ~50% of *RAS* Wild Type (*RAS*WT) will not benefit from the addition of an EGFR MoAb to standard chemotherapy. Hence, novel treatment strategies are urgently needed for *RAS*MT and > 50% of *RAS*WT mCRC patients. c-MET is overexpressed in ~50-60%, amplified in ~2-3% and mutated in ~3-5% of mCRC. Recent preclinical studies have shown that c-MET is an important mediator of resistance to MEK inhibitors (i) in *RAS*MT mCRC, and that combined MEKi/METi resulted in synergistic reduction in tumour growth in *RAS*MT xenograft models (1). A number of recent studies have highlighted the role of c-MET in mediating primary/secondary resistance to anti-EGFR MoAbs in mCRC, suggesting that patient with *RAS*WT tumours with aberrant c-MET (*RAS*WT/c-MET+) may benefit from anti-c-MET targeted therapies (2). These preclinical data supported the further clinical evaluation of combined MEKi/METi treatment in *RAS*MT and *RAS*WT CRC patients with aberrant c-MET signalling (overexpression, amplification or mutation; *RAS*WT/c-MET+). **Methods:** MErCuRIC1 is a phase I combination study of METi crizotinib with MEKi PD-0325901. The dose escalation phase, utilizing a rolling six design, recruits 12-24 patients with advanced solid tumours and aims to assess safety/toxicity of combination, recommended phase II (RPII) dose, pharmacokinetics (PK) and pharmacodynamics (PD) (pERK1/2 in PBMC and tumour; soluble c-MET). In the dose expansion phase an additional 30-42 *RAS*MT and *RAS*WT/c-MET mCRC patients with biopsiable disease will be treated at the RPII dose to further evaluate safety, PK, PD and treatment response. In the dose expansion phase additional biopsy and blood samples will be obtained to define mechanisms of response/resistance to crizotinib/PD-0325901 therapy. Enrolment into the dose escalation phase began in December 2014 with cohort 1 still ongoing. EudraCT registry number: 2014-000463-40. (1) Van Schaeybroeck S et al. Cell Reports 2014;7(6):1940-55; (2) Bardelli A et al. Cancer Discov 2013;3(6):658-73. Clinical trial information: 2014-000463-40.

TPS3633 Poster Session (Board #119b), Mon, 8:00 AM-11:30 AM

Development of a phase Ib/IIa proof-of-concept study of imalumab (BAX69), a first-in-class anti-macrophage migration inhibitory factor (MIF) antibody, as the 3rd or 4th line treatment in metastatic colorectal cancer (mCRC). *First Author: Xiaochun Liu, Baxter Healthcare Corporation, Deerfield, IL*

Background: Patients with mCRC who fail 2 or 3 lines of treatment have few effective treatment options. MIF is dramatically upregulated in CRC tissue and its serum concentration positively correlates with increased tumor aggressiveness and risk of hepatic metastasis in CRC pts. MIF appears to contribute to cancer progression in tumor-associated anti-apoptosis, angiogenic growth factor expression, neovascularization and hypoxic adaptation. Imalumab is a novel recombinant, fully-human, monoclonal antibody specific for the pathogenic form of MIF (oxMIF). Imalumab showed preliminary antitumor activity with acceptable tolerability in a phase I study (NCT01765790) in patients with cancers, including mCRC. Imalumab has synergistic effects with chemotherapeutic agents in mCRC preclinical models independent of KRAS or p53 mutational status, leading us to evaluate imalumab-based combination regimens. **Methods:** We adopted a two-step approach for this trial. A safety run-in dose escalation phase will be conducted first with imalumab at 7.5mg/kg weekly in combination with 5-FU/LV or panitumumab in mCRC patients with or without KRAS/NRAS mutation, respectively. In the absence of dose limiting toxicities (DLTs), imalumab will be escalated to 10mg/kg weekly to evaluate DLT (primary endpoint) and determine the recommended phase II dose of imalumab combined with 5-FU/LV or panitumumab. Then, a randomized (2:1) phase II portion will investigate whether imalumab plus 5-FU/LV (KRAS/NRAS mut) or panitumumab (KRAS/NRAS wild type) is superior to standard of care at the 3rd or 4th line treatment setting in prolonging progression-free survival (primary endpoint) in mCRC patients. Secondary endpoints include safety and tolerability, overall survival and response rate, the pharmacokinetic (PK) profile of imalumab in combination with 5 FU/LV or panitumumab, quality of life, and biomarker association with treatment response. An accrual of 12-24 pts for the safety run-in phase and 66 pts for the randomized phase is planned. Eligibility includes diagnosis of mCRC and failure of 2-3 lines of therapies. Clinical trial information: pending.

TPS3634 Poster Session (Board #120a), Mon, 8:00 AM-11:30 AM

Phase III study of regorafenib versus placebo as maintenance therapy in RAS wild type metastatic colorectal cancer (RAVELLO trial). *First Author: Erika Martinelli, Medical Oncology, Second University of Naples, Naples, Italy*

Background: Treatment of metastatic colorectal cancer (mCRC) has improved due to the introduction of more active chemotherapies (CT) and novel targeted agents that have significantly increased response rate (RR), progression free survival (PFS) and overall survival (OS). Recently, CORRECT and CONCUR trials have demonstrated both activity and efficacy of regorafenib, a small multi-kinase inhibitor, as monotherapy in pretreated mCRC. The wide range of action of regorafenib makes it an ideal candidate for monotherapy in earlier disease treatment lines in which different pathways could be involved in the acquisition of resistance. To improve long term efficacy of first line therapy several therapeutic approaches of maintenance treatment have been explored in mCRC. **Methods:** RAVELLO is an academic randomized, double-blind, placebo-controlled, multi-center, phase III study designed to evaluate efficacy and safety of regorafenib as maintenance treatment after first line therapy. Eligible patients: pathologically confirmed mCRC RAS wild type (KRAS and NRAS genes) treated with a first line fluoropyrimidine-based CT in combination with an anti-EGFR (epidermal growth factor receptor) monoclonal antibody for a minimum of 4 to a maximum of 8 months, with a stratification by response to the first line treatment (complete response/partial response or stable disease). 480 patients will be enrolled and randomly assigned in a 1:1 ratio to receive 160 mg regorafenib or placebo per os, every day for 3 weeks of every 4 weeks cycle, until disease progression or unacceptable toxicity. Primary endpoint is PFS. With a two-tailed alpha error of 0.05, the study will have 90% power to detect a 3-month prolongation of median PFS from randomization (corresponding to a hazard ratio of progression of 0.67 with 6-month median PFS expected in the control arm). Secondary endopoint are OS, safety, and biomarker correlative studies. Currently, one patient has been enrolled and is on treatment. EudraCT number: 2013-005428-41. Clinical trial information: 2013-005428-41.

TPS3635 Poster Session (Board #120b), Mon, 8:00 AM-11:30 AM

A phase 3 open-label, randomized, multicenter study of imprime PGG in combination with cetuximab in patients with KRAS wild type metastatic colorectal cancer. *First Author: Richard Dale Huhn, Biothera, Eagan, MN*

Background: Imprime PGG (Imprime) is a beta-1,3/1,6 glucan complex carbohydrate biologic, which harnesses innate immune effector cells to enhance killing of antibody-targeted, complement-opsonized tumor cells. In a phase 2 single-arm clinical trial in metastatic colorectal cancer (mCRC), the combination of Imprime with cetuximab resulted in 24% objective response rate (ORR), 62% disease control rate (DCR), and median time to progression (TTP) of 12 wks (Tamayo ME, Ann Onc 2010), representing approximate 100% increases vs historical control (Cunningham, NEJM 2004). ORR was 45%, DCR, 82% and TTP of 24 wks in patients (pts) with KRAS wild-type (WT) tumors (post hoc analysis). Single-agent cetuximab has been shown to improve ORR, progression-free survival (PFS) and overall survival (OS) in pts with epidermal growth factor receptor (EGFR) expressing, KRAS WT mCRC who failed oxaliplatin- and irinotecan-based therapy or are intolerant to irinotecan. The mechanism of action of cetuximab is thought to rely on competitive blockade of endogenous ligand binding and downstream signaling, internalization and down regulation of EGFR, as well as antibody-dependent cellular cytotoxicity (ADCC) (Erbitux USPI). The current trial, sponsored by Biothera and registered with ClinicalTrials.gov (NCT01309126) is to confirm these findings in phase 3. **Methods:** Eligible pts have received prior oxaliplatin- and irinotecan-based therapy or are intolerant to irinotecan, have measurable disease and ECOG performance status of 0 or 1. Approximately 795 pts will be randomized 2:1, stratified by geographic region, prior chemotherapy and site, to receive weekly open-label Imprime plus cetuximab or cetuximab alone. The primary endpoint of the study is OS and the primary analysis will occur when ~709 deaths have occurred. Secondary endpoints include PFS, ORR (based on RECIST 1.1), quality of life, safety and pharmacokinetics. Exploratory endpoints include biomarker analyses. Pt screening and enrollment is underway in the United States and Europe. Clinical trial information: NCT01309126.

4000 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. *First Author: David Cunningham, Royal Marsden Hospital, Sutton, Surrey, United Kingdom*

Background: R is a fully human monoclonal antibody to hepatocyte growth factor. A phase 2 study showed improved overall survival (OS) and progression-free survival (PFS) with R + ECX vs P + ECX in MET-pos G/GEJ cancer (*Lancet Oncol* 2014;15:1007). This phase 3 trial evaluated the efficacy and safety of R + ECX in MET-pos G/GEJ cancer. **Methods:** Key eligibility criteria: ≥ 18 yr; previously untreated, pathologically confirmed unresectable advanced G/GEJ adenocarcinoma; ECOG score 0–1; tumor MET-pos by IHC; HER2-negative. Pts were randomized 1:1 to receive ECX (IV epirubicin 50 mg/m^2 D1, IV cisplatin 60 mg/m^2 D1, oral capecitabine 625 mg/m^{2}BID D1−21) + R 15 mg/kg or P IV Q3W and stratified by disease extent (locally advanced vs metastatic) and ECOG score (0 vs 1). Primary endpoint: OS. A log-rank test stratified by randomization factors compared OS between arms. The study was powered to detect a HR of 0.69. Key secondary endpoints: PFS, 12-mo survival rate, objective response rate (ORR), safety and pharmacokinetics (PK). **Results:** 609 pts were randomized from Nov 2012 to Nov 2014. The study was stopped early based on an imbalance in deaths (R vs P: 128 vs 107 deaths, data cutoff: 27 Nov 2014). R was not superior to P for OS (one-sided test, p = 0.99). OS, PFS and ORR were statistically worse in the R arm. No subgroups seemed to benefit with R, including those with higher percentages of cells with ≥ 1+ MET expression. Most common AEs that were higher with R: peripheral edema, hypoalbuminemia, deep vein thrombosis and hypocalcemia. **Conclusions:** RILOMET-1 did not meet its primary endpoint; OS was statistically significantly worse with R. PK and MET biomarker analyses are pending. Clinical trial information: NCT01697072.

	R (n = 304)	P (n = 305)	R vs P
Median OS,* mo	9.6 (7.9–11.4)	11.5 (9.7–13.1)	HR† = 1.37 (1.06–1.78) p = 0.016
Median PFS,* mo	5.7 (5.3–5.9)	5.7 (5.5–7.1)	HR† = 1.30 (1.05–1.62) p = 0.016
12-mo survival rate*	38.4% (30.2%–46.6%)	49.7% (41.5%–57.4%)	Diff = -11.4 (-22.9–0.2) p = 0.053
ORR*	30% (24.6%–36.0%)	39.2% (33.3%–45.4%)	Odds ratio = 0.67 (0.46–0.96) p = 0.027

*95% CI shown. †Stratified.

4001 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in KEYNOTE-012. *First Author: Yung-Jue Bang, Seoul National University College of Medicine, Seoul, South Korea*

Background: Tumors use the PD-1 pathway to evade immune surveillance. Pembrolizumab, an anti–PD-1 monoclonal antibody, has shown antitumor activity in advanced cancers. We assessed the safety and efficacy of pembrolizumab in patients with advanced gastric cancer in KEYNOTE-012 (Clinicaltrials.gov identifier, NCT01848834). **Methods:** Archival tumor samples from patients from Asia-Pacific (AP) and rest of the world (ROW) with recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction were screened for PD-L1 expression using a prototype IHC assay with the 22C3 antibody. Only patients with distinctive stromal or ≥ 1% tumor nest cell PD-L1 staining were eligible. Patients received pembrolizumab 10 mg/kg every 2 weeks for up to 24 months or until complete response, progression, or unacceptable toxicity. Imaging was performed every 8 weeks. Primary efficacy end point is ORR assessed per RECIST v1.1 by independent central review. Secondary end points include duration of response, PFS, and OS. **Results:** Of the 162 patients screened, 65 (40%) were PD-L1^{+}. Of these 65 patients, 39 enrolled (19 from AP, 20 from ROW; median age, 63 years [range, 33-78]). The number of prior therapies for advanced disease ranged from 0 to 5; 67% received ≥ 2 prior therapies. Median follow-up duration was 8.8 months (range, 6.2-12.6); 13 patients (33%) remain on therapy. Four patients experienced 5 total grade 3-5 drug-related adverse events: peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis (n = 1 each). There was 1 drug-related death (hypoxia). ORR was 22% (95% CI, 10-39) by central review and 33% (95% CI, 19-50) by investigator review. Median time to response was 8 weeks (range, 7-16), with a median response duration of 24 weeks (range, 8+ to 33+). PD-L1 expression level was associated with ORR (1-sided $P = 0.10$). The 6-month PFS rate was 24%. The 6-month OS rate was 69%. **Conclusions:** Pembrolizumab demonstrated manageable toxicity and promising antitumor activity in advanced gastric cancer. These results support the ongoing development of pembrolizumab for gastric cancer. Clinical trial information: NCT01848834.

4002 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). *First Author: Derek Alderson, Queen Elizabeth Hospital, Birmingham, United Kingdom*

Background: Neoadjuvant chemotherapy (2 cycles cisplatin/5 fluorouracil) (CF) followed by surgery is a standard of care for locally advanced oesophageal cancer. We investigated whether more chemotherapy (4 cycles epirubicin/cisplatin /capecitabine (ECX)) would improve outcomes. **Methods:** A multi-centre, randomised, phase III trial comparing 2 cycles of CF with 4 cycles of ECX followed by oesophagectomy with 2-field lymphadenectomy for lower oesophageal and junctional (Types I and II) adenocarcinoma. Primary outcome was overall survival (OS); 842 patients (677 deaths) would detect an increase in 3-year survival from 30% to 38% (or 37%) with 82% (or 70%) power with $2\alpha = 5\%$. Deaths accrued more slowly than anticipated but the Independent Data Monitoring Committee considered the data sufficiently robust for release. Secondary outcomes include disease-free (DFS) and progression-free survival (PFS), pathological R0 resection rate, Mandard grade and quality of life. **Results:** From 2005-2011, 897 patients (451 CF, 446 ECX) from 72 UK centres were randomly allocated (1:1). Baseline characteristics were similar between the groups (overall, male 90%, median age 62 (IQR 56-67), staging included PET 60%, T3 N0 22%, T3 N1 65%). 96% CF received 2 cycles, 89% ECX > 3 cycles. Grade 3/4 toxicity was lower with CF (30% v 47% p < 0.001.) Of those patients having a resection R0 rates were CF 60%, ECX 66% with a Mandard grade ≤ 3 achieved in CF 15% v ECX 32% with 3 and 11% achieving complete response. Post-operative complications were similar (CF 57%, ECX 62%) as were deaths at 30 (CF 2%, ECX 2%) and 90 days post-surgery (CF 4%, ECX 5%). PFS and DFS favoured ECX, hazard ratio (HR, 95% CI) PFS 0.86 (0.74-1.01), DFS 0.88 (0.75-1.03). HR for OS was 0.92 (0.79-1.08, p = 0.3017) based on 315 CF and 298 ECX deaths, with similar 3 year survival rates CF 39% (35-44%) vs ECX 42% (37-46%). **Conclusions:** There is some evidence of a benefit from the prolonged ECX regimen, in terms of PFS, DFS and tumour regression at resection, but this does not translate into a survival benefit. Overall chemotherapy toxicity was higher with 4 cycles of ECX compared to 2 cycles of CF but surgical morbidity was not increased. Clinical trial information: 01852072.

4003 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

INTEGRATE: A randomized, phase II, double-blind, placebo-controlled study of regorafenib in refractory advanced oesophagogastric cancer (AOGC): A study by the Australasian Gastrointestinal Trials Group (AGITG)—Final overall and subgroup results. *First Author: Nick Pavlakis, Department of Medical Oncology, Royal North Shore Hospital, The University of Sydney, Sydney, Australia*

Background: REG is an oral multi-kinase inhibitor warranting evaluation in AOGC following failure of 1st or 2nd line chemotherapy (CT) where few options exist. **Methods:** International (Australia & New Zealand (ANZ), Korea, Canada (NCIC CTG)) phase II RCT with 2:1 randomization to 160 mg REG or matched Placebo (PBO) on days (D) 1-21 each 28 D cycle until disease progression (PD) or prohibitive adverse events. Primary endpoint: progression free survival (PFS). Final analysis used data to December 31, 2014. **Results:** 152 patients (pts) enrolled (November 2012 to February 2014) yielding 147 pts evaluable for analysis (97 REG and 50 PBO). M:F (118:29); primary site: OGJ (56), stomach (85); lines of prior CT: 1 (62), 2 (85); ECOG PS 0 (62): 1 (85). Median (med.) treatment wks: 8 (REG) v 4 (PBO). Med. REG dose intensity: 150 mg (130 mg Korea and 160mg ANZ/Can). 27 PBO pts received REG following PD. REG Med. PFS 11.1 wks (95% CI: 7.7 – 13.3) v PBO 3.9 wks (3.7 - 4.0), HR 0.40, p < 0.0001. Med. REG OS 25 wks (95% CI: 18.9-29.6) v PBO 19.4 wks (95% CI: 14.9 – 22.7), HR 0.74, p = 0.11. Pre-specified analyses found REG effect greater in Korea than ANZ/Can (HR 0.12 v 0.61, p = 0.0009) but consistent across age, NLR, primary site, lines of CT, peritoneal metastases (mets) presence, number of met. sites, and VEGF-A (Table). Results comparable for ITT population (n = 152). REG was well tolerated, with expected spectrum of toxicities. **Conclusions:** REG was highly effective in prolonging PFS across a broad range of pts, with a non-significant positive OS trend. Regional differences were found in the magnitude of effect but REG was effective in all regions and subgroups. A phase III trial is merited. Clinical trial information: 12612000239864.

Key sub-groups	PFS HR (95% CI)	P value	Interaction p Value
Korea (n = 54)	0.12 (0.06 – 0.27)	< 0.0001	0.0009
ANZ/Canada (n = 93)	0.61 (0.39 – 0.97)	0.03	
Lines of prior therapy			
1 (n = 62)	0.49 (0.28 – 0.86)	0.01	0.50
2 (n = 85)	0.32 (0.19 – 0.55)	< 0.001	
Neutrophil-lymphocyte ratio (NLR)			
<3 (n = 71)	0.41 (0.23 – 0.70)	0.0007	0.72
≥ 3 (n = 76)	0.37 (0.22 – 0.64)	0.0001	
Plasma VEGF-A (pg/ml)			
Low (≤ 0.14), (n = 82)	0.39 (0.24 – 0.65)	0.0001	0.72
High (> 0.14), (n = 62)	0.42 (0.23 – 0.78)	0.003	

4004 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

SWOG S0518: Phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127). *First Author: James C. Yao, Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment options for advanced carcinoid tumors (NETs) are limited. Somatostatin analogues (SSA) prolong progression-free survival (PFS) among patients (pts) who are treatment naïve or have stable disease. Interferon (INF) added to SSA has also demonstrated antitumor activity. Bevacizumab (BEV), added to SSA, octreotide (OCT), was associated with tumor regression and encouraging antitumor activity in a phase II study. The current study compares BEV + OCT to INF α-2b + OCT. Method: Pts with metastatic or unresectable, well-differentiated, G1/2 NETs with progressive disease or other poor prognostic features were randomly assigned (1:1) to receive OCT LAR 20 mg q 21 days with either BEV 15 mg/kg every 21 days or INF α-2b 5 million units three times per week. PFS by central review was the primary endpoint. Results: 427 pts were enrolled, of whom 402 were eligible, between December 2007 and September 2012. Median PFS by central review was 16.6 (95% CI: 12.9 – 19.6) months in BEV arm and 15.4 (95% CI: 9.6 – 18.6) months in the INF arm (HR 0.93; 95% CI 0.73-1.18; P = 0.55). By investigator review, median PFS was 15.4 (95% CI: 12.6 – 17.2) months in BEV arm and 10.6 (95% CI: 8.5 – 14.4) months in the INF arm (HR 0.90; 95% CI: 0.72 - 1.12; P = 0.33). TTF was significantly longer with BEV compared to INF (HR 0.72; 95% CI 0.58 - 0.89; P = 0.003). Median TTF was 9.9 (95% CI: 7.3 – 11.1) months in the BEV arm and 5.6 (95% CI 4.3 – 6.4) months in the INF arm. Confirmed radiologic response rates were 12% (95% CI: 8% - 18%) in the BEV arm and 4% (95% CI: 2% - 8%) in the INF arm. Common AEs with BEV + OCT included HTN (32%), proteinuria (9%), and fatigue (7%); and with INF + OCT included fatigue (27%), neutropenia (12%), and nausea (6%). Conclusion: BEV + OCT was associated with longer TTF compared to IFN + OCT; radiologic responses also appeared to be more frequent among pts treated with BEV + OCT. However, no significant differences in PFS were observed, suggesting that BEV and IFN have similar antitumor activity in pts with advanced carcinoid. Support: NIH/NCI grants CA180888, CA180819, CA180799, CA180820, CA180821 and CA025224, and in part by Genentech. Clinical trial information: NCT00569127.

4005 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance). *First Author: Matthew H. Kulke, Dana-Farber Cancer Institute, Boston, MA*

Background: Both VEGF pathway and mTOR inhibitors are active in pNET. Treatment with the mTOR inhibitor E improves progression free survival (PFS), but it is not known if the addition of a VEGF pathway inhibitor to an mTOR inhibitor enhances antitumor activity in pNET. This randomized phase II study evaluated E or E+B in pts with advanced pNET. **Methods:** Pts were randomized 1:1 to receive either E (10 mg po qd) or E (10 mg po qd) co-administered with B (10 mg/kg IV q 2 wks). Pts in both arms received concurrent standard dose octreotide. The primary endpoint was PFS. The potential superiority of E+B vs. E was assessed using a stratified log-rank test with 90% power (1-sided $\alpha = 0.15$) to detect a HR of 0.64. Secondary endpoints included overall survival (OS), response rate (RR), and safety. **Results:** 150 pts were randomized; 75 per arm. Pt characteristics were similar between treatment arms and included: median age 59 years (range 21-86), 56% male, ECOG PS 0 (57%) and 1 (43%), prior cytotoxic chemotherapy 24%. The median number of 28-day treatment cycles was 13 (E+B) and 12 (E), with a range of 1-44 cycles. Median follow up was 25.9 months. Pts on E+B experienced a higher frequency of grade 3 AEs, including diarrhea (14% vs. 3%; p = 0.01), hyponatremia (12% vs. 3%; p = 0.02), hypophosphatemia (11% vs. 3%; p = 0.04), proteinuria (16% vs. 1%; p = 0.001), and hypertension (41% vs. 12%; p < 0.0001). The frequency of grade 4 AEs was 11% in both arms; a single grade 5 event occurred on E. The median PFS was 16.7 mos (E+B) vs. 14 mos (E); HR = 0.80 (95% CI: 0.55, 1.17; 116 PFS events), 1-sided p = 0.12. The median OS was 36.7 mos (E+B) vs. 35.0 mos (E), HR = 0.75 (95% CI: 0.42-1.33; 49 OS events), 1-sided p = 0.16. Treatment with E+B was associated with a significantly higher RR (31%) compared to E alone (12%), p = 0.005) **Conclusions:** Treatment with E+B led to superior PFS compared to E but with more adverse events in this randomized phase II study. The RR was significantly higher in pts treated with E+B. The combination of E+B warrants further investigation in pts with advanced pNET. Clinical trial information: NCT01229943.

4006 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

High response rate and PFS with PEGPH20 added to nab-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer patients with high-HA tumors: Interim results of a randomized phase II study. *First Author: Sunil R. Hingorani, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Poor outcomes in pancreatic cancer (PDA) are associated in part with tumor stroma limiting chemotherapy perfusion. PDAs express high levels of hyaluronan (HA), which contributes to elevated interstitial pressures. PEGylated recombinant human hyaluronidase, PEGPH20, depletes HA in tumors. In a Phase Ib study of PEGPH20 with Gemcitabine (Gem), patients (pts) whose tumors were HA^{high} had improved ORR, PFS and OS compared to those with tumors that were HA^{Low}. **Methods:** This is an ongoing phase II, open-label, randomized study of PEGPH20 +Nab-Paclitaxel (Nab) + Gem (PAG) vs. Nab + Gem (AG) in previously untreated pts with Stage IV PDA. Pts receive 3 μg/kg twice weekly (Cycle 1) and then weekly (Cycle 2+) PEGPH20 in combination with standard dosing of AG. HA status was tested retrospectively. Primary endpoint is PFS, secondary endpoints include: ORR, OS and Safety. Due to a temporary clinical hold, ORR is from data through April 2014; and PFS is data through December 2014. **Results:** 146 pts were enrolled and 135 pts received at least one dose of study drug. The mean age was 65.1 yrs. (Range 29-83 yrs), 93% had a KPS of $\geq$ 80. The most common AEs related to study drugs (PAG vs. AG) were: fatigue (68% vs. 69%), nausea (55% vs. 44%), anemia (42% vs. 53%) peripheral edema (58% vs. 31%) and muscle spasms (55% vs. 2%). There was an imbalance of thromboembolic (TE) events with 42% vs. 25% of subjects having at least one TE event. Overall RR and PFS are shown in the table below. **Conclusions:** PEGPH20 + Nab/Gem is generally well tolerated in advanced PDA. Patients with HA^{high} tumors receiving PAG had greater ORR and longer PFS than HA^{high} patients receiving AG. Overall survival will be presented at the time of the meeting. ClinicalTrials.gov Identifier NCT01839487. Clinical trial information: NCT01839487.

Endpoint/Population	PAG	AG	P-value
ORR			
N = 135	25/74 (34%)	14/61 (23%)	0.17
HA^{High} N = 34	12/17 (71%)	5/17 (29%)	0.02
HA^{Low} N = 28	9/18 (50%)	5/10 (50%)	0.94
PFS			
N = 135	42/74; 5.7 months	39/61; 5.2 months	0.10
HA^{High} N = 48	12/25; 9.2 months	15/23; 4.3 months	0.03
HA^{Low} N = 58	22/36; 4.8 months	15/22; 5.6 months	0.81

4007 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

CONKO-005: Adjuvant therapy in R0 resected pancreatic cancer patients with gemcitabine plus erlotinib versus gemcitabine for 24 weeks—A prospective randomized phase III study. *First Author: Marianne Sinn, Charité - Universitätsmedizin Berlin, Medical Oncology, Berlin, Germany*

Background: Adjuvant chemotherapy with gemcitabine (Gem) for 6 months significantly improves survival of pancreatic cancer patients. CONKO-005 was designed to evaluate an additional effect of the EGFR-tyrosinkinase-inhibitor erlotinib (Erlo 100 mg p.o. daily) in combination with Gem (1000 mg/m² i.v. day 1,8,15, q29) for 24 weeks in pts after R0 resection. **Methods:** In an open-label multicenter design, pts were randomised within 8 weeks after operation to receive GemErlo or Gem; stratified by lymph node involvement, operation techniques, study centre. The primary endpoint was disease-free survival (DFS). The study was planned with a power of 80% at a significance level of 0.05 to detect an improvement of DFS from 14 to 18 months. Secondary objectives were median overall survival (OS) and treatment safety. Kaplan-Meier analyses were performed; survival data for the treatment arms compared using log-rank test. **RESULTS:** Between April 2008 and July 2013, 219 pts were randomized to GemErlo and 217 to Gem. Pts characteristics are well balanced (GemErlo/Gem): age (median 63/65 years), tumor status (T3/T4 88/86%), nodal status (N pos 64/66%), grading (G3 33/34%). After a median follow up of 41 months (March 2015), 350 events (80%) occurred. Median treatment duration was 22 weeks in both groups. Grade 3/4 toxicities were (GemErlo%/Gem%): rash 7/0.4, diarrhea 5/1, nausea 2/2, fatigue 5/2, hypertension 3/1,GGT 9/9, neutropenia 27/28, thrombopenia 5/2. There was no difference in DFS (median: GemErlo 11.6 months, Gem 11.6 months; HR 0.89, 95%CI 0.72-1.10) or OS (median: GemErlo 24.6 months, Gem 26.5 months; HR 0.90, 95%CI 0.71-1.15). There was no correlation between the grade of rash and an improved DFS in the GemErlo group (median: rash grade 0-1 vs > = grade 2 12.2 vs 11.0 months; HR 0.91, 95%CI 0.66-1.25). OS curves show a late divergence in favour of GemErlo (estimated survival after 2/3/4/5-years: 54/36/31/28% vs 53/33/22/19%). **Conclusion:** The combination therapy of GemErlo for 24 weeks did not improve DFS or OS. There is a trend in favour of long-term survival in pts treated with GemErlo. Clinical trial information: DRKS00000247.

4008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Preoperative modified FOLFIRINOX (mFOLFIRINOX) followed by chemoradiation (CRT) for borderline resectable (BLR) pancreatic cancer (PDAC): Initial results from Alliance Trial A021101. *First Author: Matthew H. G. Katz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Infusional 5-FU, oxaliplatin, leucovorin and irinotecan (FOLFIRINOX) is effective for metastatic PDAC. The tolerability and efficacy of neoadjuvant FOLFIRINOX and CRT for BLR PDAC is unknown. **Methods:** Patients (pts) with ECOG PS 0/1 and PDAC meeting any of the following centrally-reviewed radiographic criteria: 1) tumor-vessel interface (TVI) with superior mesenteric/portal vein (SMV) ≥ 180°, 2) TVI with superior mesenteric artery (SMA) < 180°, 3) TVI with hepatic artery of any degree, received mFOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 on day 1 followed by 5-FU 2400 mg/m^2 x 48 hours for 4 cycles) and CRT (50.4 Gy in 28 fractions) with capecitabine (825mg/m^2 BID) prior to pancreatectomy and postoperative gemcitabine (1000 mg/m^2 d1, 8,15 x 2 cycles). **Results:** 22 of 23 enrolled pts started therapy (median age 64 years, 64% ECOG PS 0). All pts completed mFOLFIRINOX and 21 (95%) completed CRT. The best RECIST responses during pre-op treatment were 2 CR, 4 PR, 15 SD and 1 PD. 7 patients did not undergo planned resection due either to progression (6) or refusal (1). Among the 15 (68%) patients who did undergo pancreatectomy, 14 (93%) operations were R0; 80% and 27% of operations required vein or hepatic artery resection, respectively; 7 (47%) specimens had < 5% residual tumor cells following therapy. Among all pts, 68% [95% CI (45.1 – 86.4)] underwent R0/R1 resections and 2 (9%) achieved pathologic CR. Related grade III and IV adverse events were observed in 46% (10 of 22) and 5% (1 of 22) of pts during chemotherapy, 38% (8 of 21) and 0% during CRT, and 15% (2 of 13) and 31% (5 of 13) following pancreatectomy; 1 pt died within 90 days of surgery. 18 pts are alive with an immature median follow-up of 10 months. **Conclusions:** In this multi-institutional study of pts with PDAC tumors that had a substantial radiographic interface with the SMV, SMA or hepatic artery, mFOLFIRINOX and CRT was associated with manageable toxicity that did not preclude subsequent resection. Although a RECIST response was uncommon, the efficacy of this preoperative regimen is suggested by high rates of R0 resection and pathologic response. Clinical trial information: NCT01821612.

4009 Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Comprehensive genomic profiling of biliary tract cancers to reveal tumor-specific differences and frequency of clinically relevant genomic alterations. *First Author: Jeffrey S. Ross, Albany Medical College, Albany, NY*

Background: Intrahepatic cholangiocarcinoma (IHCCA), extrahepatic cholangiocarcinoma (EHCCA) and gallbladder carcinomas (GBCA) typically present at an advanced stage and chemotherapy provides only modest benefit in most cases. We queried whether comprehensive genomic profiling (GCP) of IHCCA, EHCCA and GBCA would reveal distinctive patterns of genomic alterations (GA) and identify clinically relevant GA (CRGA) that could lead to targeted therapies. **Methods:** DNA was extracted from 412 IHCCA, 57 EHCCA and 85 GBCA. CGP was performed on hybridization-captured libraries to a mean coverage depth of > 600X for 236 cancer-related genes. The CGP assay included base substitutions, INDELs, copy number alterations and fusions/rearrangements. CRGA were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials. **Results:** Patient characteristics were similar for all three tumor types. IHCCA and GBCa were more common in females and EHCCA were more common males. Findings in the table below. Multiple antitumor responses to targeted therapies in each of the 3 tumor types will be presented. **Conclusions:** IHCCA, EHCCA and GBCA share frequent GA in cell cycle regulation (*CDKN2B*) and chromatin remodeling (*ARID1A*). IHCCA is further characterized by *FGFR* fusions, *IDH1/2* substitutions, *BRAF* substitutions and *MET* amplification with a low *KRAS* mutation frequency. EHCCA and GBCA have frequent *ERBB2* amplifications (GBCA > EHCCA) and PIK3CA/MTOR pathway alterations. *KRAS* mutation frequency is high in EHCCA and low in GBCA. The diverse landscape of CRGA in biliary tract cancers can serve as targets for therapies, either approved or in clinical trials for the majority of patients with CCA, BDCA and GBCA and have the potential to improve outcomes for patients with these aggressive forms of malignancy.

CGP Findings	IHCCA	EHCCA	GBCA
Total GA/patient	3.6	4.4	4.0
CRGA/patient	2.0	2.1	2.0
***ERBB2* Amplification**	4%	11%	16%
***BRAF* Substitutions**	5%	3%	1%
***KRAS* Substitutions**	22%	42%	11%
***PI3KCA*Substitution**	5%	7%	14%
***FGFR1-3* Fusions and Amplifications**	11%	0	3%
***CDKN2A/B* Loss**	27%	17%	19%
***IDH1/2* Substitutions**	20%	0	0
***ARID1A* Alterations**	18%	12%	13%
***MET* amplification**	2%	0	1%

4010 Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Pembrolizumab (MK-3475) for patients (pts) with advanced esophageal carcinoma: Preliminary results from KEYNOTE-028. *First Author: Toshihiko Doi, National Cancer Center Hospital East, Chiba, Japan*

Background: Expression of the PD-1 ligands PD-L1 and PD-L2 has been associated with poor prognosis in esophageal cancer. Pembrolizumab is a highly selective humanized monoclonal antibody against PD-1 designed to block the interaction between PD-1 and PD-L1 and PD-L2. We assessed pembrolizumab safety and efficacy in pts with PD-L1+ esophageal carcinoma. **Methods:** KEYNOTE-028 (NCT02054806) is a nonrandomized, multicohort, phase Ib trial of pembrolizumab for PD-L1+ advanced solid tumors. Key eligibility criteria for this cohort included squamous cell carcinoma (SCC) or adenocarcinoma of the esophagus or gastroesophageal junction, measurable disease, PD-L1 expression in ≥ 1% of cells in tumor nests or PD-L1+ stromal bands determined centrally by IHC, failure of standard therapy, ECOG PS 0-1, and no autoimmune disease. Pembrolizumab 10 mg/kg is being given every 2 weeks for up to 2 years or until confirmed progression, unacceptable toxicity, or investigator decision. Response is assessed every 8 weeks for the first 6 months and every 12 weeks thereafter. Primary end points are safety, tolerability, and ORR per RECIST v1.1 by investigator review. **Results:** Of the 90 pts with esophageal cancer who were screened, 37 (41%) had PD-L1+ tumors. Of the 23 pts treated between March and December 2014, 83% were men and median age was 65. Histology was squamous in 77% of pts, adenocarcinoma in 18%, and mucoepidermoid in 5%. Eighty-seven percent of pts received ≥ 2 prior therapies for metastatic disease; all pts received ≥ 1 platinum-based therapy. Six pts (26%) experienced drug-related adverse events (DRAEs), including 2 (9%) who experienced grade 3 DRAEs. There were no grade 4 DRAEs, and no pts died or discontinued due to a DRAE. ORR (confirmed and unconfirmed) was 23% (n = 5); best response was stable disease in 18% (n = 4) and progressive disease in 59% (n = 13). One pt did not have response assessed at the time of analysis. Six pts, including all responders, remain on treatment. **Conclusions:** Pembrolizumab has an acceptable safety profile and provides promising antitumor activity in pts with heavily pretreated, PD-L1+ advanced esophageal carcinoma. These data support further study of pembrolizumab for pts with esophageal carcinoma. Clinical trial information: NCT02054806.

4011 Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Hepatitis B- and C-associated hepatocellular carcinoma in a large U.S. cancer center: Do clinicopathologic features or patient outcomes differ by the potentially causative viruses? *First Author: Marc Isamu Uemura, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Hep B virus (HBV) and hep C virus (HCV) are the main viral causes of hepatocellular carcinoma (HCC) development and are responsible for ~50% of USA cases. Because HBV is a DNA virus (*Hepadna family*) and HCV is an RNA virus (*flavivirus family*), it is unclear whether such virologic differences influence clinico-pathologic features of HCC or patient outcomes. We evaluated such differences in a large-scale, single-center study. **Methods:** Between 1992 to 2011, 815 HCC patients (HCV = 472, HBV = 343) were referred for treatment at the Univ. of Texas MD Anderson Cancer Center. Under IRB approval, detailed patient characteristics at time of diagnosis were documented. Chi-square tests were used to assess the significance of differences in the distributions of categorical variables between HBV and HCV groups. Median survival (mos.) was calculated using Kaplan Meier product-limit method and survival rates were compared using the log rank test. **Results:** 63% of patients were Texas residents with male to female ratio = 3:1. Patients with HBV were more likely to develop HCC at younger age than HCV patients, with poorly differentiated tumor (PDT), portal thrombosis (PT), larger tumor size (> 5 cm), extensive liver involvement (> 50%), high alpha-fetoprotein, and advanced CLIP stage (3-6). On the other hand, patients with HCV were more likely to exhibit underlying cirrhosis, have a history of greater alcohol and cigarette use, and had higher co-occurrence of diabetes mellitus (DM). One-year survival rates were similar between both groups (43.3%) and median survivals were 10.9 and 9.3 mos. for HCV and HBV, respectively (P = 0.9). **Conclusions:** Significant clinico-pathologic variations exist in HCC patients associated with HCV vs HBV, which may impact patients' eligibility for treatment, but not prognosis.

Mean +/- SD (age) and proportion (%) of HCC characteristics in HCV and HBV.

	Age	PDT	PT	> 5cm	> 50%	Cirrhosis	CLIP(3-6)	Smoke	Alcohol	DM	STT	LAT	AFP
HCV	61.3 ± 10	18.8	30.2	35.2	26.6	86	36.9	73	70.1	23.5	27.5	27.4	17894 ± 4662
HBV	57.4 ± 14	26.5	35.7	49.4	42.9	59.5	44	56.4	49.3	18.3	36.9	17.2	55708 ± 1095
p	<.001	.001	.05	.02	< .001	< .001	.03	< .001	< .001	.05	< .001	< .001	< .001

4012 Poster Discussion Session; Displayed in Poster Session (Board #121), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

METGastric: A phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC). *First Author: Manish A. Shah, Weill Cornell Medical College, New York, NY*

Background: Dysregulation of the MET/HGF pathway is associated with poor prognosis in GEC. Onartuzumab (O), a monovalent anti-MET antibody, inhibits the MET/HGF pathway. We investigated first-line mFOLFOX6 + O in metastatic, HER2-, MET+ GEC. **Methods:** This double-blind, placebo-controlled phase 3 study randomized patients (pts) 1:1 to mFOLFOX6 + placebo (P) or O (10 mg/kg; q2w). Eligibility criteria: no prior treatment for metastatic disease, age ≥ 18 yrs, ECOG PS 0–1, retained organ function, HER2-, MET+ (IHC 1+, 2+ or 3+) GEC. Co-primary endpoints: overall survival (OS) in ITT and MET 2+/3+ pts. Secondary endpoints: progression-free survival (PFS), overall response rate (ORR) and safety. The study was designed to enroll ~800 pts and powered to demonstrate improvement of median OS from 9 to 12.3 mo (ITT pts; HR 0.73) and 9 to 18 mo (MET 2+/3+ pts; HR 0.49). Enrollment stopped early due to negative final results from a phase 2 trial assessing mFOLFOX6 + O. **Results:** The ITT population comprised 562 pts (enrolled 19 Nov 2012–7 Mar 2014). The treatment arms were well balanced: median age (59 yrs O, 58 yrs P), male (67% O, 65% P), and MET 2+/3+ (38% O, 39% P). Serious adverse events (AEs) were slightly more frequent with O v P (35.8% v 32.5%). Grade ≥3 AEs more commonly seen with O included neutropenia (35.1% v 29.3%), thrombocytopenia (4.3% v 1.1%), peripheral edema (4.7% v 0.4%), and pulmonary embolism (6.1% v 3.6%). At data cutoff (25 Apr 2014), 26% of ITT pts in each arm had OS events. In the MET2+/3+ subgroup, 38% of P and 33% of O pts had OS events. See Table for efficacy data. Exploratory subgroup analyses showed improved OS for the O arm in non-Asian pts and pts with no prior gastrectomy regardless of MET status. **Conclusions:** The addition of onartuzumab to mFOLFOX6 was ineffective in ITT or MET 2+/3+ pts. Subgroup analysis suggests non-Asian pts and pts without prior gastrectomy may benefit. Further analyses may delineate the role of the MET pathway in GEC. NCT01662869. Clinical trial information: NCT01662869.

	ITT		MET 2+/3+	
	P	O	P	O
Median OS, mo	11.3	11.0	9.7	11.0
HR, p value	0.82, 0.244		0.64, 0.062	
Median PFS, mo	6.8	6.7	5.7	6.9
HR, p value	0.90, 0.429		0.79, 0.223	
ORR, %	41	46	45	54
p value	0.253		0.228	

4013 Poster Discussion Session; Displayed in Poster Session (Board #122), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

FOLFOX alone or combined to rilotumumab or panitumumab as first-line treatment in patients (pts) with advanced gastroesophageal adenocarcinoma (AGEA): An open-label, randomized phase II trial (PRODIGE 17 ACCORD 20 MEGA). *First Author: David Malka, Gustave Roussy, Villejuif, France*

Background: EGFR and HGF/c-Met pathways are often deregulated in AGEA. We assessed whether EGFR or HGF inhibition with panitumumab or rilotumumab is beneficial in the first-line treatment of pts with AGEA. **Methods:** Pts ≥18 yrs with non-HER2+, measurable AGEA and ECOG performance status (PS) 0-1 were randomized (minimization procedure; stratification factors: Lauren classification, disease stage, center) to mFOLFOX6 (oxaliplatin 85 mg/m², folinic acid 400 mg/m², fluorouracil: 400 mg/m² bolus then 2400 mg/m² over 46 h) alone (arm A) or combined to panitumumab (6 mg/kg; arm B) or rilotumumab (10 mg/kg; arm C), every 2 weeks until limiting toxicity or disease progression. The primary endpoint was 4-month progression-free survival rate (4-PFS) (Fleming's one-step design, one-sided A=5%, B=10%, H0: 40%; H1: 60%; 153 evaluable pts needed). **Results:** 162 pts (median age, 64 [range, 23-87]; ECOG PS 0/1, 33/67%) were enrolled from 2011/01/14 to 2013/08/19 in 29 French centers. Most had metastatic (97%), intestinal (69%) adenocarcinoma of the stomach (50%) or GE junction (30%). Main results were (median follow-up, 23.6 months; 95%CI, 19.7-27.3): **Conclusions:** All combination regimens reached the primary study endpoint. Adding panitumumab or rilotumumab seemed more toxic and not more effective than mFOLFOX6 alone. Subgroup analyses according to tumor biomarker status (e.g., RAS/BRAF and MET) will be presented later. Clinical trial information: 2009-012797-12.

	mFOLFOX6 (n=56)	mFOLFOX6 + panitumumab (n=49)	mFOLFOX6 + rilotumumab (n=57)
Median number of cycles	10.5	9	11
G3+ adverse events [1,2]	62	83	90
Peripheral neuropathy (%)	17	6	33
Neutropenia (febrile) (%)	26 (0)	27 (8)	28 (5)
Asthenia (%)	6	17	14
Diarrhea (%)	4	15	2
Anemia (%)	4	10	5
Vomiting (%)	4	10	4
Rash (%)	2	10	2
Objective response rate (%) [95%CI] [3]	54 [40-67]	44 [30-59]	50 [36-64]
4-PFS (%) [3]	71 [57-82]	63 [48-77]	63 [49-75]
Median PFS (months) [95%CI] [3]	5.8 [5.2-7.3]	5.2 [3.7-7.6]	7.6 [4.0-9.0]
Median overall survival (months) [95%CI]	13.1 [8.7-16.9]	8.3 [6.2-16.9]	11.5 [7.9-17.1]

[1] n = 159 pts evaluable for safety. [2] G5, 1/4/3 pts, respectively. [3] n = 158 evaluable pts (intent-to-treat population).

4014 Poster Discussion Session; Displayed in Poster Session (Board #123), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A randomized, open-label phase II study of AZD4547 (AZD) versus Paclitaxel (P) in previously treated patients with advanced gastric cancer (AGC) with Fibroblast Growth Factor Receptor 2 (FGFR2) polysomy or gene amplification (amp): SHINE study. *First Author: Yung-Jue Bang, Seoul National University College of Medicine, Seoul, South Korea*

Background: The prognosis for AGC patients failing 1st line treatment is poor. FGFR2 amplification occurs in ~5-10% and polysomy in > 20% of gastric cancers (GCs). AZD is a selective FGFR1-3 inhibitor with activity in *FGFR2* amplified models. SHINE assessed the efficacy and safety of AZD in AGC patients with *FGFR2*amplification or polysomy. **Methods:** Patients with disease progression after 1 prior line of therapy were assigned to *FGFR2* amplified or polysomy arms and randomised to oral AZD (80mg bd, 2weeks on/1week off) or P. The primary endpoint was progression-free survival (PFS). Secondary endpoints included safety. FGFR2 status confirmed by FISH testing. Exploratory biomarker analysis assessed FGFR2 gene expression by nanostring and intra-tumoral heterogeneity of *FGFR2*amplification by image analysis of FISH stained sections. **Results:** Of 960 pts enrolled, 71 patients were randomised (41 AZD arm, 30 P arm). AGC *FGFR2* amp prevalence was 9%. The overall median PFS on the AZD arm was 1.8 mths vs 3.5 mths for P and for the *FGFR2* amplified arm was 1.5 mths for AZD vs 2.3 months for P. Pts on AZD mostly experienced G1/G2 AEs. Most common AEs causally related to AZD were stomatitis (8 pts/20%), dry mouth (7 pts/17.5%) and RPED (6/15% pts) and fully resolved off treatment. Elevations in plasma phosphate were observed on the AZD arm during the 2 week dosing period and resolved during the 1 week off. Only 21% of *FGFR2*amplified tumors had elevated FGFR2 expression and Image analysis showed four out of seven tumor samples, highly amplified by FISH, were amplified in < 20% of the tumor section. **Conclusions:** AZD was well-tolerated. The analysis of PFS did not show any statistically significant difference in favour of the AZD arm, compared with the P arm in *FGFR2* amplified or polysomy patients selected by FISH. Exploratory biomarker analysis revealed marked intra-tumor heterogeneity of *FGFR2* amplification and low concordance with elevated FGFR2 expression. The observed increase in plasma phosphate provides evidence that AZD at this dose and schedule causes pharmacologic target inhibition. Clinical trial information: NCT01457846.

4015 Poster Discussion Session; Displayed in Poster Session (Board #124), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Untreated metastatic diffuse gastric adenocarcinoma (DGAC): Randomized phase III study of S-1 and cisplatin vs. 5-FU and cisplatin (the DIGEST trial). *First Author: Jaffer A. Ajani, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The prognosis for metastatic DGAC is poor but the first line therapy for patients (pts) with DGAC is the same as that of without DGAC. Analyses of the FLAGS study suggested that S-1/Cisplatin might be better than 5-FU/cisplatin in DGAC. Therefore, a prospective international study was executed. **Methods:** Pts with metastatic DGAC (histology confirmed by central pathology review) with PS 0-1, adequate organ function, measurable/evaluable disease were consented and randomized to S-1 (25 mg/m² po BID on days 1-21 q 4 weeks)/cisplatin (75 mg/m² q 4 wks; CS) or 5-FU (800 mg/m² continuous infusion for 5 days q 3 wks)/cisplatin (80 mg/m2 q 3 wks; CF). Randomization was 2:1 in favor of CS, stratified by histologic subtype, extent of metastasis, ECOG PS and geographical region. The primary endpoint was overall survival (OS). The study was stopped early after 361 pts were randomized versus a target 500 pts, and 264 events (deaths) were observed versus an analysis target of 427 events. **Results:** 690 pts were screened and 361 were randomized (239 to CS and 122 to CF). Both arms were well balanced with respective pts characteristics. For ITT pts, the median OS was 7.5 months (95%CI; 6.7-9.3) for CS and 6.6 months (5.7-8.1) for CF (HR 0.99, 95%CI; 0.76-1.28, *p*= 0.9312). There was no statistical difference in progression-free survival. Overall response rate was 34.7% for CS compared to 19.8% for CF (*p*= 0.012). The median number of cycles was 4 in both arms. The dose intensity was > 90% in both arms. The rate at least one Gr. ≥ 3 AE related to study medication was 45.2% in CS and 55.9% in CF. The most frequent (≥ 5%) Gr. ≥ 3 AEs for CS were neutropenia (27.3%), anemia (16.1%), fatigue (10.4%), hyponatremia (7.7%), abdominal pain (5.7%), and asthenia (5.7%) and for CF were neutropenia (28.3%), anemia (8%), asthenia (10.2%), hyponatremia (10%), hypophosphatemia (7.9%), hypokalemia (7%), anorexia (5.9%), and hyperkalemia (5%). One drug related death occurred in both CS (0.4%) and CF (0.8%). **Conclusions:** In the DIGEST trial, CS did not prolong OS of pts with metastatic DGAC compared to CF. However, efficacy and safety were similar for CS and CF. (Supported by Taiho Oncology Inc, NJ, USA). Clinical trial information: NCT01285557.

4016 Poster Discussion Session; Displayed in Poster Session (Board #125), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Pathological response to neoadjuvant 5-FU, oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU (ECF) in patients with locally advanced, resectable gastric/esophagogastric junction (EGJ) cancer: Data from the phase II part of the FLOT4 phase III study of the AIO. *First Author: Claudia Pauligk, Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany*

Background: Pathological response can be a potent surrogate factor for efficacy of neoadjuvant chemotherapy. Data from our phase II/III study comparing perioperative FLOT with ECF(X) in resectable stages were analyzed for pathological response upon request of the German Cancer Aid in order to further sponsor the trial. **Methods:** In the FLOT4, 714 patients (pts) are stratified and randomized to either 3+3 perioperative cycles of ECF/ECX (epirubicin 50 mg/m^2, d1; cisplatin 60 mg/m^2, d1; 5-FU 200 mg/m^2 (or capecitabine 1250 mg/m^2 p.o) d1-d21, qd21) or 4+4 cycles of perioperative FLOT (docetaxel 50mg/m^2, d1; 5-FU 2600 mg/m^2, d1; leucovorin 200 mg/m^2, d1; oxaliplatin 85 mg/m^2, d1, qd14). Central pathology (by AT) is performed according to Becker classification. **Results:** Samples of 157 pts of the phase-II part of the study were analyzed. Median age was 63 yrs; 79.6% of pts were male. The primaries were gastric in 43.3%, EGJ in 56.1% and not evaluable in 0.6% of pts. In the most relevant categories complete (CR) and subtotal (SR) histopathological response, FLOT was superior to ECF with CR 12.8% vs. 5.1% and SR 16.7% vs. 10.1%, respectively, with statistical significance for CR+SR (FLOT, 29.5% vs. ECF, 15.2%, p = .036). Also, significantly more pts in the ECF-arm had no pathological regression or even did not reach surgery (ECF, 41.8% vs. FLOT, 24.4%; p = .027). See also Table. **Conclusions:** Perioperative FLOT shows more pathological remissions (CR + SR) than ECF/ECX in patients with resectable gastric cancer. Clinical trial information: NCT01216644.

4017 Poster Discussion Session; Displayed in Poster Session (Board #126), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer (JCOG0912): Analysis of the safety and short-term clinical outcomes. *First Author: Masakazu Takagi, Shizuoka General Hospital, Shizuoka, Japan*

Background: Although the number of patients undergoing laparoscopy-assisted distal gastrectomy (LADG) has been increasing, there is no confirmatory randomized controlled trial (RCT) to evaluate the efficacy of LADG compared with open distal gastrectomy (ODG). Safety and short term outcome are presented. **Methods:** We conducted a RCT to confirm the non-inferiority of overall survival (OS) of LADG to ODG in patients with clinical IA (T1N0) or IB (T1N1 or T2 [MP] N0) gastric cancer. D1 or more dissection is applied for clinical stage IA and D2 dissection for clinical stage IB. Only the credentialed surgeons can be responsible for both procedures. The primary endpoint is (OS). The planned sample size was 920. **Results:** Between March 2010 and November 2013, 921 patients (LADG 462, ODG 459) were enrolled from 33 institutions. Operating time was longer in LADG than ODG (median 278 vs 194 min, $p < 0.001$). Blood loss was smaller in LADG than ODG (median 38 vs 115 ml, $p < 0.001$). There were no grade 3 or 4 intraoperative adverse events in either arm. There was no difference in the overall proportion of in-hospital, non-hematological grade 3 or 4 adverse events excluding biochemical data (3.3%: LADG, 3.7%: ODG). The proportion of grade 3 or 4 serum AST/ALT increased was higher in LADG than ODG (16.4% vs 5.3%, $p < 0.001$). The proportion of the patients who required an analgesic on postoperative days 5–10 was smaller in LADG than ODG (50.3% vs 59.3%, p = 0.006). The median time from surgery until the first episode of flatus was shorter in LADG than ODG (2 days vs 3 days, $p < 0.001$). There was no difference in both the highest body temperatures during the first 3 days after the surgery and the highest body temperatures during hospitalization. **Conclusions:** Although the elevation of serum AST/ALT should be taken care, this trial confirmed that LADG performed by the credentialed surgeons was safe as ODG in terms of adverse event and short-term clinical outcomes. LADG will be an alternative procedure in clinical IA/IB gastric cancer if the non-inferiority of LADG in OS is confirmed by the primary analysis planned in 2018. Clinical trial information: UMIN000003319.

4018 Poster Discussion Session; Displayed in Poster Session (Board #127), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A randomized, double-blind, placebo-controlled phase III study of S-1 in patients with sorafenib-refractory advanced hepatocellular carcinoma (S-CUBE). *First Author: Masatoshi Kudo, Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan*

Background: An unmet medical need persists for patients (pts) with sorafenib-refractory advanced hepatocellular carcinoma (HCC). This study was conducted to evaluate the efficacy and safety of S-1 in pts with sorafenib-refractory advanced HCC. **Methods:** Japanese men and women (aged ≥ 20 years) with Child-Pugh (C-P) A or B liver function and disease progression with or intolerance to sorafenib were randomized in a 2:1 ratio. S-1 (80, 100, or 120 mg/day) or a placebo was administered orally, according to the body surface area on days 1–28 of a 42-day cycle until disease progression or unacceptable toxicities were observed. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety. For a statistical consideration of the heterogeneous population with advanced HCC, we conducted the subgroup analysis. **Results:** A total of 334 pts were enrolled (S-1 = 223, placebo = 111). Patient characteristics were well balanced; median age, 70.0 years; C-P A liver function, 81.0%; vascular invasion, 17.7%; and extrahepatic metastasis, 53.8%. The median OS was 337.5 days with S-1 and 340.0 days with the placebo (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.67–1.10; P = 0.220). The median PFS were 80 and 42 days, respectively (HR, 0.60; 95% CI, 0.46–0.77; P < 0.001). ORRs were 5.4% and 0.9%, respectively (P = 0.068). In the subgroup analysis showed the efficacy of S-1 on OS was different depending on patient characteristics; C-P liver function, HR was 0.79 (C-P A) and 1.19 (C-P B); Tumor stage, HR was 2.08 (Stage I/II) and 0.79 (Stage III/IV). The main adverse events (AEs) with S-1 were anorexia, fatigue, elevated total bilirubin, and diarrhea. Most AEs were mild to moderate, and the study discontinuation rate due to AEs was 19.2% in S-1 pts. **Conclusions:** Although S-1 did not statistically extend OS compared to the placebo in pts with sorafenib-refractory advanced HCC, the subgroup analysis showed S-1 has potential to improve OS in the clinically-important population. The observed benefit in the outcomes of PFS and subgroup analysis warrant further investigation. Clinical trial information: JapicCTI-090920.

4019 Poster Discussion Session; Displayed in Poster Session (Board #128), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

The protective effect of hormonal intake on risk of hepatocellular carcinoma in the United States. *First Author: Gehan Botrus, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In the United States, the incidence of hepatocellular carcinoma (HCC) has been tripled over the last two decades. Despite the overwhelming effect of several environmental risk factors of this cancer, the association between oral contraceptive (OC) and hormone replacement therapy with HCC has been poorly investigated. The current study aimed at addressing such association among American women. **Methods:** Under the IRB approval from the University of Texas MD Anderson Cancer Center, we conducted hospital-based case-control study where cases are pathological or radiological diagnosed patients with HCC. Controls are spouses of patients at MD Anderson who had cancers other than GI cancers. Between 2005 and 2014 total of 235 female cases and 257 female controls were enrolled. Cases and controls were interviewed for lifetime intake of OC, hormonal replacement, type of hormone, method of hormonal use, and duration of exposure. We performed multivariate logistic regression analyses by using all variables that were significant at $P < .05$ in the univariate analyses to estimate odds ratio (OR) and 95% confidence interval (CI). The estimated ORs were adjusted for age, race, diabetes, hepatitis C virus, hepatitis B virus, cigarette smoking, alcohol drinking, and family history of cancer. **Results:** Ever use of OC was reported by 75.1% of the controls and 61.3% of the cases ($P = .001$) leading to 43% reduction in HCC risk where the estimated OR (95% CI) was 0.57 (.35-.91). Ever intake of estrogen hormone during lifetime was recalled by 49.8% controls and 30.6% cases ($P = .001$) yielding 62% reduction in HCC risk, OR (95% CI) = .38 (.24-.59). Combined hormonal use from OC and estrogen hormonal replacement was reported by 89% of the controls and 75% of cases. The estimated OR (95% CI) was .47 (.27-.84), $P = .01$. A dose response relationship was observed with duration of exposure where the estimated OR (95% CI) were .53 (.28-1), .37 (.16-.83), and .35 (.19-.64) for lifetime years of exposure of < 5, 5-10, and > 10 years respectively. **Conclusions:** This is the largest study in USA showing protective effect of hormonal use on HCC. Experimental investigations are necessary for thorough assessment of the relationship between hormonal exposure and risk of HCC in females.

4020 Poster Discussion Session; Displayed in Poster Session (Board #129), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Multi-institutional phase II study of high dose, hypofractionated proton beam therapy (HF-PBT) for unresectable primary liver cancers: Long term outcomes in patients (pts) with intrahepatic cholangiocarcinoma (ICC). *First Author: Theodore S. Hong, Massachusetts General Hospital, Boston, MA*

Background: Modern radiotherapy (RT) techniques such as protons permit delivery of ablative doses of RT to the liver. Prior reports of PBT in hepatocellular carcinoma (HCC) demonstrate local control (LC) rates exceeding 85% but outcomes with high dose RT in pts with ICC remain lacking. We report on clinical outcomes of high dose, HF-PBT in pts with unresectable ICC. **Methods:** Pts enrolled on an NCI sponsored, multi-institutional, phase II study (NCT00976898). Key eligibility were HCC or ICC, unresectable by multidisciplinary review, Child's A/B, ECOG PS 0-2, no extrahepatic disease, no prior RT. Maximum tumor size was 12 cm if solitary, 10 cm if 2 tumors, and 6 cm if 3. PBT was given in 15 fractions to a maximum total dose of 67.5 GyE. Sample size was calculated to demonstrate $>$ 80% LC at 2 yrs for HCC pts with acceptable precision for estimating outcomes for ICC. **Results:** From 2009-2014, 93 pts were enrolled, of whom 90 were evaluable. 41 pts had ICC, 2 pts had mixed HCC/ICC, and 47 pts had HCC (reported separately). In this ICC specific-analysis (n = 43), median age was 67 (range 29-87), 16 (37%) were male. 36 (84%) and 5 (12%) pts had Child-Pugh A and B cirrhosis, respectively. 2 (4%) pts had no cirrhosis. 25 (58%) pts had prior systemic therapy. 25 (58%) pts had prior systemic therapy. 39 pts(90.6%) had 1 tumor, 2 pts (4.7%) had 2 , 2 pts (4.7%) had 3 . Median tumor size was 6.0 cm (range 2.2-10.9). Median RT dose received was 58 GyE (range 15.1-67.5). 6 (14%) pts developed Gr 3 RT-related toxicity, including thrombocytopenia (2), hyperbilirubinemia (2), gastric ulcer (1), pain (1), elevated LFTs (1), and liver failure/ascites (1). With a median follow up of 13 months (range 5d–51 mo) among 22 pts still alive, the 2 year LC was 96%. mOS was 21 months (95% CI 13-29) and mPFS was 9 months (95% CI 6-24). When excluding Child's B (N = 38), mOS was 23 months (95% CI 15-49) and mPFS was 10 months (95% CI 5-24); 2 yr OS rate was 48% and 2 yr PFS rate was 38%. **Conclusions:** High dose PBT for ICC results in high rates of LC and OS. This data forms the basis for the ongoing NRG GI-001 study, a randomized trial of gem/cis +/- hypofractionated RT. Support: NCI # P01CA2123 Clinical trial information: NCT00976898.

4021 Poster Discussion Session; Displayed in Poster Session (Board #130), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Quantification of tumor stroma as a biomarker in pancreatic adenocarcinoma. *First Author: Robert J. Torphy, UNC Chapel Hill, Chapel Hill, NC*

Background: Desmoplastic tumor stroma (TS) characterizes the primary tumor in pancreatic ductal adenocarcinoma, but its role in tumor progression and metastasis is less clear. The objective of this study was to evaluate the presence and prognostic significance of TS at primary and metastatic sites. **Methods:** Tissue sections of primary tumors from 57 patients who underwent curative resections and 46 primary and metastatic tumors from 15 patients with metastatic pancreatic cancer were digitally annotated for tumor epithelium and TS, reviewed by a pathologist, and quantified using Spectrum WebScope. Tumor stroma density (TSD) was quantified as TS per total tumor area. Resected patients received no adjuvant chemotherapy. Association of TSD with overall survival (OS) and recurrence-free survival (RFS) was performed using the multivariate Cox proportional hazards model from the "survival" R statistical package (3.1.1); where significance was determined with log-rank test p-value less than 0.05. **Results:** Median TSD in primary tumors was 0.57. TSD was no different in the primary tumors of patients who had localized compared to metastatic disease. TSD was decreased in solid organ (0.12) and lymph node metastases (0.22) (ANOVA, p = 0.0001). Furthermore in patients who underwent curative resections, high TSD was associated with longer OS (HR = 0.237; p = 0.009), with a median OS of 11 months in the low TSD ($<$ 0.57) group and 21.5 months in the high TSD ($\geq$ 0.57) group. TSD was also associated with RFS (HR = 0.286, p = 0.022), with a median RFS of 9 months in the low TSD group and 19 months in the high TSD group. The association of TSD with OS and RFS was adjusted for tumor grade, T, N and overall stage, ASA score, and smoking status. **Conclusions:** We demonstrate that stromal content is a measurable biomarker in this disease with meaningful clinical associations.Our results nominate that TSD should be used as an objective, quantitative assessment of TS in correlative and therapeutic trials of pancreatic cancer. TS appears to be associated with restraining tumor growth with decreasing TSD in patients with more aggressive disease. Also, the low TSD at metastatic sites should be considered in the context of stroma modulating therapies.

4022 Poster Discussion Session; Displayed in Poster Session (Board #131), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Prognostic value of plasma circulating tumor (ct) DNA *KRAS* mutations and serum CA19-9 in unresectable pancreatic cancer (PC) patients. *First Author: Julia S. Johansen, Department of Oncology, Herlev Hospital, Herlev, Denmark*

Background: Median overall survival (OS) time of patients with unresectable PC varies widely. Diagnostic tools are presently lacking to predict outcomes. The majority of pancreatic tumors have *KRAS* mutations. The study aim was to evaluate the utility of baseline and serial measurements of ctDNA *KRAS* mutation load, alone or in combination with serum CA 19-9, as an outcome prognostic biomarker in patients with unresectable PC undergoing palliative chemotherapy. **Methods:** In the Danish BIOPAC prospective biomarker study, plasma was collected from 182 unresectable PC patients (85 females, 97 males, median age 68, range 45-89 years; locally advanced disease n = 48; metastatic n = 134) undergoing treatment with gemcitabine (n = 151) or FOLFIRINOX (n = 31). ctDNA *KRAS* G12/13 mutation levels in archival ($\leq$ 6 years) plasma was assessed with enrichment PCR followed by next generation sequencing and standardized reporting of copies per 10^5 genome equivalents (GE). **Results:** In a prospective-retrospective study of 182 patients, interim analysis of ctDNA *KRAS* was conducted (after 168 deaths). 176 of 182 patients had evaluable baseline plasma samples. Of 176 patients, 143 (81%) had $>$ 1 copy mutant *KRAS* G12/13 ctDNA at baseline. To assess associations between *KRAS*, CA 19-9 and OS, *KRAS* and CA 19-9 values were dichotomized by finding thresholds maximizing similarity of OS in each group (thresholds: 41 *KRAS* copies/10^5 GE; 314 U/ml, CA 19-9). Both *KRAS* and CA 19-9 negatively predicted OS (Cox proportional hazards model). *KRAS* with CA 19-9 was a stronger predictor of death than either marker alone. The hazard rate (HR) of death for patients with *KRAS* $>$ 41 c/10^5GE and CA 19-9 $>$ 314 U/ml was 3.0 times as high (95% CI: 2.0 to 4.6) as those with *KRAS* $<$ 41 c/10^5GE and CA 19-9 $<$ 314 U/ml. This is compared to HR 2.1 (95% CI: 1.5 to 2.8) for patients with high *KRAS* vs low *KRAS*, and HR 1.8 (95% CI: 1.3 to 2.6) for patients with high CA 19-9 vs low CA 19-9. Shorter OS tend to associate with elevated *KRAS* and CA 19-9 during chemotherapy. **Conclusions:** Combination of pre-treatment plasma ctDNA *KRAS* mutation load and CA 19-9 is a strong prognostic factor in patients with unresectable PC receiving palliative treatment with gemcitabine or FOLFIRINOX.

4023 Poster Discussion Session; Displayed in Poster Session (Board #132), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Allelic ratio of *KRAS* mutations in pancreatic ductal adenocarcinoma. *First Author: Jochen K Lennerz, Massachusetts General Hospital, Boston, MA*

Background: Traditional sequencing studies of *KRAS* in pancreatic ductal adenocarcinoma (PDAC) delineated a mutation frequency of ~75% and that *KRAS* mutant tumors are associated with shorter overall survival. Recently highly-sensitive next-generation sequencing technologies have delineated that the *KRAS* mutation frequency in PDAC is ~93% indicative of a fraction of cases missed by traditional sequencing approaches. Here, we explored whether PDAC with *KRAS* mutations at low-allelic ratios carry prognostic differences. **Methods:** We employed the PDAC dataset (n = 142) from the International genome consortium (ICGC) initially reported by Biankin et al., 2012. We accounted for tumor purity by calculating the corrected allelic ratio (= allelic ratio/cellularity). Overall survival differences using a corrected allelic ratio cutoff of 10% were calculated employing Kaplan-Meier, log-rank, and Cox proportional hazard regression analysis (HR). **Results:** Accounting for tumor purity, we identified 115 cases (80.9%) with allelic ratios of mutant *KRAS* $\geq$ 10% while the remainder (n = 27 cases, 19.1%) harbored either mutant alleles below 10% (n = 17) or wild-type *KRAS* (n = 10). Allelic ratios span the full range from wild-type to $>$ 100% mutant *KRAS*. The lower as well as the upper end of this spectrum suggest heterogeneity within the cancer cell population (clonality) or variations in DNA content (ploidy), respectively. The subset with low-allelic ratios ($<$ 10%) of mutant *KRAS* had shorter overall survival (14.5 months) when compared to those with high-allelic ratios (20.3 months; HR 1.68 CI:0.9-3.13). While this difference did not reach statistical significance (P= 0.10), several prior studies employing thresholds around 10% (cutoff determined by sensitivity of the sequencing technology) have shown that the presence of a *KRAS* mutation is a marker of poor prognosis. **Conclusions:** *KRAS* is not simply mutated or wild-type in PDAC – it has actually never been. While over 90% of PDAC carry mutated *KRAS* alleles, the impact on PDAC biology may vary with the tumor-specific allelic ratio and dosage of mutated *KRAS*. Therefore, we propose that the tumor-specific allelic ratio of somatically mutated genes should become part of a comprehensive molecular diagnostic report.

4024 Poster Session (Board #133), Mon, 8:00 AM-11:30 AM

A phase II study of sequential capecitabine plus oxaliplatin (XELOX) followed by docetaxel plus capecitabine (TX) in patients with unresectable gastric adenocarcinoma: The TCOG T3211 trial. *First Author: Ming-Huang Chen, Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

Background: Fluorouracil and platinum can be considered a standard option for advanced gastric cancer (AGC). Docetaxel is also an effective agent with no cross-resistance with fluorouracil and platinum. Concomitant combination of docetxel with fluorouracil and platinum had been explored, but demonstrated intolerable toxicities. A different way to include all active agents in first-line treatment of gastric adenocarcinoma may be to use them sequentially. We aimed to evaluate the activity and the safety profile of sequential chemotherapy with capecitabine plus oxaliplatin followed by docetaxel plus capecitabine in the first-line treatment of AGC. **Methods:** We conducted a phase II study of first-line sequential chemotherapy in AGC. Treatment consisted of 6 cycles of capecitabine plus oxaliplatin (XELOX, Capecitabine 1000 mg/m^2 bid on day 1-10 and Oxaliplatin 85 mg/m^2 on day 1, Q2W) followed by 4 cycles of docetaxel plus capecitabine (TX, Docetaxel 30 mg/m^2 on D1 and D8, Capecitabine 825 mg/m^2 bid on day 1-14, Q3W). Primary end-point was the objective response rate. **Results:** Fifty-one patients were enrolled: median age 63 years; Male/Female: 37/14. Main grade 3-4 toxicities were ANC decreased (25.5%), diarrhea (11.8%), hand-foot syndrome (15.7%) and anemia (11.8%). The objective response rate was 56.9%. Median PFS and OS were 8.6 and 10.8 months, respectively. Five patients (9.8%) received surgery after chemotherapy and four were still on disease-free status. **Conclusions:** This sequential treatment demonstrated feasibility with a favorable safety profile and produced encouraging results in terms of activity and efficacy. Clinical trial information: NCT01558011.

4025 Poster Session (Board #134), Mon, 8:00 AM-11:30 AM

Risk of death due to heart disease after radiotherapy for esophageal cancer: A SEER study. *First Author: Jonathan Evans Frandsen, Department of Radiation Oncology, Huntsman Cancer Hospital; University of Utah School of Medicine, Salt Lake City, UT*

Background: Radiation therapy (RT) improves local control as well as overall survival when combined with chemotherapy for patients with esophageal cancer (EC). Significant doses of RT are delivered to the heart during treatment for EC, but little data exist regarding the long term heart morbidity after RT for EC. We hypothesized an increased risk of heart disease related death (HDRD) among patients in the Surveillance, Epidemiology, and End Results (SEER) database who received RT as part of their initial treatment for EC. **Methods:** Using the SEER Program, all individuals from 1973 to 2011 with EC were identified. Two cohorts were created: (1) patients who received RT as part of their initial therapy and (2) those who did not. The primary endpoint, heart disease specific survival (HDSS), was analyzed using Kaplan Meier methods. Cox proportional-hazards regression methods were used for univariate and multivariate analyses. **Results:** We identified 40,778 patients with EC. 26,377 patients received RT and 14,401 patients did not. HDSS analysis revealed increased risk of HDRD in those receiving RT ($P < 0.05$), with an absolute risk of HDRD of 2.8%, 5.3% and 9.4% at 5-, 10- and 20-years, respectively. Log rank test of HDSS revealed that the risk of HDRD became significant at 8 months with an absolute risk of HDRD of 0.4% ($p < 0.05$). The following were associated with HDRD: RT, age, race, stage at presentation, time period of diagnosis, and known comorbid condition keeping one from esophagectomy. On multivariate analysis, RT remained predictive of HDRD (hazard ratio [HR] 1.46, $p < 0.05$). When considering only candidates for definitive therapy, RT remained predictive of HDRD on univariate (HR 1.53, $p < 0.05$) and multivariate (HR 1.62, $p < 0.05$). **Conclusions:** RT plays an important part of the current treatment paradigm for EC, but the use of RT leads to increased risk of HDRD that is detectable as early as eight months from diagnosis. More research is needed to define optimal dose volume parameters to prevent cardiac death. Consideration should be given to this risk in relation to the patients expected survival.

4026 Poster Session (Board #135), Mon, 8:00 AM-11:30 AM

Phase I/II study of a combination of capecitabine, cisplatin, and intraperitonealdocetaxel (XP ID) in patients with advanced gastric cancer with peritoneal metastasis. *First Author: Hyungwoo Cho, Departments of Internal medicine, Asan Medical Center, University of Ulsan College of medicine, Seoul, Korea, Seoul, South Korea*

Background: More than one third of patients with advanced gastric cancer (AGC) have peritoneal metastasis, and their prognosis is poor. This study was conducted to determine the recommended dose (RD) of intraperitoneal docetaxel (ID) in combination with systemic capecitabine and cisplatin (XP), and to evaluate its efficacy and safety at the RD in AGC patients with peritoneal metastasis. **Methods:** AGC patients with peritoneal metastasis received XP ID, which consists of 937.5 mg/m^2 of capecitabine twice daily on days 1-14, 60 mg/m^2 of intravenous cisplatin on day 1, and ID at 3 different dose levels (60, 80, or 100 mg/m^2) on day 1, every 3 weeks. In the phase I study, the standard 3+3 method was used to determine the RD of XP ID. For the phase II study, patients received RD of XP ID until disease progression, unacceptable toxicity, or consent withdrawal. A maximum of 8 cycles of ID was provided. **Results:** In the phase I study, 3 patients experienced no dose limiting toxicity (DLT) at each of 60 or 80 mg/m^2 of ID. ID 100 mg/m^{2}was determined as the RD with 1 DLT (ileus) out of 6 patients. Between June 2011 and December 2013, 39 AGC patients with definite peritoneal metastasis were enrolled in the phase II study and received RD of XP ID. With a median follow-up duration of 20.8 months (range, 13.1-40.3) in surviving patients, median progression-free survival was 11.0 months (95% CI, 6.9-15.1), and median overall survival was 15.1 months (95% CI, 9.1-21.1). Among 30 patients with ascites, complete resolution of ascites was observed in 12 patients (40.0%), and more than 10% reduction in amount of ascites was observed in 8 patients (26.7%). The most frequent grade 3 or 4 adverse events were neutropenia (38.6%), abdominal pain (30.8%), and anemia (25.6%). Of these adverse events, the incidence of abdominal pain cumulatively increased in the later treatment cycles. There was no treatment-related mortality. **Conclusions:** Our study indicated that XP ID was effective with manageable toxicities in AGC patients with peritoneal metastasis. Considering cumulative incidence of abdominal pain probably related to bowel irritation by ID, it may be necessary to modify the dose of ID. Clinical trial information: NCT01525771.

4027 Poster Session (Board #136), Mon, 8:00 AM-11:30 AM

Masitinib plus irinotecan for second line treatment of esophagogastric adenocarcinoma: An open label phase Ib/II trial. *First Author: Aziz Zaanan, Department of Gastroenterology, HEGP, Paris, France*

Background: Masitinib (MAS) is a selective c-Kit inhibitor that efficiently inhibits mast cell function. In vitro studies have shown that MAS could enhance efficacy of 5-fluorouracil (5-FU) and irinotecan (IRI) for treatment of gastric cancer cell lines. **Methods:** Patients (pts) with measurable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction were eligible to receive MAS (6 mg/kg/day) in combination with 5-FU (400 mg/m^2 bolus then 2400 mg/m^2, 46h/2w), or IRI (350 mg/m^2/3w), or FOLFIRI, after progression to platinum based first line chemotherapy. The phase I study evaluated safety with "Dose Limiting Toxicity" (DLT) defined as grade 3 for non-hematological adverse event (AE), or any grade 4 AE related to MAS. The phase II study evaluated efficacy. **Results:** Thirty-six pts from 6 centers in France were included. The MAS + 5-FU arm was closed after 6 pts were included due to lack of efficacy on PFS (1.7 months). Reduction of dose (-25%) was performed for IRI and FOLFIRI regimens due to occurrence of DLT. In the MAS + IRI arm (n = 15), median OS and PFS was 13.4 and 3.9 months, respectively. Partial response (PR) and stable disease (SD) were reported for 1 pt and 5 pts, respectively, leading to a disease control rate (DCR) of 33%. In the MAS + FOLFIRI arm (n = 15), median OS and PFS was 10.9 and 2.4 months, respectively. SD was reported for 4 pts with 31% of DCR. No treatment related deaths occurred. In the MAS + IRI arm, 9/15 pts (60%) reported grade 3-4 AE (neutropenia, 20% and gastrointestinal disorders, 20%); and 4/15 pts (27%) reported serious AE (3 pts with neutropenia). In the MAS + FOLFIRI arm, 10/15 pts (67%) reported grade 3-4 AE (neutropenia, 47%); and 2/15 pts (13%) reported serious AE (1 pt with neutropenia). **Conclusions:** MAS + IRI seems to be active in advanced gastric cancer pts (*c.f.* median OS ~7.5 months; average from 7 studies reporting second-line IRI*) with an acceptable safety profile. A confirmatory phase III trial evaluating MAS at 6 mg/kg/day in combination with IRI in second line has been initiated.

Treatment	n	OS (months [95%CI])	PFS (months [95%CI])
MAS + IRI	15	13.4 [3.0;15.6]	3.9 [1.9;11.8]
MAS + FOLFIRI	15	10.9 [3.7;22.5]	2.4 [1.8;5.4]
Benchmark 2nd line IRI*	-	7.5	2.7

4028 Poster Session (Board #137), Mon, 8:00 AM-11:30 AM

Prognostic factor analysis of overall survival (OS) in gastric cancer from two phase III studies of second-line ramucirumab (RAM) (REGARD and RAINBOW) using pooled individual patient (pt) data. *First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA*

Background: From 2009-2012, 1020 pts were enrolled in two phase III, randomized, double-blind studies of RAM in metastatic gastroesophageal junction and gastric adenocarcinoma following progressive disease (PD) on first-line platinum- and/or fluoropyrimidine-containing therapy: REGARD (N = 355, RAM + best supportive care [BSC] vs placebo [PL] + BSC) and RAINBOW (N = 665, RAM + paclitaxel [PTX] vs PL + PTX). **Methods**: Individual pt data were pooled, and 41 key baseline covariates, common in both studies, were examined (19 clinical characteristics; 22 lab parameters). Lab tests were parameterized in two ways based on local lab abnormality assessments (high/normal/low): high vs normal or low; low vs normal or high. To identify prognostic factors for OS, univariate Cox models were first used to select covariates with $p \leq 0.05$. For these covariates, a multivariate Cox model was used to make stepwise selection with both entry and exit p=0.01. All models were stratified by treatment and geographic region. **Results**: Of 1,020 pts, 953 (93%) were included in the stepwise Cox regression, after excluding pts with missing covariate values. We identified 12 independent prognostic factors (5 clinical; 7 lab). **Conclusions**: We identified 12 independent prognostic factors for pts with second-line gastric cancer from the largest randomized, controlled, global trial dataset. A simple prognostic index using these factors to divide pts into risk groups will be constructed and presented. This information may help clinical decision-making, pt risk stratification, and planning future clinical studies. Clinical trial information: NCT01170663 and NCT00917384.

Poor Prognostic Factors	HR (99% CI) for Mortality
Peritoneal metastasis	1.49 (1.22, 1.83)
Time-to-PD on prior therapy < 6 months	1.35 (1.10, 1.66)
ECOG PS ≥ 1	1.39 (1.12, 1.73)
Tumor differentiation (poor/unknown)	1.33 (1.08, 1.64)
Primary tumor present	1.31 (1.05, 1.62)
Alkaline phosphatase (high)	1.28 (1.03, 1.60)
Sodium (low)	2.04 (1.54, 2.71)
Lactate dehydrogenase (high)	1.31 (1.05, 1.63)
Aspartate Aminotransferase (high)	1.37 (1.06, 1.76)
Albumin (low)	1.33 (1.07, 1.65)
Lymphocytes (low)	1.31 (1.05, 1.63)
Neutrophils (high)	1.52 (1.17, 1.99)

4029 Poster Session (Board #138), Mon, 8:00 AM-11:30 AM

Candidate biomarker analyses in gastric or gastro-esophageal junction carcinoma: REGARD trial of single-agent ramucirumab (RAM) vs. placebo (PL). *First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA*

Background: Vascular endothelial growth factors (VEGFs) are key regulators of tumor angiogenesis. RAM, a recombinant human IgG1 monoclonal antibody specific for VEGF receptor 2 (VEGFR2), inhibits VEGF-A, -C and -D binding to VEGFR2 and inhibits ligand-induced mitogenesis of human endothelial cells. We evaluated candidate tumor (HER2, VEGFR2) and serum (VEGF-C, -D, and soluble [s] VEGFR1 and 3) biomarkers for correlation with overall survival (OS) and progression-free survival (PFS) in patients from the randomized phase 3 REGARD trial (NCT00917384) that demonstrated survival benefits for RAM vs. PL. **Methods:** Of 355 patients randomized to RAM or PL in REGARD, there was at least one evaluable biomarker result for 152 (43%) patients using VEGFR2 immunohistochemistry (IHC) or HER2 (IHC or fluorescence in situ hybridization [FISH]) in baseline tumor tissue samples. For 32 (9%) patients, baseline serum samples were analyzed using VEGF-C, -D, sVEGFR1 or 3 validated assays. Assay analyses were blinded. **Results:** The table provides the results of the HER2 analyses in tumor tissue (N = 147) and VEGFR2 analyses in tumor blood vessels (N = 143). The small number of patients with serum samples limited interpretation for candidate circulating biomarkers. **Conclusions:** Exploratory candidate biomarker analysis of tumor biopsies and serum from REGARD patients did not identify a significant predictive marker for RAM efficacy. Further examination of the role of VEGFR2 pathway biomarkers is warranted in ongoing RAM trials. Clinical trial information: NCT00917384.

	HER2+[a] RAM n=16	HER2+[a] PL n=5		HER2-[a] RAM n=80	HER2-[a] PL n=46	
mOS[b]	5.1	2.8		6.6	4.5	
95% CI	1.3-9.6	1.3-6.7		5.5-8.5	2.5-6.4	
	High VEGFR2[c] RAM n=49	**High VEGFR2[c] PL n=23**	**HR**	**Low VEGFR2[c] RAM n=46**	**Low VEGFR2[c] PL n=25**	**HR**
mOS[b]	6.6	2.3	0.69	5.6	4.5	0.73
95% CI	5.0-9.3	1.5-4.8	0.38-1.22	3.4-7.1	2.6-6.7	0.42-1.26
mPFS[b]	2.8	1.3	0.35	2.2	1.9	0.73
95% CI	1.5-4.1	1.1-1.3	0.20-0.59	1.4-2.8	1.3-2.7	0.42-1.27

Note: Treatment-by-VEGFR2 interaction p-values, not adjusted for multiplicity, were 0.878 for mOS and 0.051 for mPFS. Abbreviations: CI=confidence interval; HR=hazard ratio; m=median. [a]Bang et al. 2010 criteria. [b]in months. [c]High= ≥ median H-score (35); low= <35.

4030 Poster Session (Board #139), Mon, 8:00 AM-11:30 AM

Phase I study of GS-5745 alone and in combination with chemotherapy in patients with advanced solid tumors. *First Author: Johanna C. Bendell, Sarah Cannon Research Institute, Nashville, TN*

Background: GS-5745 is a monoclonal antibody that inhibits matrix metalloproteinase 9 (MMP9), an extracellular enzyme involved in matrix remodeling, tumor growth, and metastasis. Inhibiting MMP9 is expected to block paracrine signaling and metastasis and to alter the immune environment within the tumor. **Methods:** The safety, pharmacokinetics (PK), and efficacy of GS-5745 alone and in combination with chemotherapy are being evaluated in a phase I dose escalation and expansion study in patients (pts) with advanced solid tumors. Dose escalation occurred at doses up to 1800 mg of GS-5745 IV every 2 weeks followed by a dose expansion at 800 mg IV every 2 weeks in pts with pancreatic adenocarcinoma combined with gemcitabine/nab-paclitaxel and pts with esophagogastric adenocarcinoma combined with mFOLFOX6. All pts continued until disease progression or unacceptable toxicity. **Results:** As of January 13, 2015, 88 pts were treated. Treatment-emergent AEs (TEAEs) in > 30% of pts included nausea (38%), dyspnea (31%), and fatigue (31%). No DLTs were observed after monotherapy treatment. Non-linear PK, suggestive of target-mediated disposition, was observed with a mean half-life of ~8 days at doses of 600 and 1800 mg. When combined with chemotherapy, the most common TEAEs were diarrhea (59%), fatigue (47%), and nausea (38%). There were no observed responses in the monotherapy escalation phase. In the expansion phase, objective response rates in pts with measurable target lesions were 64% (7/11 esophagogastric) and 41% (7/17 pancreatic) based on investigator evaluation. Two complete responses in the esophagogastric cohort were noted by central radiology review. **Conclusions:** Preliminary safety data demonstrate a manageable safety profile for GS-5745 alone and in combination with chemotherapy. The study has been expanded to enroll additional subjects with pancreatic and esophagogastric cancer to identify potential pharmacodynamic and predictive biomarkers of response.

4031 Poster Session (Board #140), Mon, 8:00 AM-11:30 AM

Adaptive immune resistance in gastro-esophageal cancer: Correlating tumoral/stromal PDL1 expression with CD8$^+$ cell count. *First Author: Ronan Joseph Kelly, The Sidney Kimmel Comprehensive Cancer Center of Johns Hopkins, Baltimore, MD*

Background: In adaptive resistance, tumors use PDL1 induction as a protective mechanism against an antitumor immune response implying underlying immuno-surveillance. By upregulating the expression of ligands for inhibitory receptors on tumor specific lymphocytes in the tumor microenvironment a growing malignancy can avoid immune elimination. Here we report the interaction between PDL1 status and the density of CD8$^+$ at the tumor stromal interface in gastric and gastroesophageal junction adenocarcinomas (G/GEJ). **Methods:** 34 invasive G/GEJ were stained for PDL1 using the 5H1 clone both at the tumor cell and associated tumor infiltrating lymphocyte/macrophages (TILs/TAMs). Tumors with greater than 5% membranous staining were considered PDL1 positive. TILs/TAMs were scored as no significant staining (0), less than 50% (focal) or greater than 50% (high). CD8$^+$ density was determined using image analysis. Survival was evaluated according to PDL1 and CD8$^+$ status. **Results:** 4/34 tumors (12%) showed membranous PDL1 expression. 45% of G/GEJ demonstrated PDL1 expression among TILs with 27% showing focal interface expression and 18% high expression. Patients whose tumors were defined as stroma high (CD8$^+$ > 500 cells/m^2) had a worse PFS, HR = 3.91 (95% CI: 1.32, 11.59) p = 0.01, and OS, HR = 3.46 (95% CI: 1.09, 10.96) p = 0.03, compared to stroma low (CD8$^+$< 500 cells/mm^2). Interestingly in the stroma, 8/9 tumors (89%, CI: 51.8%, 99.7%) with high CD8$^+$ were also positive for PDL1 while only 7/24 (29%, CI: 12.6%, 51.1%) with low CD8+ were PDL1 positive (p = 0.004). PDL1 stromal expression was identified in 33.3% stage I, 53.9% stage II, 37.5% stage III, and 66.7% of stage IV tumors (p = 0.51). Stromal PDL1 expression occurred in 60% of intestinal and 38.5% of diffuse tumors (p = 0.45). **Conclusions:** PDL1 is expressed on both tumor cells and TILs across all stages and histologies of G/GEJ. Patients with higher CD8$^+$ levels have higher PDL1 expression indicating adaptive resistance is occurring in the tumor microenvironment. Phase II and Phase III clinical trials investigating the efficacy of PD1/PDL1 inhibitors either alone or in combination with CTLA-4 inhibitors are currently ongoing in patients with advanced G/GEJ.

4032 Poster Session (Board #141), Mon, 8:00 AM-11:30 AM

Laparoscopic D2 distal gastrectomy versus conventional open surgery for advanced gastric cancer: The safety analysis from a multicenter prospective randomized controlled trial in China (CLASS-01 Trial). *First Author: Yanfeng Hu, Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China*

Background: The safety and efficacy of laparoscopic D2 distal gastrectomy for the treatment of advanced gastric cancer (AGC) with curative intent is still controversial. Thus, the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) group conducted a multicenter prospective randomized controlled trial, aiming to evaluate the surgical safety and long-term outcomes of laparoscopic D2 gastrectomy compared with conventional open surgery for AGC. (NCT01609309) **Methods:** The patients with tumor located at distal stomach at clinical T2-4a, N0-3, M0 stage were eligible for enrollment, treated by either laparoscopic D2 distal subtotal gastrectomy (LG) or open D2 gastrectomy (OG) after randomization. Fifteen qualified surgeons at 14 institutions finally participated in the study. The morbidity and mortality within postoperative 30 days were compared between the two groups. **Results:** A total of 607 consecutive patients were recruited and randomly assigned into either LG group (n = 308) or OG group (n = 299) between September 2012 and January 2014. The LG group and OG group were similar in the compliance rates of D2 lymphadenectomy (97.4% vs. 98.3%; $P = 0.591$). The rate of conversion to open surgery was 4.5%. There was no significant differences between the LG group and OG group in the incidence of intraoperative complication (5.8% vs. 4.3%; $P = 0.402$), morbidity (18.8% vs. 14.7%; $P = 0.175$), and mortality (0.6% vs. 0; $P = 0.499$). The patterns of severity grading were also comparable between the two groups. ($P = 0.372$). **Conclusions:** Laparoscopic D2 distal gastrectomy for AGC could be safely performed by experienced surgeons. Thus, our multicenter prospective study on long-term outcomes justifies continued exploration. Clinical trial information: NCT01609309.

4033 Poster Session (Board #142), Mon, 8:00 AM-11:30 AM

Pazopanib and 5-FU/oxaliplatin as first-line treatment in advanced gastric cancer: PaFLO, a randomized phase II study from the AIO (Arbeitsgemeinschaft Internistische Onkologie). *First Author: Peter C. Thuss-Patience, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Med Klinik m. S. Hämatologie, Onkologie u. Tumorimmunologie, Berlin, Germany*

Background: Pazopanib is an oral tyrosine kinase inhibitor which selectively inhibits angiogenesis via VEGFR-1, -2, -3, ckit and PDGF-R. Recent positive trials show that angiogenesis is an effective target in gastric cancer. In this randomized phase II trial we treated patients (pts) with FLO +/- Pazopanib. **Methods:** Pts with metastatic or locally advanced gastric or gastro-esophageal junction adenocarcinoma, HER2 negative and with measurable disease were randomized in a 2:1 ratio to 5-FU (2,6g/m²/24h, d1) + Leukovorin (200mg/m², d1) + Oxaliplatin (85mg/m², d1) (FLO) + Pazopanib (800mg/d d1-14, q2w) (arm A) or the same chemotherapy without Pazopanib (arm B). Analysis was planned with a Simon Minimax design with PFS rate at 6 month in arm A as the primary endpoint expecting a minimum of 40% of pts progression free. **Results:** 87 pts were randomized, eligible and evaluable were 51 pts in arm A and 27 in arm B. Pts characteristics in % (arm A/arm B): male: 72/63%, female: 28/37%; median age: 65/60 yrs; ECOG 0: 44/44%, 1: 50/48%, 2: 6/7%; localization GEJ: 59/30%, gastric body 41/70%; histology intestinal: 31/33%, diffuse or mixed: 28/30%, not specified: 41/37%. Treatment was tolerated well with possibly treatment related SAE in arm A in 12 of 51 pts + 4 SAE of special interest (ALT elevation) and arm B 4 of 27 pts. Median chemotherapy cycles administered were similar in both arms (8 cycles). Necessary dose reduction of chemotherapy were similar, arm A 37%, arm B 33% of pts. Pazopanib dose reductions were necessary in 22% of pts. PFS rate at 6 months was 31.4% in arm A and 25.9% arm B. Median PFS: 5.1 months arm A and 3.9 months arm B (HR 0.93, 95%CI 0.56-1.54). Median OS was 10.1 months in arm A and 7.0 months in arm B (HR 0.80, 95%CI 0.44-1.48), Median follow up is 12 months. **Conclusions:** Both arms had an inferior PFS than expected from the literature. Pazopanib in combination with 5-FU/Oxaliplatin showed marginal efficacy in this randomized phase II study regarding PFS. Further follow up for interesting OS data is needed. Histology specimen and multiple serum samples were collected from each pt and need to be analyzed for potential subgroups that may benefit most from Pazopanib. Clinical trial information: NCT01503372.

4034 Poster Session (Board #143), Mon, 8:00 AM-11:30 AM

MET as a prognostic biomarker of survival in a large cohort of patients with gastroesophageal cancer (GEC). *First Author: Daniel Virgil Thomas Catenacci, University of Chicago, Chicago, IL*

Background: Estimates of the frequency of genomic/proteomic alterations in MET in solid tumors vary widely, but a growing body of evidence suggests that *MET* amplification and/or Met expression are biomarkers for poor prognosis. We examined both *MET* gene copy number and Met protein expression as potential prognostic biomarkers for survival in a large set of GEC samples with full clinical annotations (staging, HER2 status, treatment, and overall survival). **Methods:** Formalin-fixed, paraffin-embedded (FFPE) GEC samples (N = 394) primarily from early-stage tumors were collected in the United States and Italy. Samples were analyzed by fluorescence in situ hybridization (FISH) for *MET* gene amplification (Dako *MET* IQFISH probe mix, research use only) and by immunohistochemistry (IHC) for Met protein expression (Dako Met IHC assay, MET4 antibody, investigational use only). All assays were performed according to the manufacturer's instructions. Samples with a *MET*/CEP 7 ratio ≥ 2.0 were considered amplified, whereas samples with ≥ 25% Met tumor membrane staining by IHC (≥ 1+ intensity) were considered Met positive. Spearman's rank correlation coefficient was used to assess correlations between parameters. Cox proportional hazards models and Kaplan-Meier estimates were applied to explore relationships between MET, overall survival, and other clinical characteristics. **Results:** *MET* gene copy number variation (≥ 5 copies) was observed in 18 of 344 samples (5.2%), and *MET* gene amplification (*MET*/CEP 7 ≥ 2.0) was observed in 16 of 344 samples (4.7%). Of the 332 evaluable IHC samples, 117 (35.2%) were positive for Met protein expression. There was considerable overlap between *MET* amplification and Met expression; 12 of 15 *MET*-amplified samples (80.0%) were positive for Met expression. Survival analyses showed that both *MET* gene amplification and Met IHC positivity were prognostic of poor outcomes. **Conclusions:** *MET* amplification was observed in ~5% of this large set of GEC samples. Prevalence of *MET* amplification and Met expression were similar to those found in previously published studies. Our results indicate that *MET* gene amplification and Met protein expression are prognostic of poor outcomes in GEC.

4035 Poster Session (Board #144), Mon, 8:00 AM-11:30 AM

Randomized phase II study of recombinant human endostatin combined with definitive chemoradiotherapy in locally advanced esophageal squamous cell carcinoma. *First Author: Jiahua Lv, Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Chengdu, China*

Background: Recombinant human endostatin (endostar) has been documented to be an inhibitor of tumor angiogenesis. The aim of this randomized phase II study was to assess the efficacy and safety of endostar combined with chemoradiotherapy (CRT) in locally advanced esophageal squamous cell carcinoma (ESCC). **Methods:** Locally advanced ESCC with a performance status of 0-1 were randomly assigned to endostar group (endostar 7.5mg/m2 D1-D14 with CRT) or the control group (CRT only). Patients in both groups were treated with docetaxel (75 mg/m2 on D1)/CDDP (25 mg/m2 on D1-D3)-based intensity-modulated radiation therapy (IMRT, 60-66 Gy/30-33f/6-7wks). CT perfusion imaging and immunohistochemical staining of tumor microvessel density (MVD) were assessed before and after the treatment of endostar. The primary end point was overall survival (OS). The secondary end points were the effect of endostar on angiogenesis, progression-free survival (PFS) and object response rate (ORR). **Results:** Between Oct. 2012 and Sep. 2014, 63 patients were enrolled and divided into endostar group (n = 32) or the control group (n = 31). The endostar group resulted in a slight improvement in ORR (62.3% vs 55.1% in the control group), and a significant increase in the 1-year and 2-year overall survival rates (78.1% vs 67.7% and 56.2% vs 45.1%, respectively). The median PFS was extended to 16.5 months in the endostar group vs 9.3 months in the control group ($P < 0.05$). Endostar combined with CRT led to a marked decrease in tumor blood flow (BF) and blood volume (BV) with correction of MVD, compared to CRT alone ($P < 0.05$). There was no significant difference in toxicities in two arms. No new or unexpected endostar-related toxicities were observed. **Conclusions:** Recombinant human endostatin combined with CRT can reduce tumor angiogenesis. The short- and long-term effects of endostar combined with CRT were an improvement over that of CRT alone in this study. Clinical trial information: ChiCTR-TRC-13003908.

4036 Poster Session (Board #145), Mon, 8:00 AM-11:30 AM

Estrogen receptor beta (ERβ) gene polymorphisms as a predictor of overall survival in patients with gastric cancer (GC) from Japan and Los Angeles County (LAC). *First Author: Anish Parekh, University of Southern California/ Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Use of menopausal hormones has correlated with a lower risk of colon cancer in women. Prostate cancer patients (pts) treated with estrogen have a reduced risk of developing GC as a second primary. Several ERβ gene (*ESR2*) polymorphisms have been associated with colorectal cancer survival (Cancer Res 2013;73:767). To better understand the role of ERβ in relation to GC outcome, we tested whether *ESR2* polymorphisms will be associated with overall survival (OS) in GC pts from 2 different regions. **Methods:** We analyzed genomic DNA extracted from blood or tumor tissues of 169 pts from Japan (64% men, stage IB-IV of AJCC-6th, median age 67, median follow-up 3.6 years, median survival 5.7 years) and 214 pts from LAC (68% men, stage 0-IV of AJCC-6th, median age 62, median follow-up 8.2 years, median survival 2.6 years), using PCR-based direct sequencing. *ESR2* polymorphisms, which were shown to be of biological significance (rs2978381, rs3020443 and rs1271572), were analyzed for association with OS in both cohorts. Multivariate Cox proportional hazard regression was conducted to test the association after adjustment for age, sex, primary tumor site, stage and other covariates. **Results:** *ESR2* rs1271572 and rs3020443 had uni- and multivariate associations with OS in the Japanese but not LAC cohort. Any C allele of *ESR2* rs2978381 (T > C) was associated with longer OS than T/T genotype in the Japanese cohort (5-year survival 63 % vs 41 %, p= 0.021) but shorter OS in the LAC cohort (5-year survival 30 % vs 51 %, p= 0.049) although these findings did not remain significant in multivariate analysis. In analysis restricted to distal GC, the *ESR2* rs1271572 (C > A) correlated with OS but the effect of A allele was in the opposite direction between the Japanese (n= 121, adjusted HR 2.19, p= 0.019) and LAC cohort (n= 116, unadjusted HR 0.62, p= 0.031). **Conclusions:** *ESR2* polymorphisms have prognostic value in pts with GC. These data also suggest that ERβ pathway may play a key role in tumor progression of GC and its prognostic impact may differ depending on histopathologic, ethnic or epidemiologic differences. Further studies to evaluate the association among different races are warranted.

4037 Poster Session (Board #146), Mon, 8:00 AM-11:30 AM

A phase I dose-escalating and safety study of AZD8931 in combination with oxaliplatin and capecitabine chemotherapy in patients with oesophagogastric adenocarcinoma. *First Author: Anne L. Thomas, Leicester Royal Infirmary, Leicester, United Kingdom*

Background: AZD8931 is a novel small-molecule inhibitor which has equipotent activity against signalling by three members of the erbB family; EGFR, erbB2(HER2), and erbB3. Our hypothesis is that combining AZD8931 with chemotherapy will be effective not just in oesophago-gastric cancer patients (pt) who overexpress high levels of HER2, but those with low HER2 expression as well. This study seeks to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of AZD8931 with oxaliplatin and capecitabine (XELOX) in patients with oesophagogastric cancer (OGC). **Methods:** Chemonaive patients with metastatic OGC were recruited into this rolling 6 dose escalating study to determine MTD, safety (NCI-CTC version 4.0) and pharmacokinetics of the combination. Patients received oxaliplatin (130 mg/m^{2}day(d) 1 every 21 days (q21) and capecitabine (X) (1250mg/m2/d) d1-21, for a maximum of 8 cycles. AZD8931 dosing was planned at 3 cohorts (20mg bd, 40 mg bd, 60 mg bd continuously). With emerging toxicity at 20mg bd, AZD8931 was also investigated at 2 intermittent schedules (14d on and 7d off, 4d on and 3d off, from d1, q21). **Results:** 24 pts (median age 60 years) were enrolled in 4 cohorts and 4 DLTs within cycle 1 were observed: diarrhoea, vomiting and skin rash (Table 1). 58% (14/24) patients showed SAE grade ≥ 3 (mostly GI disorders and infections). 95% (18/19) patients had at least stabilisation of disease as best tumour response from cycle 3 (8 stable disease, 9 partial and 1 complete response). PK data, full demographic data including HER2 status and justification of RP2D dose will be presented. **Conclusions:** In this pt group the RP2D of AZD8931 in combination with XELOX is 20mg bd 4d on and 3d off q21. We are now recruiting pts with operable disease into the randomised phase of the study with XELOX versus XELOX and AZD8931. Translational studies are ongoing. Clinical trial information: 2011-003169-13.

Dosing cohorts and DLTs.

Dose of AZD8931 bd	No of Pts enrolled (evaluable for dose escalation)	DLTs
20 mg continuous	6 (6)	1 G2 diarrhea*
20 mg 14d on and 7d off q21	7 (6)	1 G3 diarrhea*
20 mg 4d on and 3d off q21	7 (6)	0
40 mg 4d on and 3d off q21	4 (4)	1 G3 vomiting & 1 G3 skin rash

*Requiring stoppage of X

4038 Poster Session (Board #147), Mon, 8:00 AM-11:30 AM

Multicenter phase 2: Capecitabine (CAP) + oxaliplatin (OX) + bevacizumab (BEV) + trastuzumab (TRAS) for patients (pts) with metastatic esophagogastric cancer (MEGCA). *First Author: Peter C. Enzinger, Dana-Farber Cancer Institute, Boston, MA*

Background: In MEGCA, cisplatin+CAP has RR 46% and OS 12.1 mos with BEV (AVAGAST) and RR 47% and OS 13.8 mos with TRAS (ToGA). We sought to improve these results by combining CAPOX with both BEV and TRAS. **Methods:** Pts with HER2/neu IHC 3+ or FISH+ MEGCA, with 0-1 prior chemo, received a loading dose of TRAS 4mg/kg, day (d) 1. One week later, pts received BEV 7.5mg/kg/d1, TRAS 6mg/kg/d1, OX 130mg/m2/d1 and then q21d. CAP d1-14/q21d was decreased from 1700mg/m2/d to 1200mg/m2/d after 4 of the first 5pts developed G3 diarrhea. Consenting pts underwent identical research biopsies prior to and 7 days after TRAS loading dose. Primary endpoint was RR by RECIST 1.1, scored by independent Harvard Tumor Imaging Metrics Core. **Results:** Of 35 pts enrolled, median age 58 (32-80), 4F/31M, HER2/neu IHC3+: 25/FISH+: 10, ECOG PS 0: 18/ 1: 17, prior chemo 10, primary: esophagus 16/GEJ 10/gastric 9, sites of mets: LN 26, liver 19, lungs 9, bone 2, other 6. Pts have received mean 16 cycles (2-50+). Of 34 pts (1 too early), PR 24 + CR 2 = 76.5% RR (95% CI, 0.59 – 0.88) by blinded review. For all 35pts, median PFS = 13.93 mos (95%CI, 8.5 - 22.33); median OS = 26.92 mos (95%CI, 11.31 – 36.36). Safety for 30pts (enrolled after CAP dose change): 16 pts required dose modification: CAP 12, OX 14, BEV 2, TRAS 0. Pts w grade 3-4 AE: periph neuropathy 3, bleeding 3, thromboembolic event 2, hypertriglyceridemia 2, ANC 2, HTN 1, plts 1, diarrhea 1. One pt died of cardiac arrest after 3yrs on tx. **Conclusions:** CAPOX+BEV+TRAS is well tolerated in pts with MEGCA. There appears to be at least additive effect between BEV and TRAS. Combinations of anti-VEGF and anti-HER2/neu agents should be considered in future randomized studies of HER2/neu+ MEGCA. Clinical trial information: NCT01191697.

4039 Poster Session (Board #148), Mon, 8:00 AM-11:30 AM

Prognostic impact of Forkhead box-F1 (FOXF1) polymorphisms on the clinical outcome in gastric cancer patients. *First Author: Satoshi Matsusaka, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: A recent genome-wide association study reported associations between risk of Barrett's esophageal and esophageal adenocarcinoma and seven single-nucleotide polymorphisms (SNPs) in region 16q24 on chromosome 16 near the Forkhead box-F1 (FOXF1) gene. The FOXF1 gene is known to regulate mesenchymal-epithelial interactions of the lung and gut morphogenesis and to regulate cancer-associated fibroblasts to stimulate cancer cell migration. We tested whether these SNPs are associated with clinical outcome of gastric cancer (GC) patients from Japan and Los Angeles County (LAC). **Methods:** We isolated genomic DNA from blood or tissue of GC patients from two independent cohorts. A total of 150 patients with advanced GC from Japan [107 male/43 female; median age 61 year-old; median follow-up time, 3.1 years; median overall survival (OS), 13.8 months; median progression-free survival (PFS), 6.6 months] who were treated with 1st line fluoropyrimidine-based chemotherapy and 214 patients with stage IA-IV GC from LAC [146 male/68 female; median age 62 year-old; median follow-up time, 8.2 years; median OS, 2.6 years] were included. Genomic DNA was analyzed using PCR-based direct DNA sequencing. Multivariate Cox proportional hazard regression was conducted to investigate the relationship between these SNPs with clinical outcome of gastric cancer patients. **Results:** One FOXF1 SNP, rs3950627, was associated with outcome in patients from Japan and LAC. Japanese patients who had C/C genotype experienced better outcome than those with any A allele (PFS: C/C 8.2 months, any A allele 5.3 months; p = 0.037 and OS: C/C 16.4 months, any A allele 12.2 months; p = 0.043). Similarly, patients in LAC with C/C genotype showed better outcome (OS: C/C 46.8 months, any A allele 27.6 months, p = 0.022). Results were consistently strong when we restricted the analysis to male patients and those with gastric cardia cancer. **Conclusions:** Our data show for the first time that rs3950627 is a promising a prognostic marker in two cohorts of GC patients. Furthermore, rs3950627 may be useful as a predictive marker in patients treated with fluoropyrimidine-based chemotherapy, which may be gender dependent.

4040 Poster Session (Board #149), Mon, 8:00 AM-11:30 AM

The role of panitumumab in combination with ECX in perioperative chemotherapy of unselected patients with locally advanced gastroesophageal adenocarcinomas: Randomized phase II study of the German Cancer Society. *First Author: Markus H. Moehler, Johannes-Gutenberg University Mainz, Mainz, Germany*

Background: Perioperative chemotherapy (pCT) significantly improved survival of patients (pts) with locally advanced esophagogastric adenocarcinoma (la EGC). However, ~60% of pts will later die from their disease. Thus, targeted drugs are worthwhile to be investigated to further improve survival (OS). **Methods:** To evaluate the role of the EGFR-antibody panitumumab with pCT, we performed an open randomized phase II study in 22 German centres. Untreated pts with la EGC (cT3-4 N0-3 M0) were eligible and treated with standard ECX therapy with (arm 1) or without (arm 2) panitumumab (9 mg/kg body weight iv, q 3 weeks). Three cycles were given prior to and after surgery. 163 from 171 pts (83 arm 1, 80 arm 2) were eligible from 11/2010 to 7/2013. Results: Compliance and dose intensity of pCT was equal in both arms, however 49% started and only 31% completed postop. CT in arm 1 versus 50% and 40% in arm 2, respectively. The cumulative capecitabine dose was lower in arm 1 (58% vs. 70% of planned dose). No death was observed until 30 days after postop. CT. Local efficacy was slightly increased with panitumumab (75% vs. 68% without progression/death or with downstaging, p = 0.24). PFS (HR 1.21; 0.78-1.89) and OS (HR 1.30; 0.79-2.13) was not significantly lower in arm 1. Molecular analyses were possible in 76 / 163 pts (47%): c-MET overexpression was high (53%); however c-MET amplification (4%), EGFR-amplification or overexpression (7%), HER2-positivity (8%) or RAS-mutations (3%) were rarely observed. 117 plasma samples were analyzed for 25 EGFR signaling markers and ligands. At baseline, patients had slightly higher levels vs. healthy controls for BDNF , EGF, HGF, PDGF, PlGF, SCF, VEGF-A, and -D. Conclusions: Similarly to metastatic disease, adding EGFR-antibody panitumumab to ECX did not improve the results in unselected locally advanced EGC pts. The rare pt numbers with possible predictive molecular alterations made it unlikely to define subgroups who may have benefitted from the addition of panitumumab to perioperative CT. Clinical trial information: 2008-007798-18.

4041 Poster Session (Board #150), Mon, 8:00 AM-11:30 AM

Analysis of patients with esophageal cancer following trimodality therapy: Pathological complete remission (PathCR) versus non-PathCR. *First Author: Mariela A. Blum, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Trimodality therapy (chemoradiation followed by surgery) continues to be the cornerstone treatment for localized esophageal cancer; predictive models for pathCR have been not been clinically validated. The purpose of this study was to determine the association of pathCR with baseline clinical factors, overall survival (OS), and recurrence free survival (RFS) in a large population. **Methods:** We analyzed the data of 911 consecutive patients treated for esophageal cancer with trimodality therapy. Logistic regressions were used to identify independent baseline factors associated with pathCR. We applied log rank testing and univariable and multivariable Cox models to determine the association between pathCR and the time-to-event outcomes (OS and RFS). **Results:** Of 911 patients studied, 218 (23.9%) achieved pathCR. Lower clinical T stage (T1/T2) was more likely to achieve pathCR (p = 0.0006). Advanced age (OR = 0.984, p = 0.0297), poorly differentiated tumors ((OR = 0.48), p = < 0.0001), and signet ring cell histology (p = < 0.0001) were associated with lower rate of pathCR. OS and PFS rates were higher for pathCR patients (p = 0.0021 and p = 0.0011). The estimated median OS was 71.28 (95% CI: 51.71-91.63) months in pathCR patients and 35.87 (95% CI: 31.23-42.19) months in non-pathCR patients. Distant recurrences were less common in pathCR patients (p = 0.0036). **Conclusions:** Poor prognostic indicators associated with decreased rate of pathCR and OS were: older age, poorly differentiated tumors, and the presence of signet ring cell histology. Our data is the largest data set showing that pathCR confers better prognosis in patients with esophageal cancer. While recurrences were still seen in pathCR patients, distant metastases were more common in non-pathCR patients. Further biomarker-based approach might help to identify patients who are more likely to achieve pathCR.

4042 Poster Session (Board #151), Mon, 8:00 AM-11:30 AM

Prognostic significance of tumor infiltrating immune cells and PD-L1 expression in gastric carcinoma in Chinese patients. *First Author: Ruixuan Geng, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Programmed death-1 receptor (PD-1) and its ligand (PD-L1) play an integral role in the immune response against cancer. This study in Chinese patients (pts) with gastric carcinoma (GC) investigated the prognostic significance of PD-L1 expression on tumor cells and its association with tumor-infiltrating lymphocytes (TILs). **Methods:** 398 archived, formalin-fixed, paraffin-embedded GC samples were collected Oct 2007–Feb 2010 at a single institution from pts with stage I–IV GC after gastric resection and no prior chemo- or radiotherapy. The median age was 60 years (range 21–87 y). TILs were phenotyped and PD-L1 expression on tumor cells was assessed immunohistochemically, using a pre-defined cutoff (≥ 5% tumor cells with ≥ 1+). Associations of TIL and PD-L1 expression with clinico-pathologic features were evaluated using a non-zero correlation test. Survival distribution among different subgroups was compared by Kaplan-Meier and a log-rank test. A multivariate Cox regression model was used to investigate prognostic factors (TNM stage, Lauren type, TIL density, PD-L1 expression) for overall survival (OS). The median follow-up time was 44.3 months (range 0.1–79.9 m). **Results:** PD-L1 expression was observed in 14% of pts. The median OS for PD-L1(-) pts was 61.1 m. The median OS time for the PD-L1(+) pts had not yet been reached. In specimens with PD-L1(+) tumor cells, 96% (55/57) were associated with TILs, and PD-L1 expression on tumor cells was positively associated with TIL densities (*P*= 0.0018). There was no correlation between PD-L1 expression and Lauren type or TNM stage. Multivariate analysis identified both moderate (HR 0.585; 95% CI, 0.346–0.989; *P*= 0.045) and high TIL densities (HR 0.109; 95% CI, 0.026–0.462; *P*= 0.003) as independent factors associated with OS. The association between PD-L1 expression and OS did not reach statistical significance (HR 0.766; 95% CI, 0.452–1.299; *P*= 0.322). **Conclusions:** Within the tumor microenvironment, a moderate to high number of TILs is associated with a better clinical outcome and elevated tumor PD-L1 expression. These observations support a possible therapeutic role for PD-L1 inhibitors in a subset of GC pts.

4043 Poster Session (Board #152), Mon, 8:00 AM-11:30 AM

Clinical characteristics and treatment outcomes of patients with metastatic, *MET*-amplified esophagogastric cancers. *First Author: Eunice Lee Kwak, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: The Cancer Genome Atlas (TCGA) reported *MET* gene alterations in 6% of gastric cancers (Nature 2014; 513: 202–209). Though rare, *MET* amplification is a biomarker for dramatic responses to single-agent MET inhibitors in esophagogastric cancer (J Clin Oncol 33, 2015, suppl 3; abstr 1). Clinical characteristics and outcomes were evaluated in patients (pts) with *MET*-amplified esophagogastric cancers (EGC) to facilitate identification of pts and establishment of treatment paradigms. **Methods:** Pts with metastatic *MET*-amplified EGC were identified between 2007 and 2014. *MET* amplification was determined in paraffin-embedded tissue using fluorescence in-situ hybridization (FISH), with a gene to control ratio of > 2.2 defined as positive. Clinical characteristics, treatment factors, and survival were recorded. A cohort of pts diagnosed between 8/2002 and 10/2012 with metastatic non-*MET*-amplified EGCs was evaluated as a comparison group. **Results:** We identified 23 pts with *MET*-amplified EGCs, 15 of whom were identified between 2012-2014. Compared to 37 non-*MET*-amplified tumors, *MET*-amplified EGCs were more typically poorly differentiated and located in the distal esophagus or gastroesophageal junction rather than distal stomach. Patterns of metastases did not differ between *MET*-amplified and non-*MET*-amplified pts. In the 17 pts for whom HER2 status was obtained, 4/17 EGCs showed co-amplification of *MET* and *HER2*. One EGC had concurrent *MET* and *EGFR* amplification. Additionally, 1/17 genotyped tumors harbored a *PIK3CA* mutation. Progression-free survival (PFS) from the time of metastatic diagnosis was 5 months for pts with *MET*-amplified EGCs. Including 7/23 pts who had received MET-directed therapy, overall survival (OS) was 13.2 months (3.4-7.8 and 6.0-21.1, 95% CI estimate of PFS and OS, respectively). Updated OS and comparison to the non-*MET*-amplified cohort will be presented. **Conclusions:** This series represents the largest cohort of clinically annotated *MET*-amplified EGCs and highlights this subgroup as a distinct clinical entity characterized by rapid progression. Patients should be identified early and directed to appropriate MET-targeted clinical trials.

4044 Poster Session (Board #153), Mon, 8:00 AM-11:30 AM

A phase II single-arm pilot study of second-line icotinib treatment in advanced esophageal cancer with EGFR over-expression or amplification. *First Author: Jing Huang, Cancer Hospital and Institute, Chinese Academy of Medical Sciences, Beijing, China*

Background: Epidermal growth factor receptor (EGFR) has been reported to be overexpressed in esophageal cancer, suggesting EGFR-directed treatment is a potential option. Here we report the antitumor activities of icotinib, a selective EGFR tyrosine kinase inhibitor (TKI), as second-line treatment for advanced esophageal cancer with EGFR over-expression or amplification. **Methods:** In this phase II, single-arm study, eligible patients were adults with advanced esophageal cancer confirmed by histology, who had received at least first-line chemotherapy, with EGFR over-expression [immunohistochemistry (IHC), 3+] or amplification [positive fluorescence in-situ hybridisation (FISH)]. Participants were treated with oral icotinib (250 mg, three times daily).The primary endpoint was objective response rate (ORR). **Results:** Between December, 2013 and January, 2015, 38 patients were enrolled (37 with squamous cell carcinoma, 1 with adenocarcinoma) with a median age of 60, in which 36 were IHC 3+ (94.7%) and 2 were IHC 2+ with positive FISH. And as of the December 31, 2014 cutoff, 33 patients were evaluable for response. The ORR was 15.2% (5/33), consisting of 1 CR and 4 PRs, and the disease control rate was 54.5% (18/33). The median duration of treatment in 18 patients (CR + PR + SD) is 12.3 weeks with the longest being 28+ weeks. Twenty-three out of 33 patients (69.7%) experienced at least one adverse event (AE) with rash (42.4%), diarrhea (24.2%), pain (21.2%), fatigue (15.2%) and vomiting (12.1%) as the most common ones. Most AEs were mild and reversible and no grade 3 or 4 AEs were reported. **Conclusions:** Second-line icotinib treatment in advanced esophageal cancer with EGFR over-expression or amplification demonstrated favorable outcome along with a high safety profile. However, the role of EGFR over-expression or amplification as predictive biomarker still needs further exploration. Clinical trial information: NCT01855854. Clinical trial information: NCT01855854..

4045 Poster Session (Board #154), Mon, 8:00 AM-11:30 AM

Patterns of local-regional relapse after complete response by definitive chemoradiotherapy for stage II/III (non–T4) esophageal squamous cell carcinoma. *First Author: Kazuki Sudo, National Cancer Center Hospital, Tokyo, Japan*

Background: Definitive chemoradiotherapy (dCRT) has been recognized as one of treatment options for esophageal squamous cell carcinoma (ESCC) patients who are not fit for surgery. Recent studies revealed that surveillance after dCRT was important in an adenocarcinoma dominant population. However, clinical utility of surveillance for ESCC is not clear. **Methods:** The subjects of this retrospective study were patients who underwent dCRT for stage II/III (excluding T4 disease) ESCC from 2000 to 2011 at National Cancer Center Hospital in Tokyo, Japan. We reviewed the patterns of relapse after clinical complete response (cCR). Each patient was generally surveyed with computed tomography (CT) and esophagogastroduodenoscopy (EGD) every 3-6 months. We also recorded new cancers (NC) diagnosed by EGD during surveillance after cCR. Local-regional relapse (LRR) without distant metastasis was classified into luminal-only relapse (LR) and other type of regional relapse (RR) with or without luminal relapse. Overall survival (OS) was estimated using the Kaplan-Meier method. **Results:** Among 351 patients treated with dCRT, 233 (66%) achieved cCR. The median follow-up time was 64.0 months. A total of 94 (40% of 233) patients had relapse after cCR: 45 (19%) with distant metastasis and 49 (21%) with LRR including 33 with LR and 16 with RR. Of the remaining 139 patients without relapse, 20 (14%) had NC: 17 with new esophageal cancer, 2 with hypopharynx cancer and 1 with esophagogastric junction cancer. Of 49 LRR, 31 (63%) were diagnosed within 1 year of dCRT and 46 (94%) within 3 years. Fifty-three of 69 patients (77%) with LRR or NC underwent local treatment (salvage surgery, endoscopic treatment or radiation). For these 53 patients with local treatment, the median OS from diagnosis of LRR or NC was 57.1 months (95% CI, 25.3-88.9). **Conclusions:** Our data suggest that 94% of LRR occurred within 3 years of dCRT. Of patients without relapse after cCR, 14% were diagnosed with NC by EGD. Outcome of local treatment for LRR or NC was excellent.

4046 Poster Session (Board #155), Mon, 8:00 AM-11:30 AM

Multicenter retrospective analysis for elderly patients with advanced gastric cancer (AGC) received first-line chemotherapy in clinical practice. *First Author: Kenji Kunieda, Department of GI Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: Indication of elderly patients (pts) to intensive chemotherapy has not been established. We hypothesized that a survival benefit of doublet chemotherapy with fluoropyrimidine plus platinum, standard treatment might be attenuated in elderly AGC pts with decreased physiological function due to their low tolerability. **Methods:** We retrospectively investigated clinical outcomes of the elderly AGC pts, 70 years or older, who were treated with S-1 or S-1 + CDDP (SP) as the first-line chemotherapy between 2009 and 2011 at 29 medical centers participating West Japan Oncology Group. Among these pts we selected the pts considered to be fit for SP, and the efficacy and toxicity of S-1 with SP therapy was compared, calculating the propensity scores for receiving each treatment and conducted survival analyses by inverse probability of treatment weighting. **Results:** Among 464 pts enrolled this study, 446 pts were eligible for the criteria. Patient characteristics were: median age 75 years old (range 70-86); PS 0/1/2 38%/54%/8%; male/female 71%/29%; some co-morbidity +/- 68%/32%; CCr $<$ 50 ml/min/ $>=$ 50 ml/min 21%/79%; received S-1/SP 47%/53%. Between the S-1 and SP groups, there was a large imbalance in PS, better in the SP group ($p < 0.001$). Limited to the 170 pts with PS 0, 56 pts (33%) and 114 pts (67%) received S-1 and SP, respectively. Between the two groups in this subset of PS 0 showed no significant differences in gender and co-morbidity rate, but SP group showed better background such as age, ($p < 0.001$), CCr ($p < 0.05$). The median PFS in the S-1 and SP group, were 8.0 months and 7.9 months (HR = 0.999, 95 % CI 0.698-1.429, p = 0.999), and median OS were 15.0 months and 17.2 months (HR=1.116, 95 % CI 0.760-1.640, p = 0.574). The results were consistent after background factors were statistically adjusted by propensity score. Hematologic toxicities ($p < 0.001$), G3/4 adverse event ($p < 0.001$) and hospitalization due to AE ($p < 0.001$) were more frequent in the SP group. **Conclusions:** It is suggested optimal treatment strategy for elderly AGC patients should be established separately from younger patients, we are now planning the clinical trial for elderly AGC patients.

4047 Poster Session (Board #156), Mon, 8:00 AM-11:30 AM

A phase I dose expansion trial of avelumab (MSB0010718C), an anti-PD-L1 antibody, in Japanese patients with advanced gastric cancer. *First Author: Yasuhide Yamada, National Cancer Center Hospital, Tokyo, Japan*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Here we present preliminary results from a phase Ib dose expansion study (NCT01943461) evaluating safety and clinical activity in a cohort of Japanese patients (pts) with advanced gastric cancer (GC). **Methods**: Pts with previously treated progressive GC, ECOG PS 0-1, received avelumab at 10 mg/kg, Q2W. Responses were assessed according to RECIST 1.1 and modified immune-related RECIST (irRECIST). Adverse events (AEs) were evaluated by CTCAE v4.0. Initial data from a prespecified analysis are reported here. A total of 20 pts in this expansion cohort were enrolled. **Results**: As of Oct 8, 2014, 11 pts were treated with avelumab. Pts were followed-up for at least 3 weeks (wks) and the median treatment duration was 9.9 wks (range 4-12). Median age was 69 years (range 38–76) and all pts had an ECOG-PS of 0 or 1, with a median of 3 prior lines (range 1–4) of therapy. Drug-related treatment-emergent AEs (TEAEs; all grades) occurred in 10/11 pts (90.9%). The most frequently observed treatment-related TEAEs ($>$ 1 case; all grade 1 or 2) were infusion-related reactions (IRRs) (3 pts, 27.3%), hyperthyroidism, and pruritus (2 pts each, 18.2%). There were no treatment discontinuations from AEs. One pt had grade 3 anemia; it was assessed as not drug-related. At data cutoff, 2 pts (18.2%) have come off study due to disease progression. Nine patients were still on treatment. To date, partial responses according to RECIST have been observed in 3 pts. **Conclusions**: Avelumab at 10 mg/kg Q2W can be safely administered in Japanese pts with heavily pretreated, metastatic GC. Additional studies to evaluate the efficacy of avelumab in Japanese pts with GC are planned and biomarkers from tumor tissue and blood samples including PD-L1 expression and soluble factors related to immune response will be evaluated. *Proposed INN. Clinical trial information: NCT01943461.

4048 Poster Session (Board #158), Mon, 8:00 AM-11:30 AM

Evaluation of tumor MET protein expression, *MET* gene amplification, and HER2 expression in Chinese patients with advanced gastric or gastroesophageal junction (G/GEJ) cancer. *First Author: Rui-hua Xu, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Gastric cancer is a disease with high unmet medical needs in China. MET and its ligand, hepatocyte growth factor, are potential targets in G/GEJ cancer. This study evaluated overall survival (OS) according to tumor MET expression, *MET* gene amplification, and the association between MET and HER2 status in Chinese patients with advanced G/GEJ cancer. **Methods:** Baseline tumor biopsy samples (formalin-fixed, paraffin-embedded primary tumor) from patients with stage IV unresectable G/GEJ cancer, archived at Sun Yat-Sen University Cancer Center, were assessed for MET and HER2 protein levels and *MET* and *HER2* gene amplification by IHC and FISH, respectively. MET-positive: membrane protein staining in $\geq$ 25% or $\geq$ 50% of tumor cells. HER2-positive: IHC 2+ and a confirmatory *HER2* FISH-positive result (*HER2*:centromere 17 ratio $\geq$ 2.0), or IHC 3+. *MET*-amplified: *MET*:centromere 7 ratio $>$ 2.0. We evaluated associations between Kaplan-Meier OS and MET status (log-rank test), MET expression and *MET*gene amplification, and MET and HER2 status (Fisher exact test). **Results:** Of 289 eligible patients, 271 had evaluable IHC samples, and MET-positive rates were 42.1% and 25.1% by 25% and 50% cutoffs, respectively. Median OS by different levels of MET-positive expression is shown in the Table. Of 183 patients with evaluable FISH samples, 8 (4.4%) were *MET*-amplified. In 171 patients with IHC and FISH data, MET-positive expression by 25% and 50% cutoffs was associated with *MET* amplification ($P <$ 0.005, both cutoffs). In 145 patients with MET IHC, FISH, and HER2 data, the HER2-positive rate was 13.8%. Of patients who were MET-positive by 25% and 50% cutoffs, 8/48 (16.7%) and 4/29 (13.8%), respectively, were also HER2-positive. Additionally, 1/8 (12.5%) *MET*-amplified patients was HER2-positive. **Conclusions:** MET-positive status was associated with shorter OS in this population of Chinese patients with advanced G/GEJ cancer. MET high expression or *MET* amplification was not associated with HER2 expression.

Patients evaluable for IHC	MET-positive	MET-negative	*P* value
25% cutoff			
n	114	157	
OS, mo*	10.9	16.0	0.054
50% cutoff			
n	68	203	
OS, mo*	8.3	15.5	$<$ 0.001

*Median

4049 Poster Session (Board #159), Mon, 8:00 AM-11:30 AM

Prospective phase II trial of pazopanib plus CapeOX (capecitabine and oxaliplatin) in previously untreated patients with advanced gastric cancer. *First Author: Min-Young Lee, Samsung medical center, Seoul, South Korea*

Background: We designed a single-arm, open label phase II study to determine the efficacy and toxicity of the combination of pazopanib with CapeOx (capecitabine and oxaliplatin) in metastatic and/or recurrent advanced gastric cancer (AGC) patients. **Methods:** Previously untreated AGC patients received capecitabine (850 mg/m^2 bid, day 1–14) plus oxaliplatin (130 mg/m^2, day 1) in combination with pazopanib (800 mg, day 1–21) every three weeks. Treatment was continued until progression of the disease or intolerable toxicity was observed. **Results:** In all, 66 patients were treated with pazopanib plus CapeOx. The median age of the patients was 51.5 years (range, 23.0–77.0 years), and the median ECOG performance status was 1 (0–1). Among all 66 patients, one complete response and 37 partial responses were observed (overall response rate, 57.6%; 95% confidence interval (CI), 46.7–67.9%). Stable disease was observed in 22 patients (33.3%), revealing a 90.9% disease control rate. The median progression free survival and overall survival were 6.5 months (95% CI, 5.6–7.4 months) and 10.5 months (95% CI, 8.1–12.9 months), respectively. Thirty-four patients (51.5%) experienced a treatment-related toxicity of grade 3 or more during the study. The most common toxicities of grade 3 or more were neutropenia (15.1% of all patients), anemia (10.6%), thrombocytopenia (10.6%), anorexia (7.6%), nausea (3.0%), and vomiting (3.0%). There were no treatment-related deaths. **Conclusions:** The combination of pazopanib and CapeOx showed moderate activity and an acceptible toxicity profile as a first-line treatment in metastatic and/or recurrent AGC patients (ClinicalTrials.gov NCT01130805). Clinical trial information: NCT01130805.

4050 Poster Session (Board #160), Mon, 8:00 AM-11:30 AM

Quantitative measurement of HER2 levels by multiplexed mass spectrometry to predict survival in gastric cancer patients treated with trastuzumab. *First Author: Chan-Young Ock, Seoul National University Hospital, Seoul, South Korea*

Background: Trastuzumab-based chemotherapy is standard treatment for HER2-positive advanced gastric cancer (AGC). Although increased *HER2* gene amplification by fluorescent *in situ* hybridization (FISH) has been correlated with sensitivity to trastuzumab, the predictive value of HER2 protein expression levels for trastuzumab sensitivity has not been reported. In this work, we quantitate levels of HER2 using a mass spectrometry-based assay and identify a cutoff for HER2 protein levels that is predictive of enhanced response to trastuzumab. **Methods:** A multiplexed, selected reaction monitoring (SRM) mass spectrometry assay was used to determine the absolute level of the HER2 protein in patient tumors. HER2 immunohistochemistry (IHC) status, *HER2/CEP17* ratio, *HER2* gene copy number, and HER2 protein levels were compared in 249 AGC tumors, 95 of which were treated with trastuzumab. Overall survival (OS) in the trastuzumab cohort was correlated with HER2 protein levels and a predictive cutoff was determined by the lowest *p* value of log rank test. **Results:** While HER2 protein quantitation by mass spectrometry positively correlated with both FISH and IHC, a wide range of HER2 protein levels was observed in tumors classified as HER2-positive by conventional methods. Ninety five trastuzumab treated patients were stratified into two groups based on HER2 protein level: HER2 high expressers and HER2 moderate expressers. Patients classified as HER2 high expressers (n = 48), with HER2 levels above 2383 amol/ug, had twice the overall survival (OS) of patients (n = 47) classified as moderate expressers (OS: 35.0 vs. 17.5 months, HR 0.5, p= 0.007). **Conclusions:** We used a non-antibody based assay to quantify absolute levels of HER2 protein in samples from AGC patients. We found high variability in HER2 expression within a patient population that had been classified as 3+ by IHC. High levels of HER2 correlated with increased overall survival following trastuzumab. This study demonstrates the HER2 measurement by SRM could guide physicians in their patient's selection for trastuzumab-based chemotherapy.

4051 Poster Session (Board #161), Mon, 8:00 AM-11:30 AM

First-line capecitabine (X) monotherapy versus capecitabine plus oxaliplatin (XELOX) in elderly patients with advanced gastric cancer (AGC): results from the first interim analysis. *First Author: In Gyu Hwang, Division of Hematology/Oncology, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, South Korea*

Background: While doublet combination with fluoropyrimidines and platinum is currently considered standard first-line chemotherapy in AGC, there has been a price to pay in terms of toxicity. Since the main goal of AGC treatment remains palliation, this multi-center randomized phase III trial compared efficacy and safety of X monotherapy with those of XELOX combination in elderly patients with AGC. **Methods:** Patients with chemotherapy-naïve, measurable AGC, aged 70 years or older were randomized 1:1 to receive X (capecitabine 1,000 mg/m2 bid po on D1-D14) or XELOX (X plus oxaliplatin 110 mg/m2 iv on D1). Treatment was repeated every 21 days until disease progression, unacceptable toxicity, or withdrawal. Primary end point was overall survival (OS). The present report contains the results from the first interim analysis conducted at Dec 2014. **Results:** As of Oct 2014, 50 patients with a median age of 77 (range, 70 to 84) were enrolled (X, n = 26; XELOX, n = 24). The two treatment arms were well balanced with respect to baseline characteristics. No treatment-related serious adverse events or unexpected toxicities were observed. The most frequently observed toxicities were nausea and hand-foot syndrome, with fatigue and peripheral neuropathy more common in XELOX than in X patients. Median PFS was significantly longer in XELOX arm than in X arm (7 v 3 months, respectively; HR 0.33, 95% CI 0.17-0.64). OS was also longer with XELOX (14 v 6 months; HR 0.60; 95% CI 0.29-1.23). **Conclusions:** XELOX combination chemotherapy results in improved efficacy but does not increase toxicities compared with X monotherapy in elderly patients with AGC. Although HR for OS did not achieve predefined margin, an independent data monitoring committee recommended early stopping of the trial based on the evidence of superiority with XELOX. Clinical trial information: NCT01470742.

4052 Poster Session (Board #162), Mon, 8:00 AM-11:30 AM

Comparison of open esophagectomy with minimally invasive esophagectomy: An observational nationwide study in Japan. *First Author: HIROYA TAKEUCHI, Department of Surgery, Keio University School of Medicine, Tokyo, Japan*

Background: To date, there has been a very limited number of prospective multicenter trials to verify the benefits of minimally invasive esophagectomy (MIE) such as thoracoscopic esophagectomy for esophageal cancer. In this study, we focused on the comparison of MIE and open esophagectomy (OE) using a Japanese nationwide database. **Methods:** Patient registration for the National Clinical Database (NCD) commenced in January 2011. It is a nationwide project that is linked to the surgical board certification system in Japan. Propensity score matching was performed to compare the MIE with the OE by use of the 2011-2012 NCD database. **Results:** Esophagectomy for 9584 patients with thoracic esophageal cancer were categorized into MIE (n = 3589) with OE (n = 5995) in the NCD 2011-2012 database. Propensity score matching created a matched cohort of 3515 pairs of patients with MIE and with OE. The operative time was significantly longer in the MIE group than in the OE group ($P < 0.001$), whereas blood loss was markedly lesser in the MIE group than in the OE group ($P < 0.001$). There was no significant differences in overall morbidity between the MIE (42.0%) and OE groups (43.1%). In particular, the incidence of the patients who needed prolonged respiratory ventilation more than 48 hours after surgery was significantly less in the MIE group than the OE group ((8.9% vs 10.9%, $P = 0.006$). Moreover, the incidence of superficial surgical site infection was significantly less in the MIE group compared with the OE group (6.7% vs 8.1%, $P = 0.037$). However, the reoperation rate within 30 days was significantly higher in the MIE group than in the OE group (7.0% vs 5.3%, $P = 0.004$). There were no significant differences in 30-day or operative mortality rates between the MIE and OE groups (30-day mortality: MIE 0.9% vs OE 1.1%, operative mortality: MIE 2.5% vs OE 2.8%). **Conclusions:** Our results suggest that MIE is comparable with conventional OE in terms of short-term outcome after surgery and is regarded as a desirable surgical option for patients with esophageal cancer although MIE was associated with higher reoperation rates and there were no marked benefits in operative mortality.

4053 Poster Session (Board #163), Mon, 8:00 AM-11:30 AM

Phase II study of FOLFOX plus regorafenib (REGO) in patients with unresectable or metastatic esophagogastric (EG) cancer. *First Author: Yelena Yuriy Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: REGO is a VEGFR2, FGFR2 and PDGFR small-molecule inhibitor with survival benefit in metastatic colorectal cancer. We performed a phase II trial of first-line FOLFOX+REGO in metastatic EG cancer. **Methods:** Patients (pts) with previously untreated metastatic EG adenocarcinoma with measurable or evaluable disease received mFOLFOX6 q14d and oral REGO 160 mg daily on days 4 to10 and 18 to 24 q28d. The primary objective was to improve historical 6-month progression-free survival (PFS) from 40% to 61% with REGO. With target accrual of 36 pts and 5% type I error rate, FOLFOX+REGO would be considered promising if $\geq$ 20 pts are progression free at 6 months. Tumor biomarker analysis was performed on samples using an on-site next generation sequencing (NGS) assay. Secondary endpoints included safety, partial response (PR) rate, disease control rate (DCR, PR+stable disease), exploratory biomarker analysis and overall survival. **Results:** Between 8/2013 -11/2014, 36 pts (10 esophageal/16 gastric/10GEJ) were accrued to this single-center study. Median age 59 and KPS 80%. Common adverse events included: Gr 2/3 hypertension (52%), Gr 2 neuropathy (39%), Gr 3/4 neutropenia (36%), Gr 2 fatigue (28%), Gr 2/3 diarrhea (17%), Gr 2 hand-foot syndrome (14%). 11 pts (31%) had one REGO dose reduction to 120mg; 5 pts (14%) were further reduced to REGO 80mg. In 27 pts with RECIST 1.1 measurable disease, the PR rate 56% (95% CI: 38%-73%). Overall DCR rate in pts with RECIST measureable and evaluable disease was 81% (95% CI: 67%-94%). 17 of 36 pts are progression-free at 6 mos, with 3 pts still on study for $<$ 6mos. NGS of 15 tumors completed to date. 94% of tumors harbored at least one genomic alteration, TP53 mutations (73%); amplifications in KRAS (13%), EGFR (13%), CDK12 (12%), MET (7%) and FGFR2 (7%). **Conclusions:** mFOLFOX in combination with one-week on/one-week off REGO dosing is well tolerated. NGS is ongoing on additional samples. Updated survival, response and correlative molecular analysis data will be presented. Clinical trial information: NCT01913639.

4054 Poster Session (Board #164), Mon, 8:00 AM-11:30 AM

Changing chemotherapy (C) with concurrent radiation (RT) followed by surgery after sub-optimal FDG-PET response to induction chemotherapy improves outcomes in locally advanced (LA) esophageal adenocarcinoma (EA). *First Author: Anuja Kriplani, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pre-operative CRT is a standard-of-care for LA EA. We showed that PET scan after induction C prior to CRT and surgery predicts outcomes (Cancer 118:2820; 2012). PET responders (PET+, defined as $>$ 35% decrease in mSUV of tumor) had superior pathologic complete response (pCR) rates and progression-free survival (PFS) vs. PET non-responders (PET-, $<$ 35% decrease). Some Pts with progression (PD) on PET after induction C had long-term overall survival (OS) when changed to alternative C during RT. **Methods:** We retrospectively reviewed all Pts with LA EA who received induction C and chemoRT prior to planned surgery. All Pts had PET scan before and after induction C. **Results:** 201 Pts were treated between 2002 to 2013, median age 62, 76% with uN+ disease. Induction C regimens included cisplatin/irinotecan ($\pm$ bevacizumab on study) in 63% and carboplatin/paclitaxel in 29%. 113 Pts (56%) were PET+ and 88 (44%) were PET-. All PET+ received same C during RT. Of PET-, 49 (56%) continued with same C during RT (PET-/no change) and 39 (44%) received different C with RT (PET-/change). 49 Pts (24%) did not undergo surgery because of PD (16%), medical inoperability (6%), or refusal given clinical CR (2%). Of 152 operated Pts, 13/86 PET+ (15%) achieved a pCR vs. 1/35 (3%) of PET-/no change ($p = 0.046$) vs. 3/31 (10%) of PET-/change ($p = 0.26$ for PET-/no change vs. PET-/change). Median PFS (23.4 vs. 10.1 mos, $p = 0.003$) and OS (38.7 vs. 25.3 mos, $p = 0.017$) for all Pts were significantly better for PET+ vs. PET-/no change. Median PFS for PET-/change was not reached and was superior to PET-/no change ($p = 0.02$) and not different from PET+ ($p = 0.73$). The 3-yr OS rates were 48% for PET-/change vs. 31% for PET-/no change ($p = 0.18$). Median OS for PET-/change was not different than for PET-/no change (25.8 vs. 25.3 mos, $p = 0.22$). **Conclusions:** PET scan after induction C predicts for outcomes in LA EA Pts who undergo CRT and surgery. Median PFS is improved, and trends toward improved pCR rate and OS appear possible in PET- who change C during RT. The ongoing CALGB 80803 study (NCT01333033) is evaluating this strategy.

4055 Poster Session (Board #165), Mon, 8:00 AM-11:30 AM

Clinical outcomes following neoadjuvant nab-paclitaxel and cisplatin chemotherapy for locally advanced esophageal squamous cell carcinoma. *First Author: Fan Yun, Zhejiang Provincial Cancer Hospital, Hangzhou, Zhejiang, China*

Background: The combination of nab-paclitaxel and cisplatin as preoperative treatment for esophageal squamous cell carcinoma (ESCC) has not been investigated. We carried out a phase II feasibility and efficiency study of preoperative chemotherapy with nab-paclitaxel and cisplatin for locally advanced ESCC. **Methods:** Between January 2011 and October 2012, 35 patients, from stage IIA to IIIC, performance status 0-1, with 31 male and 4 females, were included in the study. All pts received nab-paclitaxel (100 mg/m^2, d1, d8, d22 and d29) and cisplatin (75 mg/m^2, d1 and d22) as neoadjuvant chemotherapy, followed by esophagectomy. Two cycles of adjuvant chemotherapy with same regimen was given in 4-6 weeks after the resection. **Results:** Thity-five enrolled patients including 31 males and 4 females, the clinical stage forIIA,IIB, IIIA, IIIB, IIIC were 3(8.6%), 5(14.3%), 10 (28.6%), 8 (22.9%) and 9 (25.7%) patients respectively. After two cycles of neochemotheray. 30/35 patients went to surgery (85.7%) and all had R0 resection (100%). Pathological complete response (pCR) was achieved in 4 patients (13.3%). Down-staging was observed in 19 of 30 patients (63.3%). 24/30 (80.0%) patients received adjuvant chemotherapy, including 7 patients (23.3%) received adjuvant chemoradiotherapy. Only 1 (3.3%) patient appeared surgical complication with anastomotic leaks. With median follow up of 27.1 months, the 16/30 patients (50.44%) still alive, and a median disease-free survival (DFS) of 22.5 months (95 % CI 14.2 - 29.8). The Median overall survival (OS) and DFS of Down-staging patients were significantly longer than non-down-staging patients (Hazard Ratio 0.30, 95% CI: 0.074 - 0.75 and Hazard Ratio 0.27, 95% CI: 0.071-0.59, respectively) ($P = 0.0158$ and $P = 0.0037$, respectively), and all of pCR patients were still DFS survival at the latest follow up. **Conclusions:** weekly nab-paclitaxel and cisplatin is effective as a neoadjuvant chemotherapy for local advanced ESCC, and its adverse effects are tolerable. Down-staging, especially the pCR patients have favorable outcome than non-down-staging patients. Clinical trial information: NCT01258192.

4056 Poster Session (Board #166), Mon, 8:00 AM-11:30 AM

Comprehensive characterization of PDL-1 and CTLA-4 in gastric cancer. *First Author: Hans Anton Schloesser, Department of General, Visceral and Cancer Surgery, University of Cologne, Cologne, Germany*

Background: Recently remarkable efficacy of immune checkpoint inhibition has been reported for several kinds of solid cancers. This study is the first comprehensive analysis of cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death 1 ligand 1 (PD-L1) in gastric cancer and the first study integrating oncogenomic analyses. **Methods:** PD-L1 and CTLA-4 were stained on paraffin embedded tumor sections of 127 patients with gastric cancer by immunohistochemistry. Genetic driver mutations were identified by next-generation Sequencing and FISH analysis. Expression of PD-1, PD-L1 and CTLA-4 on lymphocytes in tumor sections, lymph nodes and peripheral blood were studied by 10-colour flow cytometry and 4-colour immune-fluorescence microscopy in an additional cohort. **Results:** PD-L1 and CTLA-4 were expressed on primary tumor cells by 44.9%(57/127) and 86.6%(110/127) of the analyzed gastric cancer samples, respectively. Correlation to clinical and pathological parameters revealed no correlation for PD-L1, whereas CTLA-4-negativity was correlated to higher grading and diffuse type according to Lauren. Positivity of PD-L1 or CTLA-4 on tumor cells was associated with inferior overall survival. Expression of PD-1 (52.2%), PD-L1 (42.2%) and CTLA-4 (1.6%) on tumor-infiltrating T cells was significantly elevated compared to peripheral blood lymphocytes. We could identify distinct genotypic profiles comparing the subgroups of checkpoint molecule expression. **Conclusions:** Our analysis revealed a great impact of PD-1/PD-L1 and CTLA-4 on the biology of gastric cancer. Hence corresponding checkpoint-inhibitors should be evaluated in this disease and approaches combining molecular targeted therapy and checkpoint inhibition could be of additional benefit. An extensive immune monitoring should be included in these studies.

4057 Poster Session (Board #167), Mon, 8:00 AM-11:30 AM

Phase II study of everolimus as a salvage treatment after failure of fluoropyrimidine and platinum in patients with metastatic gastric cancer positive for $pS6^{Ser240/4}$ expression. *First Author: Ji Hyun Park, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Everolimus is a macrolide derivative of rapamycin which inhibits mTOR. Our previous phase II study in 2nd line setting showed that everolimus had no significant activity with 1.7 months of median progression-free survival (PFS) in unselected population with gastric cancer (GC) and suggested that $pS6^{Ser\ 240/4}$ might be a potential predictive biomarker of everolimus (Yoon et al, Br J Cancer. 2012;106:1039). In this study, we aimed to evaluate the efficacy and safety of everolimus in 2nd line GC patients selected by $pS6^{Ser240/4}$ expression. **Methods:** The primary endpoint was 4-month PFS rate. Patients with metastatic or recurrent GC positive for $pS6^{Ser240/4}$ were enrolled after failure of fluoropyrimidine and platinum. $pS6^{Ser240/4}$positivity was defined as immunostain of 10% or more cancer cells with moderate or strong intensity. Patients received everolimus 10 mg p.o. once daily until disease progression or unacceptable toxicity. **Results:** Between December 2011 and May 2013, a total of 45 patients were enrolled. Median age was 58 years (range 34-78). Thirty-nine (86.7%) patients had ECOG performance status 0-1, and 6 (13.3%) had 2. In addition to fluoropyrimidine and platinum, 14 (31.1%) and 5 (11.1%) patients received docetaxel and irinotecan, respectively. One (2.2%) patient achieved a partial response and 26 (57.8%) showed stable disease. With a median follow-up of 13.3 months (range, 9.9-24.1) in surviving patients, the median PFS was 2.6 months (95% CI, 1.9-3.2), and 4-month PFS was 25.6%. The median overall survival was 5.8 months (95% CI, 5.1-6.6). Grade 3 or 4 drug-related toxicities in $>$ 5% of patients included neutropenia (13.3%), anemia (13.3%), stomatitis (8.9%), and pneumonia (6.7%). **Conclusions:** Everolimus was safe, and it showed better activity in the current study which included biomarker-selected patients, compared with our previous study in biomarker-unselected population. Currently, further biomarker analysis is ongoing. Clinical trial information: NCT01482299.

4058 Poster Session (Board #168), Mon, 8:00 AM-11:30 AM

The prognostic impact of extracapsular lymph node involvement after neoadjuvant therapy and esophagectomy . *First Author: Sjoerd M Lagarde, Academic Medical Center, Amsterdam, Netherlands*

Background: In patients with esophageal cancer, little attention has been paid to the biological significance of extracapsular lymph node involvement (LNI) in patients who underwent neoadjuvant treatment followed by esophagectomy. Therefore, the aim of the present study was to assess the incidence, extent of extracapsular LNI and prognostic significance in a consecutive multicenter series of patients with cancer of the esophagus or gastroesophageal junction who underwent neoadjuvant chemo (radio) therapy followed by surgery. **Methods:** From a prospectively collected database, a consecutive series of patients in two high volume centers in Europe was analyzed. All patients with potentially curable adeno- or squamous cell carcinoma of the oesophagus or gastroesophageal junction were treated with neoadjuvant chemotherapy or chemoradiation therapy followed by transthoracic esophagectomy and two-field lymphadenectomy. **Results:** Between January 2000 and September 2013 a consecutive series of 707 patients underwent an esophagectomy after neoadjuvant therapy. A mean number of 29 (5-77) nodes were resected and identified. 347 (49%) patients had no evidence of lymph node metastases (N0). There were 360 (51%) with positive nodes. Extracapsular LNI was identified in 197 (27%) patients. Five-year overall survival rates were 63% for N0 patients, 45% for patients with intracapsular LNI and 14% for patients with extracapsular LNI ($p < 0.001$). On multivariate analyses ypT, ypN and the presence of extracapsular LNI were independent factors. **Conclusions:** The presence of extracapsular LNI after neoadjuvant chemo(radiation) therapy identifies a subgroup of patients with a significantly worse long-term survival. Extracapsular LNI reflects a particularly aggressive biologic behavior and has significant prognostic potential and should be considered for the future edition of the TNM staging system for esophageal cancer.

4059 Poster Session (Board #169), Mon, 8:00 AM-11:30 AM

Comparison of *HER2* gene amplification (AMP) in primary esophageal and gastroesophageal junction adenocarcinomas (EAC) and their metastatic regional lymph nodes (MLNs). *First Author: Harry H. Yoon, Mayo Clinic, Rochester, MN, Rochester, MN*

Background: The status of *HER2* AMP in primary EACs compared to their MLNs is unknown. This is clinically important since selection of patients for HER2-targeted therapy is usually based on HER2 analysis in primary tumors. Here, we report the largest HER2 evaluation of MLNs in EACs to date. **Methods:** Resected primary tumors and MLNs (209 patients) were tested for *HER2* AMP (fluorescence in situ hybridization) and protein expression (immunohistochemistry; IHC 0, 1+, 2+, 3+). Primaries were designated AMP-positive (pos) or -negative (neg) using standard criteria (*HER2/CEP17* $\geq$ 2 in $>$ 5% tumor cells). *HER2*AMP status in primaries and MLNs were compared (Wilcoxon, Fisher's). **Results:** HER2 by AMP *vs* IHC within individual MLNs (726 MLNs; median 3 MLNs per patient) were 92% concordant ($P < .0001$). *HER2* AMP status was concordant in primaries *vs* MLNs in 89% (186/209) of patients (Table). Yet among AMP-neg primaries, 7% (10/146) had at least 1 AMP-pos MLN. Importantly, among AMP-neg primaries (n = 146), those with a small AMP subpopulation (*ie,* $<$ 1% tumor cells) were more likely than uniformly AMP-neg primaries to have an AMP-pos MLN (33% *vs* 4%; $P = .001$). Among AMP-pos primaries, those with non-uniform AMP (*ie,* 6% - 49% tumor cells) were more likely than uniform AMP primaries (*ie,* $\geq$ 50% tumor cells) to have entirely AMP-neg MLNs. Across the whole cohort, among patients with at least 1 AMP-pos MLN, an average of 95% of MLNs (standard deviation 17%) was AMP-pos. **Conclusions:** *HER2* status was generally concordant between primary EACs and MLNs. But the strength of concordance diminished significantly among primaries with a small *HER2*-amplified subpopulation, where a considerably higher rate of *HER2*-amplified nodal metastases was observed compared to uniformly non-amplified primaries. These novel data suggest that testing MLNs in this subgroup may identify new candidates for HER2-targeted therapy.

	MLNs		
Primary tumor	**All MLNs are AMP-neg**	**Any MLN is AMP-pos**	***P***
AMP-neg *n = 146*			
Uniform neg *n = 131*	96% (126)	4% (5)	0.001
Small AMP subpopulation *n = 15*	67% (10)	33% (5)	
AMP-pos *n = 63*			
Uniform pos *n = 54*	17% (9)	83% (45)	0.078
Non-uniform pos *n = 9*	44% (4)	56% (5)	

4060 Poster Session (Board #170), Mon, 8:00 AM-11:30 AM

A serum microRNA biomarker panel for detection of gastric cancer. *First Author: Jimmy So, Department of Surgery, National University Hospital, Singapore, Singapore*

Background: Gastric cancer is the 2nd most common cause of cancer deaths worldwide. Currently, endoscopy is the only reliable method for early diagnosis. However, the invasiveness and cost limit its usage as a screening test. MicroRNAs (miRNAs) have been shown to be important in the pathogenesis of cancers. They are exceptionally stable in body fluids, making them potential noninvasive biomarker for cancers. **Methods:** We screened 600 miRNAs using our MiRXES qPCR technology in the sera of 236 gastric cancer subjects and 236 matched high risk subjects, serving as the discovery set. 191 miRNAs were reliably detected in all the serum samples, out of which 75 informative ones were identified to be significantly (false discovered corrected P value lower than 0.01) altered between gastric cancer and high risk subjects. Multivariate miRNA biomarker panels were then formulated by sequence forward floating search and support vector machine using all the quantitative data obtained for the expression of 191 miRNAs. **Results:** Multiple iterations of two-fold cross-validation were performed in silico where the panels with 8 or more miRNAs consistently achieved high accuracy [areas under the curve (AUC) $\geq$ 0.87 in the receiver operating characteristic (ROC) curve]. A 24-miRNA model was optimized based on the discovery set [AUC = 0.92 (95% Confidence Interval [CI]: 0.88-0.95)] and validated in two blinded studies with fixed algorithm and threshold definition; Korean case-control cohort (n = 129, 74 cancer cases) and Singaporean Chinese case-control cohort (n = 89, 20 cancer cases). The 24-miR panel showed 90% sensitivity and 81% specificity in the Korean cohort (AUC = 0.91 (95% CI: 0.86-0.96)] and had 90% sensitivity and 75% specificity in the Singaporean Chinese cohort [AUC = 0.89 (95% CI: 0.79-0.99)]. Importantly, the 24-miR panel was able to distinguish stage 1 and 2 gastric cancer in both Korean [AUC = 0.88 (95% CI: 0.81-0.96)] and Singaporean Chinese [AUC = 0.91 (95% CI: 0.80-1.00)] cohorts. **Conclusions:** We have identified a serum miRNA panel which can confidently differentiate patients with gastric cancer including the early-staged cancers from controls. This may be able to serve as a non-invasive screening test for gastric cancer which warrants study in larger cohorts.

4061 Poster Session (Board #171), Mon, 8:00 AM-11:30 AM

NeoFLOT II: Multicenter phase II study with short time neoadjuvant chemotherapy (stNACT) with 5-FU, FA, oxaliplatin, and docetaxel in rectable adenocarcinoma of the gastresophageal junction and gastric adenocarcinoma (T3, T4, and/or LN+) with high R0 resection rate over 91.5%. *First Author: Karsten Ridwelski, Klinikum Magdeburg gGmbH, Magdeburg, Germany*

Background: Perioperative chemotherapy is standard of care in locally advanced gastroesophageal cancer (GEC included adenocarcinoma of gastroesophageal junction -GEJ- and gastric adenocarcinoma) in europe. the NeoFLOT II study had examined a short time neoadjuvant chemotherapy (stNACT) with only 4 cycles FLOT. Patients(pts.)3,T4 and/or nodepositive adenocarcinoma (GEC)were eligible for this multicenter phase II study. **Methods:** For stNACT, 5-FU 2600mg/sqm/24h on day (D) 1, FA 200mg/sqm/30min on D 1, oxaliplatin 85mg/sqm/1h on D 1 and docetaxel 50mg/sqm/2h on D 1 were admistrated every 2 weeks for two cycles. Application of adjuvant chemotherapy was not part of the protocol. Primary endpoint was the R0-resection rate. Secondary endpoints were toxicity, remission rate and rate of surgical complications. **Results:** A total of 49 pts. with a median age of 64years were enrolled in 5 centers. 46 pts. completed stNACT, 1 patient had only 1 cycle and 2 pts.had 3 cycles. 47 patients underwent surgery. R0-resection rate was 91,5% (43/47). We saw no pathological complete response (pCR) and 19 partial responses (pPR 45,2%). 3/49 pts. developed progressive disease (6,1%). Grade 3-4 toxicities included neutropenia (42,9%), febrile neutropenia 8,2% and diarrhea 22,4%. 2 pats. died after resection (4,3%). **Conclusions:** StNACT with 4 cycles of FLOT is effective and tolerable in resectable GEC. R0-resection rate was very high. Clinical trial information: EudraCT-Nr. 2009-01260820 Neoflot.

4062 Poster Session (Board #172), Mon, 8:00 AM-11:30 AM

Prognostic value of tumor infiltrating lymphocytes in Epstein-Barr virus-associated gastric cancer. *First Author: Shinkyo Yoon, Department of Oncology/Hematology, Kyungpook National University School of Medicine, Daegu, South Korea*

Background: It is well known that lymphocytic infiltration around tumor can be considered as a host immune reaction against tumor cells, although prognostic implication of lymphocyte infiltration in gastric cancer are not certain. Therefore, we investigated prognostic impact of tumor-infiltrating lymphocytes (TILs) in Epstein-Barr virus (EBV)-associated gastric cancer (EBVaGC), which can be sub-classified into 3 histological subtypes according to the host immune response: lymphoepithelioma-like carcinoma (LELC), carcinoma with Crohn's disease-like lymphoid reaction (CLR), and conventional-type adenocarcinoma (CA). **Methods:** In situ hybridization for EBV positivity was performed in 1318 cases that underwent surgery or endoscopic submucosal dissection at Kyungpook National University Hospital between January 2011 and November 2014. Histopathologic analysis of percentage of TILs was performed on hematoxylin and eosin–stained sections. TILs were defined as the percentage of tumor stroma containing infiltrating lymphocytes. A tissue with TILs over 20% was considered TILs-positive. EBVaGCs were also sub-classified into 3 histological subtypes: LELC, CLR, and CA . **Results:** EBVaGC was identified in 111 cases (8.4%) from a total of 1318 gastric cancer. The median age was 62 years (32-80), and 86 patients (77.5%) were male. The pathologic stages after resection were as follows: stage I (n = 69), stage II (n = 24), stage III (n = 16), and stage IV (n = 2). TILs-positive patients were 65 patients (58.6%). The number of histologic subtypes of EBVaGC was as follows: LELC (n = 35), CLR (n = 50), and CA (n = 26). In the univariate analysis, TILs score and EBVaGC sub-classification was significantly associated with disease-free survival (DFS), respectively (p = 0.016, p = 0.001). The LELC and CLR groups with TILs-positive showed an improved DFS compared to the CA group with TILs-negative (p = 0.002). This difference was also significant in the multivariate analysis (p = 0.018). **Conclusions:** TILs and sub-classification of EBVaGC may constitute prognostic factor in EBVaGC. As a result, this finding suggests that the host cellular immune response could be useful as a prognostic marker for EBVaGC.

4063 Poster Session (Board #173), Mon, 8:00 AM-11:30 AM

Knocking on molecular alterations in advanced gastric cancer (AGC). *First Author: Fabricio Racca, Vall d´Hebron University Hospital, Barcelona, Spain*

Background: AGC represents the third leading cause of cancer related deaths. Chemotherapy for AGC is active but still of limited efficacy and targeted agents Trastuzumab and Ramucirumab have shown modest activity. Expanded molecular profile may provide critical information on druggable molecular aberrations and treatment options for these patients (pts). **Methods:** From 11/2010 to 11/2014, 101 pts with AGC underwent genetic/proteomic tumor profiling as part of the VHIO Phase I Trial Molecular Prescreening Program. Detection of mutations (mt) was performed with Multiplex-Single base extension followed by Mass-spect detection (Sequenom) or NGS (Amplicon-seq) (Illumina). Immunohistochemistry was used to assess HER2, PTEN and PDL1 expression. Amplification of *HER2, PIK3CA, FGFR1, FGFR2*, and *MET*were analyzed by in situ hybridization. **Results:** Median age of pts was 59-year, 66% men. Median prior treatment lines were 3 (1-6). Median overall survival was 18 months. As expected, HER2 was deregulated in 20%. *PIK3CA* mt and PTEN low expression were respectively found in 9% and 30%, with one pt harboring both molecular alterations. *KRAS* mt were found in 5%. *PIK3CA, KRAS, FGFR4* and *MSH6* mt coexisted in one pt. Amplification in *FGFR2* (5%), *MET* (2%), and *PIK3CA* (1%) were also detected. One pt harbored amplification in 10 genes implicated in receptor tyrosine kinase- and cell cycle- pathways. PDL1 was positive in 6%; *PIK3CA* mt and PDL1 overexpression coexisted in 3%, *ARID1A* and *SMAD4* also coexisted in another pt. Twenty-seven pts (27%) were treated with targeted therapies according to their molecular profile, with modest efficacy. **Conclusions:** Our molecular data is consistent with TCGA data. Pts. with AGC considered for genetic/proteomic tumor profile seem to derive benefit from this expanded characterization and treatment in phase I/II clinical trials with targeted agents.

Molecular aberration	Treatment	Outcome
HER2 deregulated	Chemotherapy + HER2/ HER3 inhibitors (inhib)	4 SD (stable disease $\geq$ 6 months) + 1 PD (progressive disease)
	HER2/HER3 inhib	2 SD + 3 PD
***PI3KCA* mt**	Chemotherapy + PI3KCA inhib	2 SD + 2 PD
	PI3KCA inhib	2 SD + 3 PD
PDL1 positive	PDL1 inhib	1 SD + 3 PD
MET deregulated	Chemotherapy + MET inhib	1 SD
	MET inhib	3 PD
	HGF inhib	1 PD
***FGFR4* amplified**	FGFR4 inhib	2 PD

4064 Poster Session (Board #174), Mon, 8:00 AM-11:30 AM

Accuracy of EUS-FNA for distant regional lymph nodes in the initial staging of esophageal cancer (EC). *First Author: Yusuke Shimodaira, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Accurate clinical staging is essential for making immediate treatment decisions. The role of endoscopic ultrasound (EUS) and fine needle aspiration (FNA) in altering treatment has been debated in patients diagnosed with cStage II or III EC. The purpose of this study was to assess the yield of EUS-FNA for paratracheal and subcarinal lymph nodes in distal ECs. **Methods:** We analyzed278 EC patients who had baseline EUS-FNA between 2010 and 2014. A subgroup of 85 patients with Seiwert's type I or II EC had FNAs of the paratracheal or subcarinal nodes (far away from the primary EC) were carefully reviewed. The accuracy of EUS, PET, EUS+PET, and FNA were compared using FNA as the gold standard. A McNemar's test was used to determine whether EUS+PET or FNA performed differently in identifying positive nodes. **Results:** In the subgroup of 85 patients, FNA was positive for malignancy in 27 (32%) leading to modifications of the radiation field in upper thorax. Moreover, EUS, PET, and EUS+PET had an accuracy of 83.0% (EUS), 87.1% (PET), and 93.0% (EUS+PET), respectively. Comparing FNA to EUS+PET, FNA was positive whenever EUS or PET was positive. In 6 patients, PET-negative nodes were malignant by EUS-FNA ($p = 0.03$). Of 58 cases with negative initial FNA, only one was malignant, on follow-up, when surgically removed. **Conclusions:** Our data show that in distal ECs with suspicious paratracheal or subcarinal lymph node(s), EUS-FNA is a highly effective tool to help with appropriate treatment decisions. An extremely low false negative rate (1/58) suggests that EUS/FNA is highly complimentary to PET and can also identify malignant nodes that are not FDG-avid. From U. T. M. D. Anderson Cancer Center (UTMDACC), Houston, Texas, USA. (Supported in part by UTMDACC, and CA 138671 and CA172741 from the NCI).

4065 Poster Session (Board #175), Mon, 8:00 AM-11:30 AM

A phase II study of the c-Met inhibitor tivantinib (tiv) in combination with FOLFOX for the treatment of patients (pts) with previously untreated metastatic adenocarcinoma of the distal esophagus, gastroesophageal (GE) junction, or stomach. *First Author: Shubham Pant, Stephenson Cancer Center/SCRI, Oklahoma City, OK*

Background: C-Met protein is a receptor tyrosine kinase that is amplified in gastric and esophageal cancers causing downstream activation of multiple signaling pathways. Tivantinib is an orally bioavailable c-met inhibitor. This phase II study evaluated the response rate (RR) of the combination of tiv plus FOLFOX as treatment for pts with previously untreated metastatic adenocarcinoma of the distal esophagus, gastroesophageal (GE) junction, or stomach. **Methods:** Pts with advanced GE cancer received standard mFOLFOX6 day 1 and tiv (360mg PO BID) days 1-14 of each 2-week cycle. Restaging occurred every 4 cycles. The primary endpoint was RR. Secondary endpoints included progression-free survival (PFS), time to progression (TTP), overall survival (OS), and safety. **Results:** Thirty-four pts were enrolled: median age 65 yrs (range, 34-88), 76% male, 53% KPS 90. Forty-seven percent of pts underwent prior surgery, 32% received prior radiation, and 15% received prior systemic treatment. Two pts did not receive treatment due to patient request and anemia prior to cycle 1 day 1. 32 pts were treated for a median of 8 cycles (range, 1-38). Treatment-related toxicities (% G1/2; % G3/4) included neutropenia (9%; 53%), fatigue (47%; 9%), diarrhea (41%; 9%), nausea (44%; 0), and peripheral neuropathy (44%; 0). Of the 26 pts evaluable for response, 10 pts (38%) achieved objective response (1 CR, 9 PRs), with a best response of stable disease noted in 13 pts (50%). The overall RR was 29%. Median PFS was 6.1 months (95% CI: 3.6-8) with a median TTP of 6.1 months (95% CI: 5.2-11.5). Median OS was 9.6 months (95% CI: 7.2-NA). Three pts remain on study and have been on treatment for a median of 16 months (range, 14-19). Their best response was PR (2) and SD (1). One of these pts was met high by IHC. Met status by FISH is unknown at this time. **Conclusions:** The combination treatment of tiv plus mFOLFOX6 in pts with advanced GE cancer showed a RR and PFS in the range of historical controls for first-line FOLFOX therapy. However, 3 pts had extended time on study treatment, and these pts may represent pts with met-driven tumors. Clinical trial information: NCT01611857.

4066 Poster Session (Board #176), Mon, 8:00 AM-11:30 AM

The prognostic value of a modified tumor regression grade after neoadjuvant chemoradiotherapy and resection of esophageal carcinoma. *First Author: Maarten CJ Anderegg, Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands*

Background: The tumor regression grade (TRG) is used to define the response to preoperative chemoradiotherapy for esophageal carcinoma. The aim of this study was to determine whether inclusion of the postoperative pathological nodal status could improve the prognostic value of TRG. **Methods:** All patients who underwent an esophagectomy after chemoradiotherapy between 2003 and 2013 were included in this retrospective study. Patients were classified according to a modified TRG consisting of the TRG by Mandard et al (TRG 1 = complete response in the esophagus; TRG > 1 = incomplete response) and the postoperative node category (N0 = no lymph node metastases; N+ = at least 1 lymph node metastasis). Based on the TRG by Mandard and this modified TRG Kaplan-Meier survival analyses were performed and compared. **Results:** 411 patients underwent neoadjuvant chemoradiotherapy followed by esophagectomy. After exclusion due to non-specific histology (n = 2), unknown TRG (n = 3), intraoperative detection of distant metastases (n = 3), salvage procedures (n = 17) and in-hospital mortality (n = 15) 371 patients were analysed (289 adenocarcinoma, 82 squamous cell carcinoma). A significantly improved median disease free survival was observed in patients with TRG 1 compared to patients with TRG > 1 (90.3 vs. 30.8 months, P = 0.004). After implementation of the modified TRG significant differences in median disease free survival were found between the four categories: TRG 1-N0 (n = 76) 90.3 months; TRG 1-N+ (n = 10) 20.8 months; TRG > 1-N0 (n = 146) 81.3 months; TRG > 1-N+ (n = 139) 18.1 months (P < 0.001). **Conclusions:** The TRG, determined in the primary tumor, provides insufficient information about the prognosis after chemoradiotherapy followed by resection of esophageal cancer. It is advisable to use a modified classification in which the postoperative pathological nodal status is considered.

4067 Poster Session (Board #177), Mon, 8:00 AM-11:30 AM

Signet ring cell (SRC) histology of localized gastric adenocarcinoma (LGAC) to predict response to preoperative chemoradiation. *First Author: Nikolaos Charalampakis, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients with LGAC, when treated with preoperative therapy, have heterogeneous and unpredictable outcomes. Currently, there are no clinical variables or biomarkers that can predict response to therapy. **Methods:** We analyzed 107 LGAC patients who were treated with chemoradiation followed by surgery. LGAC were grouped into categories based on: (1) presence of SRC (yes-SRC) or absence of SRC (no-SRC). LGACs with yes-SRC were further grouped by the % of SRC(s): 0%, 1-10%, 11-49%, and 50-100% and (2) histologic grade: moderately (G2) or poorly (G3) differentiated. These variables were correlated with pathologic complete response (pathCR) or < pathCR in the resected specimens. Descriptive statistics and survival analyses were utilized. **Results:** The patients were primarily males (60%), had clinical stage III LGAC (50%), and had received chemotherapy before chemoradiation (93%). Most had G3 tumors (78%) and yes-SRC (58%). Patients with yes-SRC had a lower rate of pathCR (11%) compared to no-SRC (36%, $p = 0.004$) and the association remained statistically significant even for a low percentage of SRC (1-10%) ($p = 0.014$). Higher the fraction of yes-SRC, the lower was pathCR ($p = 0.03$). The pathCR rate tended to be lower (18%) in G3 LGACs compared to G2 LGCAs (33%; $p = 0.125$). Patients with G3 tumors and yes-SRC had shorter overall survival (OS) ($p = 0.046$ and $p = 0.038$, respectively). Post-therapy pathologic stage was the only prognostic factor independently associated with OS and recurrence-free survival ($p < 0.001$). **Conclusions:** Our data suggest that yes-SRC LGACs are relatively chemoradiation resistant compared to no-SRC LGACs. A higher fraction of yes-SRC is associated with higher LGAC resistance. Validation and biomarker evaluation are warranted. From U. T. M. D. Anderson Cancer Center (UTMDACC), Houston, Texas, USA. (Supported in part by UTMDACC, and CA 138671 and CA172741 from the NCI). Dr. Nikolaos Charalampakis has been awarded a scholarship from the Hellenic Society of Medical Oncology.

4068 Poster Session (Board #178), Mon, 8:00 AM-11:30 AM

Association of high tumor infiltrating cytotoxic T cells with absence of lymph node involvement in resected colorectal and gastric cancer: Implications for immunosurveillance. *First Author: Tong Dai, Weill Cornell Medical College, New York, NY*

Background: Adaptive immune response can play an important role in restricting tumor growth, and the presence of tumor infiltrating lymphocytes (TIL) is associated with lower cancer stage and improved survival. However, the characterization of TILs with gastrointestinal malignancies, and their clinical implication, remains poorly understood. **Methods:** To characterize TIL subpopulations in different gastrointestinal cancer types, we performed immunohistochemistry (IHC) staining of CD3, CD8, CD45RO, and CD4/FOXP3 markers for all T cells, cytotoxic, memory, and regulatory T cells, respectively. Tissue microarray(TMA) from 122 colorectal, 37 gastric, and 59 esophageal cancer were included in the study, and IHC staining for each immune marker was scored as low ($<$ 5 cells/hpf), intermediate (5-50 cells/hpf), and high ($>$ 50 cells/hpf). **Results:** LN- colorectal and gastric cancer was associated with higher $CD3^+$ and $CD8^+$ cell infiltration, when compared with LN+ disease (Table 1). This was not observed in esophageal cancer. Increased memory T cell infiltration is also associated with LN- disease in gastric cancer. In addition, increased $FOXP3^+$ regulatory T cells are associated with LN- disease in colorectal cancer. **Conclusions:** Across a panel of gastrointestinal malignancies, we found that for both gastric and colorectal cancer, increased infiltration of cytotoxic T cells ($CD3^+/CD8^+$) was associated with LN- disease. These findings suggest high cytotoxic T cells may protect from LN metastasis in colorectal and gastric cancer. Regulatory $FOXP3^+$ regulatory T cells may have similar function in colorectal cancer. Understanding the spatial distribution of proteins that regulate the immune response in the tumor microenvironment will have implications for subsequent immunomodulatory treatments.

Percentage of tumor with high expression of CD3, CD8, and CD45RO.

Cancer Type	LN Status	$CD3^+$	$CD8^+$	$CD45RO^+$
Colorectal	LN+	22.6%	17.1%	52.6%
	LN-	37.7%	42.3%	44.0%
Gastric	LN+	37.0%	42.8%	43.5%
	LN-	70.0%	75.0%	80.0%
Esophageal	LN+	28.9%	36.4%	52.6%
	LN-	14.3%	41.2%	40.0%

4069 Poster Session (Board #179), Mon, 8:00 AM-11:30 AM

Phase Ib/II study of cancer stem cell (CSC) inhibitor BBI608 combined with paclitaxel in advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma. *First Author: Carlos Becerra, Texas Oncology-Baylor Sammons Cancer Center, Dallas, TX*

Background: BBI608, a first-in-class CSC inhibitor that works through inhibiting Stat3, has shown potent synergistic anti-tumor and anti-metastatic activity with paclitaxel in vivo. In a phase Ib dose escalation study in patients with advanced solid tumors, BBI608 + weekly paclitaxel was well tolerated and a RP2D of BBI608 500 mg BID was determined. **Methods:** Patients with advanced, pre-treated gastric and GEJ adenocarcinoma were enrolled in a phase Ib/II extension study to assess safety, tolerability, and preliminary anti-cancer activity in patients with advanced gastric/GEJ adenocarcinoma. Eligible patients received $\geq$ 1 line of prior treatment in the metastatic setting with a platinum + fluoropyrimidine/TS inhibitor. BBI608 was administered orally at 480 mg or 500 mg twice daily with paclitaxel 80 mg/m^2 IV weekly 3 of every 4 weeks. A sample size of 40 set the bounds of the 90% CI at $\pm$10% to 14%, assuming a DCR of 60% to 80%. **Results:** 46 patients (87% Caucasian, 7% Black, 6% Asian) were enrolled in US and Canada; 10 (22%) had 1 line of prior therapy, 16 (35%) had 2 prior lines, and 20 (43%) had 3 or more prior lines. Common adverse events (AE) were grade 1 to 2 diarrhea, abdominal cramps, nausea, and vomiting. Grade 3 AE included vomiting (10%), diarrhea of 5 days or longer (7%), fatigue (7%), and abdominal cramps, nausea, dehydration (2% each). In 20 patients who had not received a taxane in the metastatic setting, the per-protocol ORR was 31% (5/16) and DCR was 75% (12/16); median PFS was 20.6 wks and mOS was 39.3 wks. In 26 patients who failed a prior taxane (median 3 prior lines), per-protocol ORR was 11% (2/19), and DCR was 68% (13/19); mPFS was 12.6 wks and mOS was 33.1 wks. In a subset of evaluated patients who received only 1 prior line of therapy without a taxane, the ORR was 50% (3/6) and the DCR was 83% (4/6). **Conclusions:** In this first known clinical study of a CSC inhibitor in gastric/GEJ adenocarcinoma, BBI608 and weekly paclitaxel were combined safely at the full-intended doses. Encouraging signs of anti-cancer activity were observed. A phase 3 study of BBI608 in combination with weekly paclitaxel in patients with gastric/GEJ cancer who had failed first line therapy is underway. Clinical trial information: NCT01325441.

4071 Poster Session (Board #181), Mon, 8:00 AM-11:30 AM

Randomized phase II crossover trial exploring the clinical benefit from targeting EGFR or VEGF with combination chemotherapy in patients with non-resectable biliary tract cancer. *First Author: Lars Henrik Jensen, Vejle Hospital and University of Southern Denmark, Vejle, Denmark*

Background: Non-resectable biliary tract cancer (BTC) is chemosensitive but there are no clear signals of effect from inhibiting any specific molecular target. The most promising targets are EGFR and VEGF. This trial evaluated the effect of adding panitumumab or bevacizumab to chemotherapy in a crossover design. **Methods:** Eligible patients with biopsy proven non-resectable BTC, 18+ years (y), KRAS wild-type and performance status (PS) 0-2 were randomized 1:1. Patients in arm A received panitumumab 6 mg/kg + gemcitabine 1,000 mg/m^2 + oxaliplatin 60 mg/m^2 on day 1 and capecitabine 1,000 mg/m^2 b.i.d. on days 1-7 of a 2 weeks cycle. In arm B the chemotherapy was similar but added bevacizumab 10 mg/kg on day 1. At progression patients crossed over to bevacizumab in arm A and to panitumumab in arm B with the same chemotherapy backbone. The primary endpoint was the fraction of patients with PFS at six months (PFS6m). Secondary endpoints were PFS and overall response rate (ORR) both before/after crossover, overall survival (OS), toxicity, translational analysis and of second line treatment. Results: Three centres recruited 88 patients with a median age of 66 y (range 35-84). Selected base line characteristics were PS 0 (n = 23), 1 (n = 47), 2 (n = 18) and 73 metastatic/15 locally-advanced disease. Cases of grade $>$ 2 toxicity were equal with more skin toxicity in arm A and more hypertension and infection in arm B. PFS6m in arm A/panitumumab was 43% (95%CI 29-58) and in arm B/bevacizumab 55% (95%CI 40-70). ORR was 46% (95%CI 30-62) in arm A and 18% (95%CI 6-31) in arm B. Median PFS was 6.1 m (95%CI 5.8-8.1) vs 8.2 m (95%CI 5.3-10.6) and OS 9.5 m (95%CI 8.3-13.3) vs 12.3 m (95%CI 8.8-13.3) in arm A vs B. OS was 17.7, 9.5 and 5.6 m in PS 0, 1 and 2, respectively. As a phase II study, comparisons between treatment arms were exploratory and revealed no differences in PFS6m (p = 0.39), median PFS (p = 0.13) or OS (p = 0.47), but ORR was superior in arm A (p = 0.01). Conclusion: Signals of clinical benefit with respect to PFS and OS were equal for targeting EGFR and VEGF, but ORR was higher with EGFR inhibition. This might have implications for potentially resectable disease in the neoadjuvant setting. Clinical trial information: NCT01206049.

4072 Poster Session (Board #182), Mon, 8:00 AM-11:30 AM

Pazopanib (P) and trametinib (T) in advanced cholangiocarcinoma (CC): A phase Ib study. *First Author: Rachna T. Shroff, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: CC is an aggressive disease with a dismal prognosis and no clear therapy in the refractory setting. Mek inhibition and anti-angiogenic therapies have shown modest activity in advanced CC, while dual inhibition of these pathways has not been evaluated. We investigated the safety of combining of P+T in a phase I trial (previously reported). 2 patients (pts) with CC were enrolled during dose escalation with 1 prolonged partial response (PR) and the other with stable disease (SD). Based on this possible signal, we evaluated the safety and efficacy of this combination in an expansion cohort of 25 advanced, pre-treated CC pts. **Methods:** P+T were administered daily for a 28-day cycle with radiographic imaging performed every two cycles. Patients were monitored for toxicity throughout. The primary endpoint was progression-free survival (PFS) with secondary endpoints including overall survival (OS), response rate (RR) and disease control rate (DCR, partial response + stable disease). **Results:** 25 patients were enrolled (median age = 62, 20 evaluable for response). The median follow-up was 8.9 months with pts having received a median number of 2 prior therapies (range 1-9). The most common grade 3/4 toxicities attributable to study drugs included: rash, thrombocytopenia, hypertension, fatigue (all n = 3), and elevated LFT's (n = 2). ORR was 5% with a DCR of 75% (15/20 pts). Median PFS was 4.3 mths (95% CI: 3.5-7.6) with a 4-mth PFS of 56% ($p < 0.002$ compared with a pre-specified null hypothesis rate of 25%). Median OS was 6.7 mths. **Conclusions:** P+T was well tolerated with evidence of activity in refractory CC. Further studies are needed to assess the benefit of combining anti-angiogenic therapy with Mek inhibition and to explore a potential molecular phenotype in which this combination may provide a clinically meaningful benefit. *This study was approved and funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by GlaxoSmithKline.* Clinical trial information: NCT01438554.

4073 Poster Session (Board #183), Mon, 8:00 AM-11:30 AM

A phase II clinical trial on combined axitinib and transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC): Final results and evaluation of clinical predictor for response. *First Author: Stephen Lam Chan, Sir YK Pao Center for Cancer, State Key Laboratory in Oncology in South China, Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, Hong Kong*

Background: Axitinib is a potent and specific inhibitor of VEGFRs. Elevation of VEGF level in plasma and tumor is frequently observed after TACE treatment for HCC. We hypothesize that combining axitinib and TACE has synergism by inhibiting the VEGF surge after TACE. We conducted a phase II clinical trial to study the combination for treatment of inoperable HCC. **Methods:** This is an investigator-initiated, single-arm, phase II study. Key eligibility criteria include: diagnosis of inoperable HCC; Child's A function; without main portal vein thrombosis/distant metastases. Patients (pts) were started axitinib 5mg bid followed by TACE at 5thweek. Assessment of further TACE is conducted every 2 months (m). TACE is given if there is viable HCC and pts are suitable for TACE. Axitinib is withheld 24 hours before and resumed 24 hours after TACE. CT Imaging is arranged every 8 weeks (mRECIST). The primary endpoint is 2-year survival rate. Secondary endpoints include determination of response, toxicity and clinical predictors of outcome. The sample size is 50. **Results:** From May 11 to Apr 14, 50 pts have been recruited. Data cut-off date was 31 Dec 14. The median follow-up is 21.6m. Median age: 61.8 years; median tumor diameter: 6.8cm. BCLC Stage B/C: 38/12. Median cycle of TACE given is 2. The median OS is 15.9m (95% CI 13.7-31.9m) with 2-year OS rate of 41.9%. The median time-to-progression is 10.4m. Amongst 45 evaluable pts, 30 (68.2%) have partial or complete response. Total 6 pts underwent surgical resection after downstaging of HCC with 5 of the specimens showing complete tumor necrosis. Common $\geq$ grade 3 toxicities include: ALT elevation (40%), hypertension (24%) and hand-foot skin reaction (12%). The median dose density of axitinib is 90.6%. Development of hypertension (any grade) during the treatment course is associated with better OS (25.0 vs. 13.7m; p = 0.03). **Conclusions:** The combination of axitinib and TACE is efficacious with high response rate. The regimen is well tolerated without significant safety concern. Selected pts could be converted to operable state after downstaging. Further clinical development is indicated. (NCT01352728) Clinical trial information: NCT01352728.

4074 Poster Session (Board #184), Mon, 8:00 AM-11:30 AM

Efficacy and safety of nintedanib (N) versus sorafenib (S) in Caucasian and Asian patients with advanced hepatocellular carcinoma (HCC): Pooled analysis of two randomized phase II trials. *First Author: Tim Meyer, University College London Cancer Institute, London, United Kingdom*

Background: N is an oral, triple angiokinase inhibitor of vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor receptors. Two randomized, open-label, Phase II studies evaluated the efficacy and safety of N versus S in patients with advanced HCC in Europe (NCT01004003; 1199.37) and Asia (NCT00987935; 1199.39). **Methods:** Patients with unresectable, advanced HCC, ECOG-PS $\leq$ 2, Child–Pugh score A, alanine/aspartate aminotransferase (ALT/AST) $\leq 2 \times$ upper limit of normal and $\geq$ 1 untreated measurable lesion or previously treated lesion with progression (by RECIST 1.0) were randomized 2:1 to N 200 mg bid or S 400 mg bid continuously in 28-day cycles, until intolerable adverse events (AEs) or disease progression (PD); treatment beyond PD was allowed if clinical benefit was perceived. The primary endpoint was time to progression (TTP) by independent central review (ICR; RECIST 1.0); secondary endpoints included overall survival (OS) and objective tumor response (OR) by ICR. **Results:** 188 patients received N (1199.37: n = 62; 1199.39: n = 63) or S (n = 31; n = 32). Main patient demographics/baseline characteristics were balanced between treatments in both trials except for macrovascular invasion (N vs S; 48% vs 31%) in 1199.39. TTP was comparable between N and S (median 3.7 vs 3.9 months; HR 1.31 [95% CI: 0.89–1.91]), as were OS (median 11.4 vs 11.0 months; HR 0.91 [95% CI: 0.65–1.29]) and OR rate (4% vs 5%). The rate of Grade $\geq$ 3 AEs (62% vs 87%) and AEs leading to dose reduction (19% vs 51%) was lower with N than S; more N-treated patients had AEs leading to drug discontinuation (34% vs 29%). The most frequent ($>$ 5% of patients in any group; N vs S) Grade $\geq$ 3 AEs were diarrhea (10% vs 5%), fatigue (7% vs 2%), increased AST (8% vs 13%) and ALT (6% vs 8%), anemia (7% vs 6%), thrombocytopenia (5% vs 8%), skin reaction (1% vs 6%) and hand-foot skin reaction (0 vs 19%). **Conclusions:** Pooled analysis of two trials in Caucasian and Asian patients showed similar efficacy between N and S. AEs were as expected based on the safety profile of both agents. Further studies of N in patients with advanced HCC are warranted. Clinical trial information: NCT01004003 and NCT00987935.

4075 Poster Session (Board #185), Mon, 8:00 AM-11:30 AM

Proposal of a new staging system for intrahepatic cholangiocarcinoma: Analysis of surgical patients from a nationwide survey of Liver Cancer Study Group of Japan. *First Author: Yoshihiro Sakamoto, Hepato-Biliary-Pancreatic Surgery Division, The University of Tokyo, Tokyo, Japan*

Background: In the current AJCC/UICC staging system 7thed. for intrahepatic cholangiocarcinoma (ICC), tumor size was excluded and "periductal invasion" was added as a new factor determining T-category. However, prognostic significance of tumor size and periductal invasion remains unclear. **Methods:** Of a total of 1216 patients who underwent surgical resection for ICC between 2000 and 2005 on Japanese nationwide database by Liver Cancer Study Group of Japan (LCSGJ), 756 patients with histologically confirmed mass-forming dominant ICC were studied. A multivariate analysis of the clinicopathological factors on the survivals of patients were performed using the data of 419 patients with complete set of the valid data. A new staging system was customized based on the results of the multivariate analyses. **Results:** The overall survivals were best stratified with a cut-off value of 2 cm with the minimal p-value to discriminate the survivals of patients. The 5-year survival rate of the 15 patients with ICC $<$ / = 2cm without nodal metastasis or vascular invasion was 100%, suggesting surgical resection offers cure of the disease and these cohort can be defined as T1. Multivariate analysis of prognostic factors for all 419 patients showed that tumor size (HR = 2.487, CI = 0.912-6.780), tumor number (HR = 2.570, CI = 1.814-3.643), nodal metastasis (HR = 2.818, CI = 1.992-3.987) and distant metastasis (HR = 2.940, CI = 1.258-6.869) were independent and significant prognostic factors. The survival curves of N0M0 patients were well-stratified using a new T classification regulated by the 1) tumor size ($<$ / = 2cm, $>$ 2cm), 2) tumor number and 3) portal vein, arterial or major biliary invasion. The survivals of patients with T1-3N1M0 were as good as those of T4N0M0 patients, and thereby categorized as Stage IVA, discriminating from Stage IVB, a group of T4N1M0 or M1. **Conclusions:** Tumor size with a cut-off value of 2cm and major biliary invasion were important prognostic factors for survival. The proposed new staging system would be useful for assigning surgical indication for selected patients even with nodal metastasis.

4076 Poster Session (Board #186), Mon, 8:00 AM-11:30 AM

Sorafenib plus intra-arterial cisplatin versus sorafenib alone in patients with advanced hepatocellular carcinoma: A randomized phase II trial. *First Author: Masafumi Ikeda, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Intra-arterial cisplatin therapy for advanced hepatocellular carcinoma (HCC) has been reported a favorable tumor-shrinking effect and long-term survivals even in pts with highly advanced HCC. The aim of this trial was to evaluate the efficacy and safety ofsorafenib plus intra-arterial cisplatin (SP) vs. sorafenib alone (S) for advanced HCC. **Methods:** In this multicenter open-labeled randomized phase II trial, advanced HCC pts with no prior chemotherapy and Child Pugh A or B7 were randomly assigned 2:1 to receive SP (sorafenib: 800 mg, twice daily; intra-arterial cisplatin: 65 mg/m2, day 1, every 4 to 6 weeks up to a maximum of 6 cycles) or S (800 mg, twice daily) with portal vein tumor thrombosis and extrahepatic metastasis as dynamic allocation factors. The primary endpoint was overall survival. If the median survival of S is assumed as 7.0 months and that of SP as 9.5 months, the hazard ratio (HR) is 0.74. SP would be judged as favorable if HR is 0.74 or lower. A total of 105 pts was needed to estimate the 1-year survival rate with an accuracy of $\pm$10%. **Results:** From June 2011 to December 2013, 108 pts were randomized (SP, n = 66; S, n = 42) and followed up to December 2014. In the full analysis set of 106 pts, the patient characteristics were well-balanced, except for portal vein tumor thrombosis and hepatitis C viral infection. The median survivals in the SP and the S arms were 10.6 and 8.7 months, respectively (crude HR [95% CI], 0.68 [0.44-1.04], p = 0.073; and stratified HR by the allocation factors [95% CI], 0.60 [0.38-0.96], p = 0.031). The median time to progression was 3.1 and 2.8 months in the SP and S arms (HR [95% CI], 0.78 [0.52-1.16], p = 0.212; stratified HR [95% CI], 0.78 [0.59-1.21]). The following adverse events were more frequent in the SP arm than in the S arm, (percentage in the SP/S arms): neutropenia, 60.0/43.9; leukocytopenia, 75.4/43.9; hemoglobin, 89.2/73.2; thrombocytopenia, 89.2/80.5; hyponatremia, 81.5/53.7; nausea, 41.4/19.5; and hiccups, 9.2/0.0, respectively. **Conclusions:** According to the prespecified HR of 0.74, SP yielded favorable overall survival as compared to S in pts with advanced HCC. A further phase III trial is warranted to confirm these results. Clinical trial information: UMIN000005703.

4077 Poster Session (Board #187), Mon, 8:00 AM-11:30 AM

Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma following first-line therapy with sorafenib: Patient-focused outcome (PFO) results from the phase 3 REACH study. *First Author: Ian Chau, Royal Marsden, London & Surrey, United Kingdom*

Background: REACH did not demonstrate a significant improvement in overall survival (OS) in the ITT population, but pts in the RAM group with an elevated baseline alpha-fetoprotein (AFP) ≥400ng/mL (pre-specified) had meaningful improvement in OS (HR 0.67, $p < 0.05$). Here we present PFOs (pt-reported FACT Hepatobiliary Symptom Indexes [FHSI-8] and clinician-reported Eastern Cooperative Oncology Group [ECOG] performance status [PS]) from the REACH study. **Methods:** Eligible pts had advanced HCC; Child-Pugh A; ECOG PS 0 or 1; and prior sorafenib. Pts were randomized 1:1 to receive RAM (8 mg/kg) or placebo (PBO) on day 1 of an every 2 week cycle. The FHSI-8 was completed at baseline, cycles 4, 10, 16, and end of treatment. PS was assessed at baseline, each cycle, and end of treatment. Time to deterioration (TtD) in FHSI-8 was defined as the time from the randomization date to the first date with a ≥3-point decrease (based on 32-point scale) from baseline. TtD in PS was defined as the time from the randomization date to the first date a change to PS ≥2 was observed. Kaplan-Meier method and Cox regression were used to assess TtD. **Results:** Compliance with FHSI-8 was balanced between treatment arms. In the ITT population, TtD in FHSI-8 and PS were similar between RAM and PBO. In the elevated AFP population, there was a strong trend toward a delay in the deterioration of symptoms in FHSI-8 ($p = 0.054$) and PS ($p = 0.057$) for RAM treated pts compared to PBO. **Conclusions:** In the ITT population, symptom score and TtD were comparable between treatment arms; RAM did not result in the detriment in symptoms or pt functioning. Delay in symptom and PS deterioration coupled with survival benefit was observed in pts treated with RAM in the elevated AFP population. Clinical trial information: NCT01140347.

	ITT		AFP ≥400 ng/ml	
	RAM	PBO	RAM	PBO
FHSI-8 Compliance Baseline, %	96.5	94.7	99.2	94.7
FHSI-8 Compliance End of Treatment, %	62.1	72.5	67.2	76.6
FHSI-8 Score Change from Baseline, mean	-2.44	-2.86	-2.21	-3.73
TtD FHSI-8, mo				
HR (95% CI)	1.04 (0.80-1.34)		0.69 (0.47-1.01)	
P value	0.78		0.054	
TtD ECOG PS ≥2, mo				
HR (95%CI)	0.89 (0.65-1.22)		0.64 (0.41-1.02)	
P value	0.47		0.057	

4078 Poster Session (Board #188), Mon, 8:00 AM-11:30 AM

Gemcitabine (G), capecitabine (C) and bevacizumab (BV) in patients with advanced biliary cancers (ABC): final results of a multicenter phase II study. *First Author: Renuka V. Iyer, Roswell Park Cancer Institute, Buffalo, NY*

Background: Role of antiangiogenic therapy is still undefined in ABC. We examined BV combined with G + C, a standard chemotherapy for ABC when the study began. **Methods**: Pts with ABC (inoperable stage III or IV), ECOG PS 0-1, normal organ and marrow function. Schema: BV 15 mg/ kg q 21 days; C 650 mg/m2 bid x 14 days, both starting day 1; G 1000 mg/m2 days 1 & 8; cycles repeated q 21 days. Primary objective was progression free survival (PFS), secondary objectives were overall survival (OS) toxicity, quality of life (QOL) using the FACT HEP tool and circulating tumor cell (CTC) number. **Results:** Fifty pts enrolled at 2 sites; 11(22%) gall bladder (GB), 29(58%) intrahepatic cholangiocarcinoma (IHC) and 10(20%) extrahepatic cholangiocarcinoma (EHC). Median age 63 (range 25- 84 years), 52% male, inoperable 16% and metastatic 84%. Cycles: median 8 cycles/patient (range 1- 33), median time on treatment was 5.8 months. Responses (RECIST): PR 12(24%), SD 24 (48%), PD 6(12%) and 8 (16%) 2 too early/6 clinical progression (nonevaluable). Clinical benefit rate (PR + SD) = 72 %. Median PFS: 8.1months (95% CI:5.3, 9.9). Median OS: 11.3 months (95% CI:8.1, 13.1). One year survival rate was 0.47 (95%CI: 0.32-0.60). Grade 3/4 toxicities (> 5%): hematologic 28(58%), GI 18 (36%), infections 14 (28%) and thromboembolic events 6 (12%). Treatment discontinuation for toxicity (10%), progression (64%), death (4%), or other reasons (22%). Median OS in 21 (46%) pts with detectable CTCs was 9.4 months compared to 13.7 months in the 25(54%) pts without detectable CTCs at baseline.Patients with QOL scores after one and two cycles of therapy that were above median score at baseline for the whole group had higher OS of 13 months compared to 11.3 months. **Conclusions**: PFS and OS in ABC with the combination of gemcitabine, capecitabine and bevacizumab is relatively comparable to that reported with gemcitabine and cisplatin with acceptable toxicity. Lack of detectable CTCs and higher than median QOL score after one/two cycles of therapy may serve as biomarkers to predict improved outcome. **Acknowledgement**: Study is supported by a grant from Genentech. Clinical trial information: NCT01007552.

4079 Poster Session (Board #189), Mon, 8:00 AM-11:30 AM

Evaluation of the value of serum glycomics (GlycoCirrhoTest) for risk prediction of hepatocellular carcinoma in compensated cirrhosis. *First Author: Xavier Verhelst, Department of Hepatology and Gastroenterology, Ghent University Hospital, Ghent, Belgium*

Background: Cirrhosis is a major risk factor for the development of hepatocellular carcinoma (HCC) with a yearly incidence ranging from 1 to 8%. EASL and AASLD guidelines recommend systematic screening with liver ultrasound at 6 months interval in cirrhotic patients. A glycomic based test, called GlycoCirrhoTest, based on to the respective abundance of bisecting GlcNAc residues and triantenarry glycans on serum proteins, has shown a 79% sensitivity and 86% specificity for the diagnosis of cirrhosis among patients with chronic liver diseases. The aim of the present study was to determine whether serum glycomics are predictive for the development of HCC in compensated cirrhotics. **Methods:** Blood samples of 132 cirrhotic (Child A or B) patients collected between 1995 and 2005 were analysed. Seventy percent suffered of Hepatitis C. In the remaining patients, the cause of cirrhosis was HBV infection, alcohol and autoimmune diseases. Cirrhosis was confirmed by liver biopsy. The patients were followed until the appearance of a HCC, death or liver transplantation. At the moment of serum sampling there was no evidence of HCC. GlycoCirrhoTest was performed using capillary electrophoreses as previously described by Callewaert et al. (Nature Medicine 2004). **Results:** After a median follow up of 4 years (IQR: 3.6–8.06), 35 (26.5%) of the patients developed a HCC. Mean follow up in the patients who did not develop HCC was 3.7 years (IQR: 3.4-9.9; ns) . There was a significant increase of the mean baseline GlycoCirrhoTest value in the patients who developed a HCC during follow up ($p < 0.001$) as compared to those who did not. ROC Curve analysis showed an AUC of 0.716 (95% CI: 0.611-0.820) for the prediction of HCC in the patients with a follow up of at least 1 year. An 0.1 increase in the value of the GlycoCirrhoTest was associated with a 27% increase in the risk for developing HCC (OR 1,27; 95%CI: 1,098-1,475). **Conclusions:** This study suggests that an analysis of the serum protein glycome could generate a useful biomarker for the identification of cirrhotic patients at high risk for the development of HCC. GlycoCirrhoTest may help to stratify cirrhotic patients according to the risk of HCC and optimize screening.

4080 Poster Session (Board #190), Mon, 8:00 AM-11:30 AM

A multicenter cohort study on transarterial chemoembolization with or without sorafenib for intermediate-stage hepatocellular carcinoma: Reconsidering combination-therapy trial design. *First Author: Yan Zhao, Department of Liver Disease and Digestive Interventional Radiology, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, China*

Background: The proof of the superiority of combination therapy with sorafenib and transarterial chemoembolization (TACE) over TACE alone for hepatocellular carcinoma (HCC) in term of survival is lacking. We conducted this multicenter retrospective study to evaluate the efficacy of combination therapy over TACE alone, and to compare the overall survival (OS) between patients with ≥ grade 2 sorafenib-related dermatologic adverse events (AEs) in the combination therapy group and patients treated with TACE alone. **Methods:** From January 2009 to December 2012, 606 consecutive patients with intermediate stage HCC, Eastern Cooperative Oncology Group performance status 0-1, and Child-Pugh class A-B (≤ 7) were included. Of them 202 received combination therapy and 404 received TACE alone therapy, respectively. **Results:** There was no significant difference between the two groups in median OS although a trend toward longer survival was observed in the combination therapy group (22.3 vs. 18.1 months, *P*= 0.281). After propensity score matching the difference in OS was still not different (22.3 vs. 17.9 months, *P*= 0.343). Of note, in the combination therapy group, 119 patients with ≤ grade 1 dermatologic AEs within the first two months of sorafenib initiation, which were defined as non-responders, had increased risk of death compared with 83 patients with ≥ grade 2 dermatologic AEs which were defined as responders (HR = 1.85; 95%CI 1.27-2.68; *P*= 0.001). By using the second propensity score matching to balance the baseline differences between responders subgroup and TACE alone group, a significantly prolonged median OS was observed in the responders subgroup (27.9 vs.18.3 months, *P*= 0.046). **Conclusions:** Combination therapy, not in all, but in responders to sorafenib, results in longer overall survival than TACE alone. Sorafenib-related dermatologic AEs may be considered a possible clinical marker to stratify responders from all patients. Before the appearance of any assured biomarkers, the design of prospective comparative studies needs to focus on the responders to treatment who are evaluated by clinical markers.

4081 Poster Session (Board #191), Mon, 8:00 AM-11:30 AM

A pilot study of tremelimumab – a monoclonal antibody against CTLA-4 – in combination with either trans catheter arterial chemoembolization (TACE) or radiofrequency ablation (RFA) in patients with hepatocellular carcinoma (HCC). *First Author: Austin G. Duffy, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Tremelimumab is a fully human monoclonal antibody that binds to CTLA-4 expressed on the surface of activated T lymphocytes and results in inhibition of B7-CTLA-4-mediated downregulation of T-cell activation. Both transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) have been shown to induce a peripheral immune response which may enhance the effect of anti-CTLA4 treatment in patients with advanced HCC. **Methods:** Patients with HCC [Childs Pugh A/B7; Barcelona Clinic Liver Cancer Stage B/C; ECOG 0/1; sorafenib refractory/intolerant (BCLC stage C only)] were enrolled in a pilot study of Tremelimumab at 2 dose levels (DL1 and DL2) until PD (irRECIST). Subtotal TACE or RFA was performed during study week 6 with DLT evaluation period encompassing first 8 weeks of study. Tumor biopsy at baseline and at time of RF/TACE. **Results:** 20 pts were enrolled with N = 18 evaluable for primary endpoint. Baseline characteristics: M:F 15:3; Median age = 54(range 42-76); Cirrhosis present in 13pts; BCLC Stage B/C: 4/14; Hepatitis B/C/neg: 4/10/4. 8 pts received TACE, 10 underwent RFA during week 6 of tremelimumab therapy. No DLT encountered. Most common toxicity was pruritus. One patient developed pulmonitis and was taken off study but remains disease-free at 16months. Of N = 10 pts evaluable for response outside of TACE/RFA-treated lesion 4 (40%) achieved confirmed partial responses. 5 of 7 pts with quantifiable HCV experienced a marked reduction in viral load. 6-week tumor biopsies showed immune cell infiltration on all evaluable patients. Median PFS for the study population (N = 17) was 7.4months. **Conclusions:** Tremelimumab in combination with subtotal TACE or RFA in patients with advanced HCC is safe and feasible. Obtaining tumor biopsies at baseline and at the time of RFA/TACE is safe. Evidence of immune cell infiltration was seen on evaluable patients. Encouraging clinical activity has been seen with objective confirmed responses, TTP 7.4m and possibly surrogate reductions in HCV viral load. Clinical trial information: NCT01853618.

4082 Poster Session (Board #192), Mon, 8:00 AM-11:30 AM

Panitumumab in combination with gemcitabine/cisplatin (GemCis) for patients with advanced kRAS WT biliary tract cancer: A randomized phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *First Author: Arndt Vogel, Hannover Medical School, Hannover, Germany*

Background: Biliary tract cancer encompasses a group of genetically heterogeneous tumors. Panitumumab is a human EGFR inhibitor and has shown anti-tumor activity in RAS WT colorectal cancer. **Methods:** Pts with advanced KRAS wild type biliary tract or gallbladder adenocarcinoma were 2:1 randomized to receive Cis (25mg/m2) followed by Gem (1000mg/m2) on days 1 and 8 of a 21-day cycle, plus Panitumumab (6mg/kg) in arm A until disease progression. Primary endpoint was the progression-free survival rate at 6 months. For genetic profiling, massive parallel multigene sequencing was done by using a custom designed cholangiocarcioma multigene panel on an IonTorrent Proton. Mutations (21 genes) as well as amplifications and deletions (19 genes) were identified by panel tailored bioinformatic algorithms. **Results:** 93 pts were enrolled (63 per arm A and 30 arm B). Pts characteristics (panitumumab vs. control): median age 61.5 vs. 58.5 years; 59% vs. 50% male; intrahepatic, extrahepatic, gall bladder (%): 63, 16, 17 vs. 71, 11, 11; ECOG PS 0, 1, 2 (%): 64, 33, 2 vs. 45, 55; prior resection (%): 46 both arms. The most common grade 3-4 non-haematological adverse event (AE) was skin toxicity (39% vs 0%). Distribution of other grade 3-4 haematological and non-haematological AEs were not significantly different between both arms. 6-months PFS rate was not significantly different (55% vs 73%), mPFS was 6.7 vs. 8.2 mo, HR (95% CI, Gem/Cis ref.): 0.73 (0.43 – 1.24), p = 0.24; mOS was 12.8 vs. 21.4 mo, HR (95% CI, Gem/Cis ref.): 0.74 (0.39 – 1.4), p = 0.35; response rate (in evaluable pts): panitumumab (28/63 [45%] vs. control 11/28 [39%]. The most frequent genetic variations were detectable in p53 (34%), IDH1/2 (19%) and SMAD4 (11%) with up to 9 events per patient. The prognostic and predictive role of the variants is currently under investigation and will be presented. **Conclusions:** Panitumumab in combination with chemotherapy does not improve response rate, PFS and OS in patients with advanced bilary tract cancer. Further investigations of chemotherapy in combination with anti-EGFR antibodies are not warranted. Clinical trial information: NCT01320254.

4083 Poster Session (Board #193), Mon, 8:00 AM-11:30 AM

A phase 1/2 study of TRC105 in combination with sorafenib in hepatocellular carcinoma (HCC). *First Author: Austin G. Duffy, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Endoglin (CD105) is an endothelial cell membrane receptor highly expressed on proliferating tumor vasculature, including in HCC. CD105 is essential for angiogenesis and its expression is upregulated by hypoxia and VEGF inhibition. TRC105 is a chimeric IgG1 anti-CD105 monoclonal antibody that inhibits angiogenesis and causes ADCC and apoptosis of proliferating endothelium. Sorafenib is the only FDA-approved drug in HCC and anti-endoglin antibody potentiates sorafenib in preclinical models **Methods:** Patients with HCC (Childs Pugh A/B7), ECOG 0/1, were enrolled in a phase I study of TRC105 at 3, 6, 10, 15mg/kg q 2wks plus sorafenib 400mg bid. Correlative biomarkers included DCE-MRI, color Doppler ultrasonography, circulating endothelial and endothelial progenitor cells, plasma levels of angiogenic factors, soluble CD105 and tumor IHC for CD105. Samples were also collected for analysis of immune subsets and pharmacokinetics. **Results:** 21 pts were enrolled (N = 2 inevaluable); 12 with cirrhosis; Hep B/C/NA: 2/10/7; M:F 13:6; Mean age of 60 (range 18-76); 1 DLT (increased AST) occurred at 10mg/kg. The most frequent toxicity was low grade epistaxis. One patient experienced an infusion reaction and was replaced. One patient with coronary stenosis developed a fatal myocardial infarction and one patient developed G3 cerebral tumor hemorrhage. Four of sixteen (25%) pts evaluable for response achieved PR by RECIST (3/6 at Dose Level 4). Four patients had confirmed stable disease, one of whom was treated for 22 months. Median PFS was 4.1 months for first N = 18 patients, 5 months at dose level 4. **Conclusions:** TRC105 combined with sorafenib was well tolerated at the recommended single agent doses of both drugs. Encouraging evidence of activity (PR rate 25%) was observed and the study is now in the phase 2 stage. Full correlative and clinical data will be presented. Clinical trial information: NCT01306058.

4084 Poster Session (Board #194), Mon, 8:00 AM-11:30 AM

Objective response by mRECIST to predict survival in hepatocellular carcinoma: A multivariate, time-dependent analysis from the phase III BRISK-PS study. *First Author: Josep M. Llovet, Liver Cancer Program, Division of Liver Diseases, Mount Sinai School of Medicine, New York, NY*

Background: mRECIST (modified Response Evaluation Criteria In Solid Tumors) was developed to overcome the limitations of standard RECIST in hepatocellular carcinoma (HCC) response assessment. Retrospective studies have correlated objective response (OR) by mRECIST with overall survival (OS) in patients treated by loco-regional therapies. We investigated whether OR by mRECIST predicted OS using data from a double-blind, placebo-controlled, randomized phase III trial. **Methods:** In the BRISK-PS study, 395 patients with advanced HCC who progressed on/after or were intolerant to sorafenib were randomly assigned (2:1) to receive brivanib plus best supportive care (BSC) or placebo plus BSC. Tumor assessments were performed every 6 weeks by contrast-enhanced computed tomography or magnetic resonance imaging. Assessment of response was done by central radiological review using mRECIST. Multivariate models using time-dependent covariate analysis defined variables with independent prognostic value (SPSS 18 and SAS 9.2). **Results:** 210/226 (93%) patients in the brivanib arm and 101/108 (94%) in the placebo arm, who had baseline and on-study scans available for central blinded review, were evaluable according to mRECIST. 26/210 patients on brivanib and 2/101 on placebo achieved partial response ($p < 0.01$). At the end of follow up, 284 patients had died, the median OS for the brivanib arm being 9.4 months. As per mRECIST response assessment, median OS was 16.4 months (n = 26; 95% CI, 15.7 – NA) for brivanib responders and 8.3 months (n = 237; 95% CI, 7.2 – 9.7) for brivanib non-responders (hazard ratio, 0.28; 95% CI, 0.14 – 0.55, $p < 0.01$). Independent predictors of OS at multivariate time-dependent analysis were ORR by mRECIST, vascular invasion/extrahepatic spread, AFP > 200 ng/mL and bilirubin > 1.5 mg/dl. **Conclusions:** ORR by mRECIST is an independent predictor of OS in HCC patients receiving a systemic multikinase inhibitor, brivanib. mRECIST response is a marker of antitumor activity and warrants further evaluation in prospective clinical trials exploring novel agents in HCC patients. Clinical trial information: NCT0901901.

4085 Poster Session (Board #195), Mon, 8:00 AM-11:30 AM

Changes in plasma biomarkers over time in patients (pts) with advanced biliary tract cancer (ABC) treated in the UK ABC-03 randomized phase II trial. *First Author: Alison Catherine Backen, University of Manchester (Institute of Cancer Sciences), Manchester, United Kingdom*

Background: ABC-03 was a randomized phase II trial of cediranib (C; AZD2171) [inhibitor of VEGFR-1, -2 and -3 tyrosine kinase and VEGF-induced signaling] or placebo (P) in combination with cisplatin/gemcitabine for pts with ABC. Changes in plasma biomarkers including angiogenic proteins and a marker of cell death (CK18) have not been reported in ABC. **Methods:** ELISA was performed for 15 angiogenesis or inflammatory-related proteins and CK18 in plasma of pts with repeated sampling during treatment and at disease progression. Tumor markers were also evaluated. Overall survival (OS) was analyzed using Cox model for baseline (BL) biomarkers and time-varying covariate Cox model (TVC) for biomarkers with serial measurements. **Results:** Plasma samples were available from 117 of 124 pts (59 in C arm, 58 in P). After adjusting for treatment and pt characteristics, higher BL VEGFR2 ($p = 0.02$), CK18 ($p = 0.005$), CEA ($p < 0.001$), CA19-9 ($p = 0.03$) and CA125 ($p = 0.001$) correlated with shorter OS, as did incremental increases in CK18 (HR 1.08, 95%CI 1.05-1.11, $p < 0.001$) and IL-6 (HR 1.02, 95%CI 1.00-1.03, $p = 0.008$) using TVC. There was evidence for interaction between treatment and BL CA19-9 and PDGFbb for OS: incremental increases in CA19-9 were associated with an increased risk of death (C: HR 1.44, 95%CI 1.16-1.80; P: HR 1.03, 95%CI 1.00-1.05, $p = 0.001$) and higher values of PDGFbb were associated with a decreased risk of death with C (HR 0.82, 95%CI 0.68-1.00) and an increased risk of death with P (HR 1.15, 95%CI 0.99-1.34, $p = 0.01$). In TVC, there was evidence of interaction between treatment and VEGFA ($p = 0.03$), PDGFbb ($p = 0.08$), VEGFC ($p = 0.06$) and SDF1b ($p = 0.06$). Higher values of VEGFA were associated with increased risk of death with P (HR 1.31, 95%CI 1.06-1.62) but not with C (HR 0.99, 95%CI 0.86-1.15) ($p = 0.03$). **Conclusions:** High BL VEGFR2, CK18 and tumor markers are associated with a poor outcome in pts with ABC. Increasing levels of CA19-9 and PDGFbb from BL were associated with increased and decreased risk of death, respectively, in C-treated pts. Changes in VEGFA correlated with OS for pts on P but not C. These findings may inform future clinical trial stratification and design. Clinical trial information: NCT00939848.

4086 Poster Session (Board #196), Mon, 8:00 AM-11:30 AM

Molecular characterization of 350 hepatocellular carcinomas to identify biomarker aberrations with potential novel therapeutic options. *First Author: Celina Ang, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Effective treatment strategies for hepatocellular carcinoma (HCC) remain limited. Identification of additional therapies remains paramount as currently available agents have resulted in marginal improvements in overall survival or are not appropriate for this patient population. **Methods:** 350 HCC sampleswere evaluated on a commercial platform, for both genetic and proteomic aberrations. Tests included Sanger or next generation sequencing (NGS), protein expression by immunohistochemistry (IHC) and gene amplification by in situ hybridization (ISH). **Results:** TP53 was mutated in 34%, CTNNB1 in 20%, and BRCA2 in 18%; other gene mutation rates were < 5%.TP53-mutated tumors show significantly higher TOP2A (89% vs. 39%, $p<0.0001$), TS (70% vs. 32%, $p=0.0067$) and RRM1 expression (40% vs. 12%, $p=0.017$), implying high rates of proliferation and DNA synthesis. CTNNB1-mutated tumors showed significantly higher SPARC (67% vs. 21%, $p=0.0013$) and AR expression (53% vs. 22%, $p=0.025$). Changes in protein expression are shown. Metastatic HCC ($N=124$) exhibited significantly higher PD-1 (79% vs. 50%, $p=0.047$) and TS expression (31% vs. 14%, $p<0.0008$) than non-metastatic ($N=226$). Analysis of outcomes in a subset of patients treated based on biomarker-therapy associations is ongoing. In 1 patient an EGFR mutation (predictive of response to erlotinib in NSCLC) was identified, and the patient has begun treatment with erlotinib. **Conclusions:** The molecular profile in HCC suggests potential targeted therapies, such as tyrosine kinase inhibitors, anti-PD1 agents, or PI3 kinase pathway inhibitors. Immuno-modulatory agents may be an option, particularly in metastatic HCC, based on levels of PD-1. Concurrent protein changes in CTNNB1-mutated tumors suggest potential benefit of combination therapies when targeting the WNT pathway. Review of responses to targeted therapies, such as is being tried with erlotinib in the patient with EGFR mutation may provide additional insight into efficacious therapies.

% of samples with change, by IHC.

High expression levels						Low expression levels			
EGFR	TOPO1	PD-1	TOP2A	SPARC	cMET	RRM1	TS	PTEN	MGMT
83	52	60	38	36	25	82	80	72	31

4087 Poster Session (Board #197), Mon, 8:00 AM-11:30 AM

The influence of tumor-infiltrating lymphocytes (TILs) and their prognostic value in cholangiocarcinoma. *First Author: Yaman Suleiman, Moffitt Cancer Center, Tampa, FL*

Background: Cholangiocarcinoma is a malignancy arising from the epithelial cells of the biliary tract with poor prognosis. Tumor-infiltrating lymphocytes (TILs) have a prognostic impact in various solid tumors. We aimed to investigate TIL expression and programmed cell death ligand PD-L1 and their clinical relevance in cholangiocarcinoma. **Methods:** Formalin-fixed paraffin-embedded tumor samples from 47 pts with resected and histologically verified cholangiocarcinoma between 1990 and 2011 were immunohistochemically (IHC) stained with anti CD8, anti CD45RO and the anti-PDL1 mouseIgG1 (clone 5H1; Thompson) antibodies on a Leica automated IHC platform. The stains were semiquantitatively analyzed using the AllRed score system (range 1 to 8). IHC score > 3 considered positive. The association between PDL1, CD45R0, OS and PFS was investigated using Kaplan-Meier survival and COX proportional hazard regression analyses. **Results:** Median age was 65 (41-85) with 51% male. 24%, 45%, 24% and 7 % were stage I, II, III, and IV respectively, CD8 was positive in 11/47 (23%), PD-L1 was positive in 42/47 (89 %), CD45R0 (lymph node like structure) was positive in 18/47 (38%), 17/18 (95%) of CD45R0+ tumors were PD-L1 positive. Pts with tumors exhibiting lymph node (LN) like structures (CD45R0+) has better median OS (63 months vs 18 months, $P = 0.003$) and median PFS (29 months vs 14.7 months, $P = 0.06$) than patients lacking LN like structures (CD45R0-). 5 yrs. OS in CD45R0+ was 61% vs 26% in CD45R0- (P 0.005) whereas 5 yrs. PFS in CD45R0+ was 44% vs. 18% in in CD45R0- pts (P value 0.02). Correlating PDL1 with OS and PFS was not feasible due to high expression of PD-L1 (89 %). **Conclusions:** Presence of LN like structures (CD45R0+) was associated with significant better outcome reflecting the immune-mediated killing of tumor cells. This LN like structures need to be further characterized to understand how they escaped the inhibitory effect of PD-L1. The high expression of PD-L1 on cholangiocarcinoma cells represents a potential therapeutic target which may enhance the immunologic response and improve the prognosis of this dismal cancer. Future trials involving PD-L1 inhibitors are warranted.

4088 Poster Session (Board #198), Mon, 8:00 AM-11:30 AM

A phase II trial of bevacizumab and erlotinib as second line therapy for advanced hepatocellular carcinoma. *First Author: Ahmed Omar Kaseb, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The objective of the study was to evaluate the efficacy and tolerability of bevacizumab (B) and erlotinib (E) combination as second line therapy for advanced hepatocellular carcinoma (HCC). **Methods:** Patients who had advanced HCC that was not amenable to surgical or regional therapies, had shown progression with sorafenib therapy; Childs-Pugh score A or B liver function; Eastern Cooperative Oncology Group performance status 0, 1, or 2 received bevacizumab 10 mg/kg every 14 days and erlotinib 150 mg orally daily, continuously, for 28-day cycles. The tumor response was evaluated every 2 cycles by using Response Evaluation Criteria in Solid Tumors Group criteria. The primary objective will be to assess progression-free survival (PFS) measured at 16 weeks following initiation of therapy .The secondary objective will be to assess time to progression (TTP) and overall survival (OS). **Results:** A total of 44 patients were included. PFS at 16 weeks was 43% (95% CI 28% -59%), the Median TTP was 3.9 months (95% CI 2.0-8.3) and median overall survival (OS) was 9.9 months (95% CI, 8.3-15.5). Grade 3-4 adverse events included fatigue (13.3%), acne (11.1%), diarrhea (8.8%), anemia (6.6%), upper gastrointestinal hemorrhage (6.6 %). **Conclusions:** Bevacizumab and Erlotinib combination showed promising activity in this first US study in the second line setting. Validation studies are warranted. Clinical trial information: NCT01180959.

4089 Poster Session (Board #199), Mon, 8:00 AM-11:30 AM

Prognostic score in high-grade gastrointestinal neuroendocrine tumours (GI-NETs). *First Author: Angela Lamarca, Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Outcomes of patients with high-grade GI-NETs are poor; prognostic markers for risk-stratification are needed. **Methods:** Consecutive patients, diagnosed with high-grade GI-NETs between 1997-2014, were included. Prognostic factors were identified by the Log-rank test, Cox regression and logistic regression and ROC curve comparisons performed for prediction accuracy. Internal validation of the score by Bootstrap-corrected Harrell Concordance Index (C-index) and Resampling Model Calibration were performed. **Results:** One-hundred and nine patients were eligible for analysis. Median follow-up time was 9.7 months (1.3-102.9). Median age: 67.7 years (16.3-84.1); 62% male, 84% metastatic; 19% foregut, 5% midgut, 19% pancreas, 28% hindgut and 29% unknown primary. Median ki67: 70% (20-100); ECOG PS 0: 26%, 1: 52%; 70% received chemotherapy. Baseline median alkaline phosphatase (ALK) and LDH were 109 IU/l (45-2035) and 70 IU/l (258-11069), respectively. The maximum model included stage, PS, LDH, Na, ALK, ki67, number of metastatic sites, presence of liver and presence of lung metastases. The score, selected by the lowest Akaike Index Criterion, included liver metastases, PS, ki67, LDH and ALK with 0-6 points assigned to each, resulting in 4 risk groups (A-D) with predicted risk of death, detailed in Table. There was no difference in the survival prediction accuracy between the maximum model and the score. On multivariable analysis, the score was prognostic for overall survival (HR 1.95, 95%CI 1.55-2.47; $p < 0.001$) and had good discrimination (C-index, 0.76) and calibration (mean error, 0.021; percentile 90, 0.037). **Conclusions:** This simple score identified high-grade GI-NET patients with meaningful differences in survival and may inform clinical decision-making and trial design.

Prognostic group (points)	Risk of death at 3 months (%)	Risk of death at 6 months (%)	Risk of death at 9 months (%)	Risk of death at 12 months (%)	Risk of death at 18 months (%)	Risk of death at 24 months (%)
A (0-1)	0.9	10.1	20.3	32.1	58	71.9
B (2)	4.2	26.01	43.6	57.3	79.7	88.2
C (3)	16.4	52.4	70.3	79.3	91.8	95.6
D (4-6)	46.9	77.5	87.8	91.6	96.9	98.5

4090 Poster Session (Board #200), Mon, 8:00 AM-11:30 AM

Association of progression-free survival with overall survival (OS) in patients (pts) with neuroendocrine tumor (NET) treated with somatostatin analogs. *First Author: Monica Ter-Minassian, Dana-Farber Cancer Institute, Boston, MA*

Background: Progression-free survival (PFS) is commonly used as a primary endpoint in NET clinical trials. Whether PFS is associated with OS is uncertain. We assessed the association between PFS and OS in a large observational cohort of pts with NETs treated with somatostatin analogs (SSA). **Methods:** We enrolled 1330 pts to a prospective observational study, beginning in 2003. Of these pts, we identified 440 with metastatic NETs who had received single-agent SSA and were evaluable for tumor progression, based on medical record review. We used a landmark analysis to assess OS in pts with progression (PD) or without PD at 6 month intervals, from 6 to 24 months after treatment initiation. Adjusted hazard ratios were assessed with Cox proportional hazards models. Kaplan-Meier estimates were used to calculate median OS for pts with PD vs. those without PD at each landmark time. PFS was defined as time of treatment initiation to time of first progression or death. OS was defined as time of treatment initiation plus the landmark time to time of death. **Results:** Of the 440 pts, 224 had small bowel NETs, 93 had pancreatic NETs and 123 other NETs. 311 pts progressed and 215 died. Median follow-up was 7.6 yrs. PFS was associated with OS at the 6, 12, 18, and 24 month landmarks: those who progressed by each landmark time had shorter median OS times than those who did not progress (see table). A trend suggesting association of PFS with OS was seen across tumor subgroups. **Conclusions:** In this observational cohort of pts with metastatic NETs treated with SSA, PFS was associated with OS. Our findings support the use of PFS as an endpoint in NET clinical trials.

PFS and OS in NET patients treated with SSA (N = 440).

Landmark time	No PD (N)	No PD (Median OS)	PD (N)	PD (Median OS)	Adjusted HR[a] (95%CI)
6 mo	327	7.52 yrs	107	3.62 yrs	1.72 (1.25, 2.37), p = 0.0009
12 mo	249	7.02 yrs	169	4.71 yrs	1.47 (1.07, 2.00), p = 0.017
18 mo	181	7.10 yrs	220	3.97 yrs	1.77 (1.25, 2.51), p = 0.0014
24 mo	147	6.79 yrs	219	4.21 yrs	1.58 (1.07, 2.32), p = 0.02

[a]Adjusted for age, gender, tumor grade, tumor origin, and post-progression treatment.

4091 Poster Session (Board #201), Mon, 8:00 AM-11:30 AM

Everolimus in patients with advanced, progressive pancreatic neuroendocrine tumors: Overall survival results from the phase III RADIANT-3 study after adjusting for crossover bias. *First Author: Marianne E. Pavel, Charité Berlin Campus Virchow-Klinikum, Berlin, Germany*

Background: In the RADIANT-3 study, everolimus (EVE) improved progression-free survival (PFS) by 6.4 mo versus placebo (PBO; HR, 0.35; 95% CI, 0.27-0.45; $P < 0.001$) in patients (pts) with advanced, progressive pancreatic neuroendocrine tumors (pNET). Here we present final overall survival (OS) results of the RADIANT-3 study with updated safety and also report OS adjusted for confounding due to crossover. **Methods:** A total of 410 pts with advanced, progressive, low-/intermediate-grade pNET were randomized to EVE 10 mg/d (n = 207) or PBO (n = 203), both with best supportive care. Upon disease progression in double-blind phase, crossover from PBO to open-label EVE was allowed at investigator's discretion. At the end of core phase, ongoing pts from both arms were unblinded and switched to open-label EVE. OS was analyzed by one-sided stratified log-rank test. Rank-preserving structural failure time (RPSFT) analysis was performed to estimate treatment effect corrected for crossover bias. **Results:** A total of 225 pts received open-label EVE; including 85% (172 of the 203) pts randomized to PBO arm. Median OS (95% CI) was 44.0 (35.6-51.8) mo for pts initially randomized to EVE and 37.7 (29.1-45.8) mo for those randomized to PBO (HR, 0.94; 95% CI, 0.73-1.20; P= 0.30). RPSFT analysis showed a relative survival benefit of 3.27 (95% CI, 0.10-13.93) with survival rates of 82.6% vs 74.9% and 67.7% vs 55.6% at 12 and 24 mo, respectively for EVE vs RPSFT corrected PBO arm. The most frequently reported drug-related adverse events included stomatitis (45%), rash (37%), and diarrhea (26%) in open-label EVE arm. **Conclusions:** The randomized, placebo-controlled, phase III RADIANT-3 study reports unprecedented median OS of 44 mo with EVE in advanced, progressive pNET. Although statistically not significant, a survival benefit of 6.3 mo with EVE was observed, consistent with PFS benefit reported previously. A stronger OS advantage with EVE after a correction for crossover effect confirms that crossover of majority of PBO pts (85%) likely confounded the survival results. The safety profile of EVE remained consistent with earlier experience. Clinical trial information: NCT00510068.

4092 Poster Session (Board #203), Mon, 8:00 AM-11:30 AM

Phase Ib study of pasireotide (P), everolimus (E), and selective internal radioembolization therapy (SIRT) for unresectable neuroendocrine hepatic metastases. *First Author: Bassel F. El-Rayes, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Pasireotide (P) is a somatostatin (SST) analogue active against receptors 1, 2, 3, and 5. Everolimus (E) is an mTOR inhibitor. mTOR and SST pathways activate angiogensis, survival and increase radio-resistance. **Methods:** Major eligibility criteria: unresectable bilobar liver metastasis from low or intermediate grade NET, prior therapy with octreotide LAR 30mg, evidence of disease progression by RECIST 1.1, hemoglobin A1C less than 7, and adequate liver functions. A 3+3 dose escalation design was used. Everolimus dose levels were 2.5 mg, 5 mg, and 10 mg every day. Standard dosing and administration was used for Sir-sphere$^{(R)}$. E and P (600mcg BID) were given 1 week prior to SIRT and until 29 days after second SIRT when E (10mg daily) and P LAR (60 mg q 28days) were started. Dose limiting toxicities (DLT) were defined as the occurrence of any treatment related grade 4 hematologic or grade 3 non-hematologic toxicities lasting more than 7 days or grade 4 non-hematologic toxicity. Serum pharmacodynamic markers (VEGF, FGF, PIGF, Il-8, IGF-1, IGF-2, IGF binding proteins) were collected at baseline, prior to and 24 hours after first SIRT. QOL patients were assessed monthly by the Norfolk QOL-NET questionnaire. **Results:** 13 patients (pts) were enrolled in the study. 1 pt was in-evaluable for toxicity. Pt characteristics were median age 61 yrs, 7 males, primary site (midgut 4 pts, pancreas 3, lung 2, unknown 2, gastric 1, colon 1), and low grade (11). 3 pts had liver only disease. No DLT was observed. The grade 3 toxicities throughout the study were: hyperglycemia (6 pts) and thrombocytopenia (2pts). Liver toxicities observed in the first 28 days were bilirubin grade 1 (1 pt), bilirubin grade 2 (1 pt), and AST/ALT elevation grade 1 (8 pts). Best response was PR (6 pts), SD (3 pts), PD (3 pts- 2 had extrahepatic progression). 6 pts (50%) are still with no progression and median PFS is 9 months (95%CI 4-21). **Conclusions:** The RP2D is everolimus 10 mg QD and pasireotide 600 mcg BID. **P**, E and SIRT was well tolerated with minimal liver toxicity. The preliminary results for activity appear promising and control of liver disease is excellent with only 1 pt (8%) having progressive disease in the liver. Clinical trial information: NCT01469572.

4093 Poster Session (Board #204), Mon, 8:00 AM-11:30 AM

Novel score to predict outcome in resected pancreatic neuroendocrine tumors (pNET). *First Author: Antonio Viudez, Department of Medical Oncology, Complejo Hospitalario de Navarra-Fundacion Navarrabiomed, Pamplona, Spain*

Background: MGMT expression can predict response to temozolomide-based treatment. In pNET PHLDA-3 silencing is a common event while the expression of NDRG-1 and its functional role is unknown. We conducted a retrospective review of immunohistochemistry (IHC) expression of MGMT, NDRG-1 and PHLDA-3 in pNET and investigated their potential role as prognostic biomarkers. **Methods:** IHC nuclear staining for MGMT and PHLDA-3 was scored as 0, 1-5%, 6-50% and ≥ 51%. For NDRG-1, we used a cytoplasmic score from 0 to 3 based on staining intensity. Based on the long-rank test result between 2 clusters for each IHC staining, we designed an IHC score (IHC-S, score from 0 to 3). Finally a Global Score (GS) was developed with those variables that showed most significant differences in the univariate analysis (IHC-S and margin). **Results:** 92 samples from patients (pts) with resected pNET and follow-up > 24 moths were analyzed. Median follow-up was 55.5 months (mo). Pts had a median age of 56.5 y (16-88) and R0 resection occurred in 84.8%. Median DFS was 77 mo while median OS has not been reached yet. Significant statistical differences were observed in DFS based on surgical margin status (R0: 118 m vs R1: 34 m; p = .005), ypN0 vs ypN1 (p = .004) and ki67 < 2% (< 2% vs 2-20% p = .015). DFS was significantly poorer in pts without any expression of MGMT (p = 0.045), in pts with low-expression of NDRG-1 (0 or 1, p = 0.03), and in pts with high-expression of PHLDA-3 (≥ 51%, p = 0.01). Significant differences were observed between pts with IHC-S = 0 vs IHC-S = 1 (p = 0.009), IHC-S = 2 (p = 0.012) or IHC-S = 3 (p = 0.0001). Pts with IHC-S = 0 never recurred while up to 70% of pts with IHC-S = 3 progressed during follow up. Using the Cox proportional hazards regression, GS was found as independent prognosis factor for DFS (HR: 5.043; 95%CI: 1.278-19.901). **Conclusions:** Our results suggest the potential use of MGMT, NDRG-1 and PHLDA-3 IHC expression as predictor of outcome in pNET. Our Global Score may be able to discriminate between pts that will be cured after surgery from those with high risk of relapse.

4094 Poster Session (Board #205), Mon, 8:00 AM-11:30 AM

Study of the therapeutic management of gastric carcinoid tumors from data of the French national cohort of neuroendocrine tumors: CARGAS study. *First Author: Sylvain Manfredi, CHU Pontchaillou, Rennes, France*

Background: 4 types of gastric NETs are described: type 1 developed on atrophic gastritis (70-80% of cases), type 2 (5-6% of cases) as part of MEN 1, sporadic type 3 (14-25% of cases), and Type 4 corresponding to poorly differentiated NETs (6-8%) (1). The natural history of types 1 and 2 is usually benign, while type 3 and 4 are more aggressive. Treatments of these four types are different and based on European guidelines (2). Those recommendations are based on data of small series. **Methods:** The objective of this study was to study of the treatment and monitoring of gastric NETs registred prospectively in a national cohort. Secondary objectives: epidemiology, overall survival. The National Register of GTE records all TNE via e-crf. **Results:** At the end-point of the study 197 gastric NETs were recorded (2.5% of all the NETs registred, 11th frequency tumor). A study of each case, on site, was conducted. 181 (91.9%) complete records were analyzed. The characteristics of these tumors are presented in the table below. Gastrin was measured in 31% of patients and chromogranin A in 36.9%. A somatostatin analogue was administered to 16 patients (8.8%). **Conclusions:** This cohort represents the largest cohort known to date. It provides us important data on epidemiology of these tumors and their management. There are very likely over-reporting of type 3 and 4 in this register.

181 gastric NETs	Type1 (84)	Type 2 (5)	Type 3 (49)	Type 4 (43)	p
%	46.4%	2.8%	27.1%	23.8%	
Male	35.7%	60%	65.3%	72.1%	< 0.0001
Age at diagnosis	53.3	49.7	59.0	60.3	0.02
Size < 1cm	47.6%	20.0%	16.3%	2.3%	< 0.0001
Median size mm	11.3	29.8	35.3	39.4	< 0.0001
n tumor < 6	52.4%	40.0%	71.4%	81.4%	< 0.0001
Stage at diagnosis	-	-	-	-	-
- local	94.1%	100%	28.6%	14.0%	< 0.0001
- locoregional	6.0%	-	16.3%	18.6%	
- metastasis	-	-	55.1%	65.1%	
Differenciation	-	-	-	-	-
- benign	47.6%	40.0%	2.0%	11.6%	< 0.0001
- well differenciated	46.4%	60.0%	58.7%	88.4%	
- poor differenciated	3.6%				
Treatment	-	-	-	-	-
- endoscopic	92.7%	60.0%	43.7%	6.0%	< 0.0001
- surgery		40.0%	41.2%%	42.4%	
- chemotherapy			5.9%	39.4%	
5 years survival	98.3%	100%	60.6%	39.6%	< 0.0001

4095 Poster Session (Board #206), Mon, 8:00 AM-11:30 AM

Characteristics, prognosis and treatments of 294 patients with poorly differentiated neuroendocrine carcinoma: The FFCD-GTE national cohort. *First Author: Thomas Walter, Hopital Edouard Herriot, St Didier Au Mont D'or, France*

Background: Data on poorly differentiated neuroendocrine carcinoma (NEC) are limited or retrospective. We designed a French cohort to describe characteristics, prognosis and treatments of NEC **Methods:** All patients with a diagnosis of NEC (WHO 2010) performed between 01/01/2010 and 31/12/2013 could be included in this national prospective cohort. Patients with small-cell NEC from lung, mixed tumors, and well-differentiated neuroendocrine tumors (NET) were not included **Results:** 294 patients from 49 centers were included: median age was 66 (range: 23-92) years, 6 (2%) had functional tumors, performance status (PS) was 0-1 in 79% of patients, fortuitous diagnosis was done in 10 (3%) patients. Main primary locations were pancreas (18%), colorectal (24%), oeso-gastric (15%), large-cell lung NEC (15%), and unknown (17%). Most of the patients were metastatic (75%). At that time, 85 (29%) pathological specimens have been reviewed by the French national referent pathological network (TENpath). Pathological data showed: small/large cell NEC in 38%/62%, with necrosis in 79%, and a median Ki67 index of 70% (range: 10%-100%). Median overall survival (OS) was 15.7 months (95% CI: 13.9-17.8). GEP-NEC had similar characteristics and survival than other NEC. Factors associated with worse OS in multivariate analysis were PS > 1 (HR = 2.9, p < 0.001), metastatic disease (HR = 2.2, p < 0.001), NSE > 2 ULN (upper limit of normal) (HR = 4.1, p < 0.001), and LDH > 2ULN (HR = 2.7, p < 0.001). Ki67 index > 55% and primary location were not significantly associated with different OS. OS were 11.8 months from first-line (L1) systemic palliative chemotherapy (n = 202 pts), 7.6 months from L2 (n = 117), and 5.9 months from L3 (n = 58). The type of L1 was mainly platinum-etoposide (n = 176), whereas folfiri (79 patients) and folfox (37 patients) were mainly given in L2 or further lines. Efficacy of these treatments will be presented at the meeting **Conclusions:** This is the largest prospective series of NEC showing that worse prognosis factors are performance status, tumor burden, and elevated biologic markers (NSE and LDH). Further prospective studies are needed to improve treatment in L2

4096 Poster Session (Board #207), Mon, 8:00 AM-11:30 AM

Multicenter prospective phase II trial of bevacizumab (bev) for progressive pancreatic neuroendocrine tumor (PNET). *First Author: Timothy J. Hobday, Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN*

Background: Single agent trials of mTOR inhibitors and VEGF receptor TKIs in PNET yield response rates < 10%. We previously demonstrated a 39% PR rate in PNET with the combination of temsirolimus and bev in patients with progressive PNET. There are no data regarding the efficacy of single agent bev in PNET. **Methods:** We conducted a multicenter phase II trial of bev at a dose of 10 mg/kg IV q 2 weeks in patients (pts) with well or moderately differentiated PNET, adequate organ function, and ECOG PS of 0-1. Important eligibility criteria included requirement for progression of disease by RECIST within 7 months of study entry. No prior anti-VEGF pathway inhibitor therapy was allowed. Ongoing octreotide was allowed at stable dose if required for symptom control. Primary endpoint was response with null hypothesis of 10% and promising result was defined as 30%. Planned enrollment was 21 pts. **Results: :** 22 pts enrolled from 10/2012 through 6/2014 were eligible for The primary endpoint of response assessment. 9 patients remain on therapy. Confirmed PR rate is 9% (2/22). 6 month progression free survival (PFS) was 95% (20/22). 15 out of 22 pts have follow-up on study > 12 months. The Kaplan-Meier 12 month PFS was 54% (95% CI: 34-85%). Median PFS is 13.6 months (95% CI 10.6-NA). Therapy was well tolerated with no grade 3-4 AEs except 36% grade 3 hypertension. **Conclusions:** Bev therapy for PNET is associated with a 9% PR rate in this trial. For a population required to have RECIST criteria progression within 7 months prior to study enrollment, the 6 and 12 month PFS rates of 95% and 54% are promising with minimal systemic toxicity. Clinical trial information: NCT01010126.

4097 Poster Session (Board #208), Mon, 8:00 AM-11:30 AM

Bronchial neuroendocrine neoplasms: A Surveillance Epidemiology and End Results (SEER) database review of demographics and survival in 187,991 cases. *First Author: Mark Andrew Lewis, MD Anderson Cancer Center, Sugar Land, TX*

Background: Bronchial neuroendocrine neoplasms (NENs) are a biologically heterogeneous group of malignancies whose differences are incompletely understood. We aimed to study the demographics and survival of patients with these neoplasms by reviewing the SEER database. **Methods:** We identified 945,331 cases in the SEER database with malignancies of the lung and extracted 187,991 bronchial NENs to examine patient characteristics & clinical outcomes by histology and stage. **Results:** By histology and grade, there were 130,092 cases of small cell carcinoma, 44,520 cases of large cell carcinoma, 3,349 cases of neuroendocrine carcinoma (grade 3/4), 9,135 cases of typical bronchial carcinoid (grade 1), and 895 cases of atypical bronchial carcinoid (grade 2). The ethnic predilection was Caucasian (87%, with 9% black and 4% other). Overall there were more cases in men (55% of the entire cohort), but women accounted for 66% of the carcinoid cases. Mean age at diagnosis for all NENs was 66, with typical carcinoids having the youngest mean age (60) than any other type. By SEER stage, 13% of NENs were localized, 24% were regional, and 63% were metastatic, with median survivals of 39.7, 14.4, and 4.3 months, respectively. Survival by histology is summarized in the table below. **Conclusions:** Bronchial NENs vary widely in their clinical behavior. By histology, large cell carcinomas carry the worst prognosis, whereas typical carcinoids are associated with the longest survival, as well as lowest age at diagnosis & female sex, Atypical carcinoids bear more semblance to typical carcinoids than to small cell, large cell, or neuroendocrine carcinomas in their biology.

Tumor type	Median survival (months) [95% CI]
Large cell carcinoma	6.0 [5.9-6.1]
Small cell carcinoma	7.0 [6.9-7.1]
Neuroendocrine carcinoma	9.0 [8.5-9.5]
Atypical carcinoid	101.0 [80.8-121.2]
Typical carcinoid	201.0 [191.7-210.3]

4098 Poster Session (Board #209), Mon, 8:00 AM-11:30 AM

Bronchial neuroendocrine neoplasms: A Surveillance Epidemiology and End Results (SEER) database review of treatment outcomes. *First Author: Mark Andrew Lewis, MD Anderson Cancer Center, Sugar Land, TX*

Background: Bronchial neuroendocrine tumors (NENs) are a biologically heterogeneous group of malignancies with varied approaches to treatment. We queried the SEER database about outcomes of surgery and radiation. **Methods:** We identified 945331 cases in the SEER database with malignancies of the lung and extracted 187991 bronchial NENs – 130092 cases of small cell carcinoma, 44520 cases of large cell carcinoma, 3349 cases of neuroendocrine carcinoma (grades 3/4 [G3/4]), 9135 cases of typical bronchial carcinoid (grade 1 [G1]), and 895 cases of atypical bronchial carcinoid (grade 2 [G2]) – to examine clinical outcomes by treatment modality, including radiation in 82157 cases and surgery in 21352. **Results:** Surgical intervention on the primary NEN became less frequent as SEER stage become more extensive; operations were performed in 56.0% of cases of localized disease, 19.9% of regional disease, and 4.5% of distant disease. Proportionately more surgery was performed on lower-grade histologies (e.g. 84% of all-stage G1 NENs vs. 27% of large cell carcinomas). Significantly higher median survivals were seen across all SEER stages and histologies with surgical intervention vs. none (e.g. $>$ 240 vs. 68 mos. for localized G1 NENs, $p < .001$). Across SEER stages, large cell carcinoma was the histology treated proportionately the most often with radiation, given to 52.3% of all cases, followed by 44.8% of small cell, 38.9% of G3/4 NENs, 15.3% of G2 NENs and 4.9 % of G1 NENs. Typical carcinoids did not benefit from radiation regardless of SEER stage, with the largest decrement in median survival in localized disease receiving radiation (37 mos.) vs. none (232 mos., $p < .001$). **Conclusions:** Patients undergoing surgery for bronchial NENs had longer survivals than those who did not undergo surgery, regardless of histology or SEER stage. G1 NENs treated with radiation had median survivals poorer than those who did not receive radiation. It is unclear if those patients receiving radiation had positive margins after surgery, initially inoperable disease, or other prognostic factors associated with worse outcomes. Nonetheless, there is no evidence of benefit for radiation administered to G1 NENs of any SEER stage.

4099 Poster Session (Board #210), Mon, 8:00 AM-11:30 AM

Identification of response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors. *First Author: Jonathan R. Strosberg, Moffitt Cancer Center, Tampa, FL*

Background: Capecitabine and temozolomide are active in the treatment of metastatic pancreatic neuroendocrine tumors (pNETs), with response rates ranging from 30% to 70%. Several small retrospective series have suggested that MGMT deficiency may predict response to temozolomide, however expression of MGMT has not been validated as a predictive biomarker. Cytotoxic chemotherapy is thought to be most active in aggressive tumors, however the ki-67 index has not been formally evaluated as a predictive factor. It is unclear whether chromosomal instability (which correlates with alternate lengthening of telomeres) predicts response. **Methods:** 144 patients with pNET who underwent treatment with capecitabine/temozolomide were retrospectively evaluated for radiographic response. The predictive role of ki-67% and MGMT by immunoistochemestry as well as ALT activation by FISH was assessed on up to 59 evaluable archival specimens. Frequently altered genes in pNETs were also sequenced and their status was correlated to the radiographic response. **Results:** The ORR was 63%. Response to treatment was significantly higher in tumors with ki-67 $>$ 5% ($n = 28$) as compared to tumors with ki-67 $\leq$ 5% ($n = 31$) (ORR: 64% vs 29%; $p = 0.006$). MGMT status ($p = 0.358$) and ALT pathway activation ($p = 0.174$) were not predictive of response. **Conclusions:** pNETs with ki-67 $>$ 5% are more likely to respond to capecitabine/temozolomide. MGMT status appears to have no correlation with response.

4100 Poster Session (Board #211), Mon, 8:00 AM-11:30 AM

A phase II study of axitinib in advanced carcinoid tumors: Preliminary results. *First Author: Mauro Cives, Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Neuroendocrine tumors (NETs) are highly vascular neoplasms overexpressing VEGF as well as VEGFR. Axitinib is an inhibitor of receptor tyrosine kinases with picomolar potency against VEGFR-1, -2 and -3 and nanomolar potency against PDGFR-β. **Methods:** We performed a phase II trial of axitinib 5 mg twice daily in patients with unresectable or metastatic low to intermediate grade carcinoid tumors. Prior antiangiogenic therapy with a dedicated VEGF pathway inhibitor was not permitted. The primary endpoints were PFS and 12-month PFS rate. H_0= 12 mo PFS rate of 36% (corresponding to median PFS of 8.1 months); H_a= 12 mo PFS rate of 56.5% (corresponding to median PFS of 14.6 months). Preliminary findings are reported. **Results:** 30 patients were enrolled and assessable for toxicity; 22 were assessable for response. Primary sites included small intestine (19 patients), lung (3), unknown (3), colon (2), rectum (2), and thymus (1). 21 patients had low-grade and 9 patients had intermediate-grade tumors. Carcinoid syndrome was diagnosed in 16/30 patients. Median TTF was 8.99 months (SD $\pm$7.18) and the 12 mo PFS rate was 65% (SD $\pm$13%). Median PFS not yet determined due to small number of events. The 1-year OS rate was 93% (SD$\pm$4.9%). Best radiographic response was PR in 1/30 (3.3%) and stable disease in 21/30 (70%); 8/30 patients (27%) unevaluable due to toxicity (4/30) and consent withdrawn (4/30). Among 25 patients with baseline elevated chromogranin A levels, 4 (16%) experienced major reductions ($>$ 50%) of the tumor marker. 90% of patients experienced hypertension (any grade). Grade 3 and 4 hypertension were seen in 18 (60%) and 2 (7%) patients respectively. Hypertension led to treatment discontinuation in two cases, however, axitinib interruption prompted a fast recovery without sequelae. **Conclusions:** The 12 mo PFS rate associated with axitinib in advanced carcinoid tumors appears promising when compared to results observed in phase II studies of other antiangiogenic TKIs such as sunitinib or pazopanib. Although associated hypertension is common, axitinib treatment was overall well tolerated. Clinical trial information: NCT01435122.

4101 Poster Session (Board #212), Mon, 8:00 AM-11:30 AM

Randomized, phase III trial of adjuvant adefovir vs. therapeutic lamivudine in post-operative BCLC stage 0 or A HBV-related HCC: The Taiwan Cooperative Oncology Group T1206 study. *First Author: Li-Tzong Chen, National Institute of Cancer Research, National Health Research Institutes, Tainan City, Taiwan*

Background: To investigate the role of adjuvant anti-viral nucleoside in tertiary prevention of HCC relapse in post-operative BCLC stage 0 or A HBV-related HCC. **Methods:** Patients with curative resection of BCLC stage 0 or A and solitary tumor < 5 cm, HBV-related (HbsAg+/anti-HCV-) HCC were eligible. Accruals were stratified by HBV genotype (C vs. non-C) and serum viral titer (< 20,000 vs. > 20,000 IU/mL) and randomly assigned to receive either 3 years of adefovir treatment from study entry or observation alone, in which 18 months of lamivudine would be given when their HBV DNA titer > 20,000 IU/mL and ALT > 2.0 x UNL. The primary endpoint was late RFS. **Results:** Between April 2007 and August 2010 (early terminated because lamivudine was no longer the standard care for chronic HBV infection), a total of 117 patients were enrolled. The demographic characteristics were well-balanced between adefovir (N = 58) and control (N = 59) arms. At a median follow-up of 57.9 months, 53 (45.3%) had recurrence and 17 (14.5%) were deceased. The cumulative 5-year FRS and OS rates of ITT cohort were 52.6% and 86.4%, respectively. The median RFS were not reached yet in adefovir arm and 6.4 years in control arm; while the 5-year RFS rate in corresponding arm was 53.8% (95% confidence interval [CI], 38.8% to 66.6%) and 51.6% (95% CI, 37.4% to 64.0%), respectively (P = 0.692, log-rank test). In Cox's regression univariate analysis, only baseline HBeAg and HBV DNA titer significantly affected RFS, with a HR of 2.988 (95% CI: 1.489 - 5.994, p = 0.0021) and 1.916 (95% CI: 1.083 - 3.388, p = 0.0255), respectively. Late RFS in those with RFS > 2 years was also similar between two study arms. **Conclusions:** Despite earlier trials showed adjuvant anti-HBV nucleoside (*vs.* no treament) can significantly improve the RFS and OS in post-operative HBV-related HCC (JCO 2013 and Ann Surg 2015). In current study, 3 years of adjuvant adefovir did not reduce the postoperative recurrence as well as late recurrence of HBV-related HCC as compared to observation followed by lamivudine when their HBV DNA titer > 20,000 IU/mL and ALT > 2.0 x UNL. This study is registered at ClinicalTrials.gov, identifier NCT00455091 Clinical trial information: NCT00455091.

4102 Poster Session (Board #213), Mon, 8:00 AM-11:30 AM

Phase II studies of BEZ235 in patients with advanced pancreatic neuroendocrine tumors (pNET). *First Author: Ramon Salazar, Institut Català d'Oncologia-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain*

Background: The PI3K/AKT/mTOR signaling pathway is upregulated in pNET. Everolimus (EVE) is an mTOR inhibitor (mTORi) approved to treat advanced pNET, but resistance occurs. PI3K pathway activation is associated with mTORi resistance. The dual mTOR/PI3K inhibitor BEZ235 (BEZ) may provide enhanced antitumor effects. **Methods:** Ph II studies (Study [S]1 [NCT01628913]; S2 [NCT01658436]) investigated BEZ in patients (pts) with advanced pNET. S1 enrolled pts with disease progression within 12 months (mo) and no prior mTORi, who were randomized 1:1 to BEZ (400 mg BID) or EVE (10 mg QD). Stage 1 of S2 (single arm) enrolled pts with advanced pNET after mTORi failure, who received BEZ (400 or 300 mg BID [starting dose reduced]). Primary endpoint for S1 was progression-free survival (PFS) assessed only for descriptive purposes, and 16-week (wk) PFS rate for S2. Interim futility analysis was performed after stage 1 of S2 (31 pts observed ≥16 wk). Futility rejection criteria: ≥60% 16-wk PFS rate and ≥0.9 posterior probability of 16-wk PFS rate ≥40%. **Results:** At database lock, treatment discontinuation was 87% of pts in BEZ arm and 71% in EVE arm of S1, and 94% in S2, mainly due to progressive disease (S1: BEZ 36% vs EVE 45%; S2: 48%) and adverse events (AEs [S1: BEZ 39% vs EVE 16%; S2: 36%]). All-grade AEs regardless of study treatment relationship (≥35%) are listed. Median PFS in S1 was 8.2 mo (95% CI: 5.3–NE) and 10.8 mo (95% CI: 8.1–NE), for the BEZ and EVE arms, respectively; hazard ratio 1.53 (95% CI: 0.72–3.25). In S2, 16-wk PFS rate was 52% (90% CI: 35.7–64.3); posterior probability that 16-wk PFS rate is ≥40% was 0.9 (futility criteria met). **Conclusions:** BEZ as 1st- and 2nd-line (post-mTORi) therapy had limited clinical activity. S1 showed BEZ was not better tolerated than EVE; in S2, poor tolerability after EVE led to dose reduction. Clinical development of BEZ in pNET was terminated, but targeting the PI3K pathway warrants further exploration. Biochemical response data in S1 will be presented at the meeting. Clinical trial information: NCT01628913 and NCT01658436.

	S1		S2
AEs (%)	BEZ 400 mg BID N=31	EVE 10 mg QD N=31	BEZ 300 or 400 mg BID N=31
Diarrhea	90	55	71
Stomatitis	74	65	36
Nausea	55	32	48
Vomiting	48	23	32
Asthenia	42	42	23
Abdominal pain	39	26	26
Rash	36	42	16
Hyperglycemia	32	36	36
Decreased appetite	29	42	26
Anemia	26	36	–

4103 Poster Session (Board #214), Mon, 8:00 AM-11:30 AM

Lanreotide depot/autogel (LAN) vs. placebo (PBO) for carcinoid syndrome (CS) in patients with neuroendocrine tumors (NETs): Subgroup analysis of the ELECT study. *First Author: Aaron Vinik, Eastern Virginia Medical School, Norfolk, VA*

Background: ELECT, a large phase 3 study of the long-acting somatostatin analog (SSA) LAN for symptomatic control of CS in NET patients showed significant improvement over PBO in % days with short-acting octreotide use as rescue medication. Here, we investigate reduction in use of rescue medication for LAN vs PBO in subgroups defined by baseline characteristics. **Methods:** Patients with histologically confirmed NETs and history of CS received double-blind LAN 120 mg (n=59) or PBO (n=56) every 4 wks for 16 wks, with access to short-acting octreotide for breakthrough symptoms (NCT00774930). Least-squares mean differences in % of days rescue octreotide use for LAN vs PBO were calculated by ANCOVA within subgroups. **Results:** The significant reduction for LAN vs PBO in rescue medication use in the overall population (Table; approximately one-third lower for LAN group relative to PBO group) was generally consistent with reductions favoring LAN over PBO across subgroups, except small subgroups in which CIs were wide (e.g. BMI ≥30). **Conclusions:** Beneficial effects of LAN for CS symptom control in NET patients are consistent regardless of baseline characteristics. Clinical trial information: NCT00774930.

		Short-acting octreotide use, % days*		
Subgroup		LAN	PBO	Treatment difference (LAN – PBO) [95% CI]*
Overall population (n=115)		33.7	48.5	-14.8 [-26.8, -2.8]
Age	<65 y (n=78)	35.8	53.2	-17.4 [-34.1, -0.6]
	≥65 y (n=37)	25.8	45.5	-19.7 [-35.5, -3.9]
Gender	Male (n=48)	36.7	60.8	-24.1 [-45.7, -2.5]
	Female (n=67)	33.7	39.1	-5.4 [-21.5, 10.7]
BMI	<25 (n=41)	29.9	48.5	-18.6 [-39.6, 2.3]
	>25 to <30 (n=50)	30.9	52.7	-21.8 [-39.6, -4.1]
	≥30 (n=21)	37.4	31.6	5.8 [-32.4, 44.0]
Race/ethnicity	Caucasian (n=96)	34.2	48.7	-14.5 [-27.6, -1.4]
	Other (n=19)	21.9	46.6	-24.8 [-70.4, 21.0]
Region	US (n=40)	19.6	30.2	-10.7 [-32.5, 11.2]
	Ex-US (n=75)	39.5	55.8	-16.3 [-31.6, -1.0]
Prior SSA	No (n=51)	25.3	44.3	-18.9 [-37.0, -0.9]
	Yes (n=64)	33.9	44.2	-10.3 [-26.5, 5.9]
Time since diagnosis	<1 y (n=41)	39.1	53.3	-14.2 [-36.3, 7.9]
	≥1 y (n=74)	28.8	38.3	-9.5 [-24.4, 5.4]

*LS mean, from subgroup ANCOVAs containing treatment, stratification factor(s) and baseline parameters (octreotide, diarrhea and flushing events), intent-to-treat population.

4104 Poster Session (Board #215), Mon, 8:00 AM-11:30 AM

Lanreotide depot/autogel (LAN) in midgut neuroendocrine tumors (NETs): A subgroup analysis from the CLARINET study. *First Author: A. Dasari, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In CLARINET, progression-free survival (PFS) was significantly prolonged with the somatostatin analog LAN 120 mg vs. placebo in patients with metastatic grade 1 or 2 (Ki-67 <10%) non-functioning intestinal and pancreatic NETs (hazard ratio [HR] for progressive disease [PD]/death: 0.47 [95% CI: 0.30, 0.73]. Here, we more fully characterize treatment effects in the midgut subgroup (tumors of small intestine/appendix). **Methods:** CLARINET was a 96-week randomized double-blind trial. Patients received LAN 120 mg or placebo every 4 weeks, administered by deep subcutaneous injection (NCT00353496). Subgroup analyses were undertaken to investigate only the consistency of treatment effects as the study was not otherwise designed or powered for such analyses. **Results:** 73 patients with midgut NETs received LAN (n=33) or placebo (n=40). At baseline, mean age was 64 yrs, 34% had liver burdens >10% (19% with burdens >25%), 96% had stable disease, 88% had received no previous treatment, and 48% had undergone previous NET surgery. Median PFS in the midgut subgroup was not reached at study end with lanreotide vs. 21 months with placebo; treatment response was consistent in midgut NETs with liver tumor burdens above or below 10% (Table). Adverse events occurred at similar rates with lanreotide vs placebo (overall: 85 vs 93%; treatment-related: 42 vs 33%). Few patients on LAN or placebo had serious AEs (n=5 vs n=7; none treatment-related) or AE-related withdrawal (n=0 vs n=1). **Conclusions:** These data indicate antitumor effects and a favourable safety/tolerability profile that support LAN as a first-line midgut NET treatment. This is consistent with previous reports in the overall CLARINET study population. Clinical trial information: NCT00353496.

Midgut NET patients	N	LAN PFS*	PBO PFS*	Logrank p-value	HR (95% CI)
All	73	Not reached	85 wks	p=0.009	0.35 (0.16, 0.80)
Liver burden ≤10%	48	Not reached	98 wks	p=0.044	0.30 (0.08, 1.04)
Liver burden >10%	25	Not reached	60 wks	p=0.007	0.21 (0.06, 0.72)

*Median PFS estimated by Kaplan-Meier method.

4105 Poster Session (Board #216), Mon, 8:00 AM-11:30 AM

Low objective response and high toxicity to single-agent mitotane in patients with metastatic adrenocortical carcinoma (ACC): A 25 year experience at MSKCC. *First Author: Betty Y Lung, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ACC is a rare but devastating disease, with short life expectancy in the setting of metastatic, unresectable disease. Mitotane, an oral adrenocorticolytic agent, is often used as a systemic treatment though its therapeutic window is narrow. We retrospectively assessed outcomes of patients (pts) with metastatic ACC who received single-agent mitotane therapy to determine treatment toxicities and effectiveness. **Methods:** In this retrospective IRB-approved study, we identified 35 pts with metastatic ACC treated with single-agent mitotane at MSKCC from 3/15/1989-9/18/2014. All pts had follow-up at MSKCC and all imaging was reviewed according to RECIST 1.1 by reference radiologists. We reviewed pt demographics, clinical symptoms, toxicity (based on CTCAE Version 4), and treatment outcomes. **Results:** 35 pts were identified with mean age of 53 years (range, 23-87), 60% female. 18/35 tumors (51%) were functional: estradiol (n = 1), cortisol (n = 12), testosterone (n = 3), or both testosterone and cortisol (n = 2). Grade 3 toxicities were observed in 15 of the 35 pts (43%). Severe toxicities included anorexia (9%), depression (6%), fatigue (20%), rash (6%), nausea (11%), vomiting (11%), and abdominal pain (6%). Radiographic progression of disease occurred in 30 of 35 pts (86%) and 1 pt (3%) experienced clinical progression. 2 pts (6%) had a complete response, 1 pt (3%) had partial response, and 1 pt (3%) had stable disease. The 3 pts (9%) with response (CR+PR) were asymptomatic prior to initiating mitotane; all had low volume indolent disease limited to one site (1 pt lung only; 1 pt retroperitoneal LN; 1 pt liver). All 3 pts experienced grade 3 toxicities on mitotane requiring treatment interruption and/or discontinuation. **Conclusions:** Among pts with ACC treated with mitotane-based therapy, 43% experienced grade 3 toxicities and 89% experienced POD. Response was noted in only 9% of pts and came with significant toxicity. The tumors in these responders are currently undergoing next generation sequencing analysis and results will be reported at the annual meeting. More effective and less toxic therapies are desperately needed in this rare disease.

4106 Poster Session (Board #217), Mon, 8:00 AM-11:30 AM

Clinical diagnostic utility of a blood-based multi-transcriptome assay for gastroenteropancreatic disease. *First Author: Irvin Mark Modlin, Yale School of Medicine, New Haven, CT*

Background: Current blood-based biomarkers for the diagnosis and follow-up of neuroendocrine tumors (NETs) do not achieve acceptable metrics of sensitivity and specificity. We report the sensitivity and selectivity of the PCR-based test, the NETest, to detect tumors with reference to other benign and malignant gastrointestinal diseases. We report the utility of a 51 transcript peripheral blood signature, the NETest, in comparison to Chromogranin A (CgA) measurement in pancreatic NETs. **Methods:** One hundred and seventy nine cases (Set 1: gastrointestinal tumors: n= 81 including NETs (n= 41) and gastrointestinal carcinomas (n= 40); Set 2: pancreatic disease: n= 98 including NETs (n= 45), pancreatitis (n= 4), cysts (n= 31) and adenocarcinoma (n= 14)) were prospectively collected and analyzed by the NETest (disease activity index > 20% [0-100 score]) or by chromogranin A (CgA) ELISA to determine metrics for detecting small intestinal and pancreatic NETs. Marker gene expression (qPCR) and CgA (DAKO) were compared (χ^2, non-parametric) in Set 1. For Set 2, selectivity was assessed; sensitivity and specificity metrics were calculated for the entire cohort (n= 179). **Results:** Set 1: For intestinal disease, the accuracy of the NETest was 93% (all NETs positive, .CgA was positive in 80% but 29% (n= 7) of colorectal cancers were CgA positive and 3 (7.5%) colorectal tumors were NETest positive)). Set 2: For pancreatic disease, the NETest accuracy was 92% (96% NETs positive, 2 (6%) *intraductal papillary mucinous neoplasms (*IPMN) positive) while for CgA it was 56% (29% of pancreatic NETs were CgA positive). Overall, the NETest was significantly more sensitive than CgA for the detection of small intestinal (AUC 0.98±0.01 versus 0.75±0.06 $p<$ 0.0001) and pancreatic NETs (0.95±0.02 vs. 0.5±0.06, $p<$ 0.0001). When CgA was normal, The NETest was elevated (93%). **Conclusions:** This "real-world" study comparing NETs to unknown gastroenteropancreatic diseases demonstrates the sensitivity and specificity of a blood-based multianalyte NET gene transcript measurement for identifying small intestinal and pancreatic neuroendocrine tumor disease.

4107 Poster Session (Board #218), Mon, 8:00 AM-11:30 AM

Recurrence following surgical resection of gastroenteropancreatic neuroendocrine tumors (NETs): An analysis from the NCCN oncology outcomes database. *First Author: Katherine Van Loon, University of California, San Francisco, San Francisco, CA*

Background: Resection of gastroenteropancreatic NETs is known to prolong survival. Current NCCN guidelines recommend that complete surgical resection of the primary tumor and metastases should be performed if possible. However, large multicenter studies of recurrence patterns following resection have not been performed. **Methods:** Patients ≥18 years who presented to 7 participating NCCN institutions after 2004 with a new diagnosis of a small bowel, pancreas, or colorectal NET were included. All underwent complete (R0) resection of the primary tumor and of synchronous metastases if present. Descriptive statistics were used to determine recurrence rates. Kaplan-Meier estimates were used to calculate time-associated endpoints. Comparisons were assessed by the log-rank test. **Results:** Of 1,125 patients with small bowel, pancreas, or colorectal NETs in the database, 301 patients underwent R0 resection. 50% of patients included in the analysis were male, 88% were Caucasian, and 99% had an ECOG PS 0-1. The median age was 55 years (range 20-90); however, patients with a colorectal NET were younger (p<0.001). Median follow-up time from R0 resection was 62.1 months. Among patients with small bowel NET (n=110), 18% recurred. Among patients with pancreatic NET (n=141), 26% recurred. Among patients with colorectal NET (n=50), 10% recurred. The proportion of patients without recurrence and the proportion alive at 12, 24, 36, 48, and 60-month follow-up are below. Stratification according to stage will be presented. **Conclusions:** R0 resection was associated with variable risk of recurrence across subtypes during 5 years of follow-up. Greater than 90% of patients who underwent an R0 resection were alive at 5-year follow-up; similarly, the majority of patients were disease-free. Further inquiry into appropriate surveillance strategies following R0 resection is needed.

	Small bowel	Pancreas	Colon/rectum
Follow-up (months)		Proportion without recurrence following R0 resection (p=0.01)	
12	95%	96%	95%
24	93%	86%	90%
36	87%	74%	90%
48	83%	69%	90%
60	78%	62%	90%
		Proportion alive following R0 resection (p=0.5)	
12	98%	98%	100%
24	97%	96%	100%
36	92%	96%	96%
48	92%	95%	96%
60	92%	94%	96%

4108 Poster Session (Board #219), Mon, 8:00 AM-11:30 AM

Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): Analysis of REACH pts by Child-Pugh (CP) score. *First Author: Andrew X. Zhu, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: REACH was a global, randomized, double-blind, phase III study evaluating the efficacy and safety of RAM as a single-agent treatment of pts with advanced HCC after prior sorafenib therapy. The primary outcome for the ITT population was presented at ESMO 2014. The overall survival (OS) HR for the ITT population (RAM 283; placebo [PBO] 282) was 0.866 (95% CI 0.717, 1.046; p = 0.1391). In pts with baseline alpha-fetoprotein (AFP) ≥ 400 ng/mL (RAM 119; PBO 131), OS HR was 0.67 (95% CI 0.51–0.90; p = 0.0059). **Methods**: Efficacy and safety of RAM based on CP score are presented for all pts enrolled in REACH inclusive of ITT (n = 565) and CP B (n = 78) population. **Results**: In REACH, pts with CP5 (N = 177 RAM, N = 180 PBO), CP6 (N = 108 RAM, N = 100 PBO), and CP7+8 (CPB) (N = 39 RAM, N = 39 PBO) were enrolled. Baseline pt characteristics were generally balanced between treatment arms by CP score. The table below shows OS, PFS, ORR and DCR according to CP score. The safety profile of RAM in pts with CP5 and CP6 was similar, and consistent with that observed in the ITT analysis of CP A pts. In pts with CP7+8 (CP B), an increase in liver events grade ≥ 3 was observed on the RAM vs PBO arm (56% vs 41%), including an increase in hepatic encephalopathy grade ≥ 3 (10% vs 0%). This observation led to exclusion of CP B pts from enrollment after 441 total pts were randomized during the study. **Conclusions**: A greater RAM treatment benefit was observed in pts with lower CP scores. In the CP B pt population, an increase in liver adverse events was observed for RAM, specifically hepatic encephalopathy. A consistent and clinically meaningful improvement in OS, regardless of CP score, was observed in pts with elevated baseline AFP levels (≥ 400 ng/mL). Clinical trial information: NCT01140347.

		CP A	CP A	CP B
		CP5	CP6	CP7+8
REACH efficacy population				
OS	HR	0.796	0.955	0.998
	95% CI	0.625, 1.015	0.712, 1.280	0.623, 1.599
	p	0.0647	0.7609	0.9946
PFS	HR	0.587	0.778	0.738
	95% CI	0.469, 0.735	0.581, 1.041	0.457, 1.194
	p	< 0.0001	0.0912	0.2219
ORR	RAM	8.5%	5.6%	0%
	PBO	0.6%	1.0%	2.6%
DCR	RAM	62.1%	47.2%	48.7%
	PBO	46.1%	45.0%	28.2%
REACH pts with baseline AFP ≥ 400 ng/mL*				
OS	HR	0.611	0.639	0.674
	95% CI	0.429, 0.870	0.418, 0.978	0.332, 1.368
	p	0.0058	0.0384	0.2756

4109 Poster Session (Board #220), Mon, 8:00 AM-11:30 AM

A phase I/II study of bavituximab and sorafenib in advanced hepatocellular carcinoma (HCC). *First Author: Adam Charles Yopp, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Bavituximab, a first-in-class immunomodulator targeting phosphatidylserine (PS), a membrane lipid externalized on tumor and endothelial cells. In preclinical HCC models, sorafenib upregulated PS externalization providing more bavituximab targets altering the tumor environment from immunosuppressive to immunoreactive. **Methods:** In the 3+3 phase I trial, adults with advanced HCC, ECOG PS $\leq$ 2, and Child-Pugh class A or B7 received escalating doses of bavituximab weekly (0.3, 1, and 3 mg/kg) and sorafenib 400 mg bid for one 4-week cycle to determine the MTD of bavituximab. In the phase II trial with the same eligibility, patients received 3 mg/kg bavituximab and sorafenib until progression or toxicity. The primary endpoint was radiologic time to progression (TTP). Secondary endpoints included safety, 4-month progression free survival (PFS), overall survival (OS), and response rates. Correlative studies from pre- and post-treatment tumor biopsies included IHC analysis of immune infiltrates. **Results:** Ten patients were enrolled in the phase I trial without DLTs, demonstrating a MTD of 3 mg/kg of bavituximab and 400 mg PO of sorafenib. In the phase II trial, 38 patients were accrued, with 4 remaining on treatment at the time of this submission. Median follow-up is 6.1 months. Patient characteristics: median age: 60.5 years, male: 74%, HCV: 79%, macrovascular invasion: 84%, previous treatment: 40%, and metastases: 24%. Median TTP is 6.7 months (95%CI 4,14). Median OS is 6.2 months (95%CI 5,7). Four month PFS is 61% and two patients achieved partial response. Treatment related AEs include seven grade 3 but no grade 4 or 5 events. Most common all grade events were diarrhea (32%), fatigue (26%), and anorexia (24%). Six patients had tissue analyzed pre- and post-treatment, two of the six had significant increase tumor infiltration of CD4+, CD8+, and macrophages with a corresponding decrease in T regulatory cells. **Conclusions:** Bavituximab and sorafenib were well tolerated in advanced HCC. When compared with historical controls, combination therapy in a patient population with more unfavorable disease biology demonstrated an improvement in TTP and 4-month PFS. Combination therapy increased immune tumor infiltrates. Clinical trial information: NCT01264705.

4110 Poster Session (Board #221), Mon, 8:00 AM-11:30 AM

Prospective identification of potentially actionable molecular alterations in cancers of unknown primary. *First Author: Anna M. Varghese, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients with cancers of unknown primary (CUP) represent a heterogeneous population, and the frequency of actionable molecular alterations in their tumors remains unknown. These patients are frequently excluded from most Phase II/III studies as most require a histologic diagnosis with a primary site of disease; consequently, little progress has been made in developing targeted therapies for these patients. **Methods:** We prospectively identified patients with CUP seen for initial consultation at MSKCC from 01/2013 through 11/2014. We excluded patients with a likely primary disease site based on subsequent pathologic and radiographic tests. Tumors and matched normal samples underwent testing by MSK-IMPACT, a comprehensive molecular profiling platform performed in a CLIA-compliant laboratory using targeted deep sequencing of 341 cancer-associated genes to identify sequence mutations, copy number alterations, and select rearrangements. We collected tumor histology and defined potentially actionable molecular alterations as those for which investigational or FDA-approved targeted agents exist. **Results:** Of 34 patients identified with CUP, pathologic review demonstrated 44% adenocarcinoma (15/34) and others, including carcinoma (Ca), squamous cell Ca, neuroendocrine Ca, and sarcoma. 334 alterations were identified with a median 7 alterations / patient (range 0-41). Alterations were seen most commonly in *TP53* (19/34), *CDKN2A* (7/34), *ARID1A* (7/34), *KRAS* (7/34), and *SMARCA4* (7/34). Potentially actionable alterations were present in 41% (14/34) of patients and included *BRAF* V600E, *AKT1* E17K, and *ERBB2* S310F, among others. Actionable alterations identified in 10 patients made them eligible for inclusion in targeted therapy studies available at our institution. Updated treatment and response information will be presented at the meeting. **Conclusions:** CUPs harbor potentially actionable mutations. Patients with CUPs might benefit from expanded treatment opportunities and possibly improved outcomes through increased access to clinical trials in which eligibility criteria is based on molecular status rather than histologic diagnosis based on a primary site of disease.

4111 Poster Session (Board #222), Mon, 8:00 AM-11:30 AM

Long-term outcomes of cytoreduction and HIPEC for malignant peritoneal mesothelioma. *First Author: Gleneara Elizabeth Bates, Mesothelioma Center Columbia College of Physicians and Surgeons New York-Presbyterian Hospital, New York, NY*

Background: The prognosis of malignant peritoneal mesothelioma (MPM) has improved over the past decade in patients undergoing operative extirpation and intraperitoneal chemotherapy (IC). This study investigates the largest reported cohort of patients operated on for MPM. **Methods:** Kaplan-Meier curves and univariate cox proportional hazards model was used to estimate survival and significant treatment and prognosis factors, for 195 patients who underwent cytoreductive surgery and or HIPEC treatment between 1995-2014; patients were not excluded for bicavity disease or for unresectable disease. **Results:** The median survival time was 3.21 years with (95% CI: 2.38- 5.53), with median follow-up of 3.44 years (SD = 3.4, minimum = 0.014 and maximum = 16.752) years from first operation. The mean age at diagnosis was 54.8 years [HR: 1.027 (95% CI: 1.012-1.042)] with 111 men (57%) and 84 women (43.1), with female gender having favorable survival [HR: 0.442 95% CI: 0.296-0.659)]. Asbestos exposure was reported in 77 patients (39.5%) with n = 80 (41.0%) having no known asbestos exposure and in 38 patients (19.5%) asbestos exposure was not documented. The majority of patients had epithelioid histology (n = 161(82.6%), with the remainder biphasic/sarcomatoid (n = 34, 17.4%), with increased risk of death with non-epithelioid histology [HR: 2.46(95%CI 1.59-3.82)], (P = 0.001). Of the 195 patients who received cytoreductive surgery, 71(36.1%) received 1 HIPEC treatment, while 124 (63.9%) received 2 HIPEC treatments, with completion of protocol having an associated favorable prognosis [HR: 0.161 (95%CI 0.109-0.237)] (p = 0.001). Of those who received a full treatment course of cytoreductive surgery and 2 HIPEC treatments, 66 (33.8% CI: 95%) were still alive at the median follow-up. **Conclusions:** This large cohort illustrates that long-term survival is possible in MPM, although there is continued significant decline after 3 years from diagnosis. While the treatment of MPM continues to evolve, a comprehensive treatment approach may give the best chance for long-term survival.

4112 Poster Session (Board #223), Mon, 8:00 AM-11:30 AM

Importance of tumor grade in stage III mucinous appendiceal carcinoma: An analysis of the SEER Database. *First Author: Olivia Fukui, Carolinas Healthcare System, Charlotte, NC*

Background: Appendiceal cancers are rare tumors with prognostic heterogeneity and treatment-responses dependent upon histologic characteristics. In the 7th edition AJCC manual, mucinous tumors were separated from non-mucinous. Histologic grade was used to distinguish stage IVa from IVb in mucinous tumors. We examined SEER data to investigate the impact of cancer grade on all stages of appendiceal cancer. **Methods:** We identified patients (pts) with primary appendiceal cancer from the SEER data. Disease-specific survival (DSS) was analyzed based on histologic subtype, stage, and grade. Hazards ratios were calculated using Cox models. Tumor grades were grouped according to AJCC criteria (Grade 1 vs. Grade 2 and above). **Results:** From 1988-2011 a total of 4491 appendiceal adenocarcinomas were identified in the SEER database; 2026 (45%) pts had mucinous histology and 1578 (35%) had non-mucinous histology. Tumor grade had no impact on DSS in stage I and II tumors. However, in Stage III and IV mucinous tumors higher tumor grade was significantly correlated with worse survival. In pts with Stage III mucinous disease, those with grade 1 tumors had significantly longer DSS than those with tumors $\geq$ grade 2, with 5-year survival of 75% vs. 44%, respectively (p = 0.02, HR 3.15, 95% CI 1.11 - 8.96). Survival for mucinous stage III grade 1 tumors was similar to stage II tumors. **Conclusions:** Tumor grade is a strong prognostic indicator in pts with stage III mucinous appendiceal carcinoma. We propose that tumor grade should be included in AJCC staging for stage III mucinous appendiceal cancers, and should not be limited to Stage IV disease as in the AJCC 7th staging manual. Continued investigation into the clinical implications of the observed difference in survival in patients with Stage III appendiceal mucinous adenocarcinoma is warranted, and may potentially alter adjuvant treatment recommendations in selected pts.

4113 Poster Session (Board #224), Mon, 8:00 AM-11:30 AM

Prognostic impact of different FDG-PET uptake according to histology in advanced gastric cancer. *First Author: Hong Jae Chon, Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*

Background: This study aims to investigate the role of preoperative FDG-PET/CT as a prognostic factor in advanced gastric cancer (AGC). **Methods:** A total of 953 AGC patients who underwent FDG-PET/CT and subsequent curative surgical resection were enrolled from 2003. Afterward, 548 patients with pathologically proven T stage 3 or 4 were visually reassessed and, in patients with positive FDG-PET/CT findings, SUVmax were evaluated as prognostic factors according to histologic subtype for cancer recurrence and death. **Results:** Of 548 patients, 497 (90.1%) showed positive FDG-cancer uptake. In terms of WHO classification, well or moderately differentiated adenocarcinoma (WMD) demonstrated the highest mean SUVmax, followed by poorly differentiated (PD) and signet ring cell carcinoma (SRC) (WMD: 9.3; PD: 6.4; SRC: 4.8; $P < 0.001$). Based on Lauren's classification, intestinal type displayed significantly higher mean SUV_{max} than diffuse type (Intestinal: 8.5; Diffuse: 5.3; $P < 0.001$). While mean SUV_{max} of WMD or intestinal type GC were well correlated with primary tumor size (both $P < 0.001$), those of SRC or diffuse type GC were not well correlated. TNM stage was not associated with SUV_{max} regardless of histologic subtype. When patients were divided into two groups (low vs. high SUV_{max}) based on median SUV_{max}, High SUV_{max} group had significantly shorter disease-free survival (DFS; SRC: $P = 0.004$; Diffuse: $P < 0.001$) as well as shorter overall survival (OS; SRC: $P = 0.007$; Diffuse: $P < 0.001$) than low SUV_{max} group in SRC or diffuse type GC. However, WMD or intestinal type GC did not demonstrate significant survival difference between low and high SUV_{max} groups. Multivariate modeling confirmed that high SUV_{max} patients with diffuse type GC had a significantly increased risk of recurrence and death than those with low SUV_{max} after adjusting for age, sex, pathologic stage (DFS: HR, 1.73; $P < 0.001$; OS: HR, 1.84; $P < 0.006$). **Conclusions:** FDG uptake of gastric cancer is different according to histologic subtype.FDG PET/CT could provide prognostic information on the prognosis after surgical resection of gastric cancer in SRC or diffuse type GC.

4114 Poster Session (Board #225), Mon, 8:00 AM-11:30 AM

Safety, pharmacokinetics, pharmacodynamics, and antitumor activity of necuparanib combined with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer: Phase 1 results. *First Author: Eileen Mary O'Reilly, David M. Rubenstein Center for Pancreatic Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Preclinical studies have shown necuparanib (necu)'s ability to bind growth factors, adhesion molecules, and chemokines to inhibit tumor progression, invasion, metastasis, and angiogenesis. Necu is being evaluated in a phase I/II trial with nab-paclitaxel (nabP) + gemcitabine (gem) in patients (pts) with metastatic pancreatic cancer (ClinicalTrials.gov NCT01621243). Part A is an open-label safety/pharmacokinetic (PK)/pharmacodynamic (PD) study to determine a Part B dose; Part B will evaluate efficacy, safety, and PK/PD relative to nabP + gem. **Methods:** In Part A, necu was given as daily escalating s.c. doses in combination with i.v. 125 mg/m^2 nabP and 1000 mg/m^2 gem (Days 1, 8, 15 of each 28-day cycle). The necu start dose was 0.5 mg/kg, with escalation via a modified 3+3 design until the maximum tolerated dose (MTD) was determined. The protocol was amended to include nabP after 2 necu + gem cohorts were completed. **Results:** As of January 15, 2015, 39 pts in 7 cohorts (0.5 and 1 mg/kg + gem; 1, 2, 4, 6, and 5 mg/kg + nabP + gem) received necu. Two dose-limiting toxicities (DLTs) occurred: increased AST/ALT at 0.5 mg/kg necu (N = 1) and cellulitis at injection site at 6 mg/kg (N = 1). Mild aPTT increases were observed at 4-6 mg/kg. There were no increases in known AEs of chemotherapy across doses. PK data (C_{max}, AUC) increased linearly from 2 mg/kg. Release of heparin-binding proteins (e.g. HGF, a PD marker) from heparan sulfate stores increased with dose and plateaued at 4-5 mg/kg. Given the cellulitis and mild aPTT increases at 6 mg/kg, 5 mg/kg was considered MTD. 16 pts treated with necu + nabP + gem completed Cycle 1 and had ≥ 1 scan on treatment; 8 (50%) achieved RECIST partial response and 6 (38%) more achieved stable disease, for an overall disease control rate of 14/16 (88%). Of 15 CA19.9 evaluable pts, 15 (100%) had > 20%, 14 (93%) had > 50%, and 7 (47%) had > 90% decreases from baseline. **Conclusions:** The MTD was necu 5 mg/kg combined with nabP + gem. Acceptable tolerability and encouraging signals of activity were observed with the combination. These results supported the initiation of the randomized, double-blind, phase II trial. Clinical trial information: NCT01621243.

4115 Poster Session (Board #226), Mon, 8:00 AM-11:30 AM

A multicenter, phase II trial of preoperative gemcitabine and nab-paclitaxel for resectable pancreas cancer: The AGITG GAP study. *First Author: Andrew Barbour, University of Queensland, Brisbane, Australia*

Background: Recent pancreatic cancer (PC) series show 41% (95%CI 40-43%) of patients (pts) achieve an R0 resection (margin clearance ≥ 1mm). In neoadjuvant chemotherapy trials for resectable PC, only 54-89% undergo pancreatic resection with R0 rates of 74-80%. Nab-paclitaxel(nab-pacli) and gemcitabine(GEM) chemotherapy(CX) is an active regimen in metastatic disease. We aimed to determine feasibility and R0 resection rate of 85% with peri-operative nab-pacli and GEM for resectable PC. **Methods:** Pts with operable PC received 2 cycles of neo-adjuvant nab-pacli 125mg/m^2 followed by GEM 1000mg/m^{2}CX on days(D) 1, 8 and 15(28D cycle) followed by resection and then post-operative CX(4 cycles). **Results:** Forty-one pts were enrolled (2012-14). Median age = 65 (range 43-79), 41% male. Thirty-six (88%) pts underwent surgery, while five (12%) did not (2 disease progression, 2 refused surgery, 1 cholangitis). Only 4/36 (10%) had grade ¾ septic events, no grade ¾ pancreatic leak, and no treatment related deaths. Thirty pts had pancreatic resection (73%; 29 had evaluable cancer and 15/29 (52%) had grade 0-2 tumour regression; one did not have cancer on central pathology review). Six (15%) pts had unresectable disease at surgery. Pre-operative nab-pacli and GEM produced an R0 rate of 52% (15/29; 95%CI 34-69%) with a minimum 1mm margin and an R0 rate of 86% (25/29; 95%CI 68-96%) with a 0mm margin. 39/41 (95%) completed planned induction CX (although dose modifications/omission were required - mostly omission of D15). Post-operatively, eighteen pts (18/30, 60%) commenced CX, with 14/18 (78%) completing all 4 cycles of planned CX; whilst four pts commenced chemoradiation, but 2 withdrew due to disease progression. **Conclusions:** Pre-operative nab-pacli and GEM was delivered safely and achieved an R0 resection rate clinically significantly higher than the mean of surgical series using similar pathology criteria. Our pre-operative regimen was delivered to 95% of patients, but in contrast post-operative CX was less achievable with only 60% commencing treatment. Neoadjuvant nab-pacli and GEM is an encouraging strategy to improve outcomes in resectable PC and merits testing in a randomised setting. Clinical trial information: ACTRN12611000848909.

4116 Poster Session (Board #227), Mon, 8:00 AM-11:30 AM

Randomized phase II study of S-1 and concurrent radiotherapy with versus without induction chemotherapy of gemcitabine for locally advanced pancreatic cancer (JCOG1106). *First Author: Akira Fukutomi, Divison of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: Most patients (pts) with locally advanced pancreatic cancer (LAPC) are treated with chemotherapy (CT) alone in Japan. Chemoradiotherapy (CRT) is also a treatment option, but the role of radiotherapy (RT) remains controversial. Recently, induction CT followed by CRT is recognized as one potentially promising strategy. The aim of this study is to evaluate the efficacy and safety of CRT with and without induction CT to determine which is more promising CRT strategy. **Methods:** LAPC pts with an ECOG PS of 0-1, aged 20-80, and adequate organ function were randomized to CRT (Arm A) or induction CT followed by CRT (Arm B). Pts in Arm A received RT (50.4 Gy/28 fr over 5.5 weeks) with concurrent S-1 (40 mg/m^2/dose, b.i.d. on the day of irradiation). Pts in Arm B received induction gemcitabine (GEM) (1,000 mg/m^2, iv, days 1, 8 and 15, every 4 weeks) for 12 weeks, and then, only pts with controlled disease received same CRT as Arm A. After CRT, GEM was continued until disease progression or unacceptable toxicity in both arms. Primary endpoint was overall survival (OS). The sample size was 100 to detect ≥10% difference in 1-year OS with a probability of at least 0.9. Arm B will be considered to be more promising if point estimate of hazard ratio (HR) of OS for Arm B to Arm A is smaller than 1.186. **Results:** From 12/2011 to 9/2013, 102 pts were randomized, but 2 pts were ineligible because of metastasis. Therefore, 100 pts (Arm A/B n=51/49) were evaluated in this analysis. 50 pts received CRT in Arm A, while 34 pts in Arm B. 1-year OS for Arm A/B were 66.7/69.3% (HR 1.16 [95%CI 0.71-1.89]; p=0.56), and 1-year PFS were 39.2/46.6% (HR 1.05 [0.68-1.61]; p=0.84). Incidences of grade 3/4 toxicities in Arm A/B were leukopenia 62/61%, neutropenia 54/57%, anemia 18/12%, thrombocytopenia 10/14%, anorexia 16/4%, fatigue 8/4%, nausea 8/2%, diarrhea 6/4%, gastroduodenal (GD) hemorrhage 8/6%, GD ulcer 6/4%, and biliary infection 20/27%. Two treatment-related deaths occurred in Arm A (pneumonitis, duodenal hemorrhage). **Conclusions:** Induction CT followed by CRT was considered more promising as the test arm for a subsequent phase III trial comparing with CT alone. Clinical trial information: 000006811.

4117 Poster Session (Board #228), Mon, 8:00 AM-11:30 AM

A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. *First Author: Aaron James Scott, University of Colorado Denver, Aurora, CO*

Background: Rigosertib (ON 01910.Na), a first-in-class Ras mimetic and small molecule inhibitor of multiple signaling pathways including polo-like kinase 1 (PLK1) and phosphoinositide 3-kinase (PI3K), has shown efficacy in preclinical pancreatic cancer models. In this study, rigosertib was assessed in combination with gemcitabine in patients with treatment-naïve metastatic pancreatic adenocarcinoma. **Methods:** Patients with metastatic adenocarcinoma of the pancreas were randomized in a 2:1 fashion to gemcitabine 1000 mg/m^2 weekly for 3 weeks of a 4-week cycle plus rigosertib 1800mg/m^2 via 2-hr continuous IV (CIV) infusions given twice weekly for 3 weeks of a 4-week cycle (RIG+GEM) versus gemcitabine 1000mg/m^2 weekly for 3 weeks in a 4-week cycle (GEM). **Results:** A total of 160 patients were enrolled globally and randomly assigned to RIG+GEM (106 patients) or GEM (54). The most common grade 3 or higher adverse events were neutropenia (8% in the RIG+GEM group vs. 6% in the GEM group), hyponatremia (17% vs. 4%), and anemia (8% vs. 4%). The primary outcome of the study, median overall survival (OS), was 6.1 months for RIG+GEM versus 6.4 months for GEM (hazard ratio (HR), 1.24; 95% confidence interval [CI], 0.85-1.81). The median progression-free survival (PFS) was 3.4 months for both groups (HR = 0.96; 95% CI, 0.68-1.36). The partial response rate by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 was 19% versus 13% for RIG+GEM versus GEM, respectively. Of 64 tumor samples sent for molecular analysis, 47 were adequate for multiplex genetic testing and 41 were positive for mutations. The majority of cases had *KRAS* gene mutations (40/47, 85%). Other mutations detected included *TP53* (13 cases) and *PIK3CA*(1 case). No correlation between mutational status and efficacy was detected. **Conclusions:** The combination of RIG+GEM failed to demonstrate an improvement in survival or response compared to GEM in metastatic pancreatic adenocarcinoma. Rigosertib had a similar safety profile to that observed in other trials of the IV formulation. Clinical trial information: NCT01360853.

4118 Poster Session (Board #229), Mon, 8:00 AM-11:30 AM

A phase Ib study of the anti-cancer stem cell agent demcizumab (DEM) & gemcitabine (GEM) +/- paclitaxel protein bound particles (nab-paclitaxel) in pts with pancreatic cancer. *First Author: Manuel Hidalgo, Centro Integral Oncológico Clara Campal, Madrid, Spain*

Background: Delta-like ligand 4 (DLL4) activates the Notch pathway. DEM is a humanized IgG_2anti-DLL4 antibody that inhibits tumor growth & decreases cancer stem cell frequency in human tumor xenograft models. In addition, DEM has an antiangiogenic effect & synergistic activity when combined with GEM & nab-paclitaxel in pt derived xenograft models of pancreatic cancer. **Methods:** Pts with 1st line pancreatic cancer were enrolled. Pts in cohorts 1-3 received DEM (2.5 every 2 or 4 wks or 5 mg/kg every 4 wks including 3 truncated pts) & GEM 1000 mg/m^2 7 of 8 wks, then 3 of 4 wks. Pts in cohorts 4, 5 & 6 received truncated DEM (2.5, 3.5 or 5 mg/kg every 2 wks through Day 70) & nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^{2}3 of 4 wks. The primary objective was to determine the MTD. Other objectives were safety, efficacy, immunogenicity, PK & biomarkers. **Results:** 47 pts were enrolled; 8, 8, 8, 6, 8 & 9 pts received 2.5 mg/kg every 2 wks, 2.5 mg/kg every 4 wks, 5 mg/kg every 4 wks, 2.5 mg/kg every 2 wks (truncated), 5 mg/kg every 2 wks (truncated) & 3.5 mg/kg every 2 wks (truncated), respectively. Related AEs in $>$ 20% of pts were fatigue (38%), nausea (34%), vomiting (28%), decreased appetite (21%), hypertension (21%) & diarrhea (21%). Hypertension was managed with anti-hypertensives. Increased BNP is an early indicator of the cardiac effects of DEM & mildly elevated values were used to initiate cardioprotective therapy with an ACE inhibitor or carvedilol. One pt who received 5 mg/kg continuously developed reversible pulmonary hypertension & heart failure on day 143. As a result, DEM was limited to 70 days in cohorts 4, 5 & 6. In cohorts 1-3, 4 of 16 (25%) pts had a PR & 7 had SD. In cohorts 4, 5 & 6, 9 of 22 (41%) pts had a PR & 10 had SD. The median PFS for 2.5 & 5 mg/kg every 4 wks & 2.5 mg/kg, 2.5 mg/kg (truncated), 3.5 (truncated) & 5 mg/kg (truncated) every 2 wks were 1.7, 7, 3.4, 9.1, not reached & not reached, respectively. **Conclusions:** This therapy was generally well tolerated with fatigue, nausea & vomiting being the most common related AEs. Encouraging clinical activity was observed. Biomarker analysis showed pharmacodynamic modulation of the Notch pathway. Final data will be presented. Clinical trial information: NCT01189929.

4119 Poster Session (Board #231), Mon, 8:00 AM-11:30 AM

SWOG S1115: Randomized phase II trial of selumetinib (AZD6244; ARRY 142886) hydrogen sulfate (NSC-748727) and MK-2206 (NSC-749607) vs. mFOLFOX in pretreated patients (Pts) with metastatic pancreatic cancer. *First Author: Vincent M. Chung, City of Hope, Duarte, CA*

Background: Over 90% of pancreatic cancers (PC) have mutant *KRAS* that is at present not druggable. Activating mutations lead to signaling through RAF/MEK/ERK and PI3K/AKT/mTOR pathways leading to cell growth, proliferation and survival. Pre-clinical data suggest that simultaneously blockade of these pathways is effective in treating *KRAS*mutant tumors. Our trial evaluated this novel, molecularly targeted treatment approach in pancreatic cancer versus mFOLFOX chemotherapy. **Methods:** 113 pts (PS 0-1) with metastatic PC failing gemcitabine-based therapy were randomized to MK-2206 135 mg weekly plus selumetinib 100 mg daily (MS) or mFOLFOX6 (without bolus 5FU) every 2 weeks. Overall survival (OS) was the primary endpoint with secondary objectives evaluating toxicities, objective tumor response and progression free survival (PFS). **Results:** Pt characteristics and results are in the table. 34 pts had grade 3 toxicities in the MS arm vs. 19 in the mFOLFOX arm. The most common grade 3 toxicities in the MS arm include rash, mucositis, dehydration and fatigue while for mFOLFOX arm, hematologic toxicities, fatigue, nausea and vomiting. In the MS arm vs. mFOLFOX, there were 0 vs 3 pts with a partial response and 8 vs 9 pts with stable disease, respectively. Shorter survival was observed in the MS arm (median OS 4.0 vs 7.5 mos, hazard ratio (HR) 1.46, 95% CI 0.90-2.38; median PFS 2 mos for each, HR 1.43, 95% CI 0.93-2.20). Approximately 50% of the patients on the mFOLFOX arm went on to receive additional therapy as compared to 30% on the MS arm. **Conclusions:** MS did not improve OS in pts who previously failed gemcitabine chemotherapy. Collected tissue will be analyzed for potential biomarkers. Clinical trial information: NCT01658943.

	mFOLFOX (n=60)		AZD-6244 + MK-2206 (n=53)	
AGE (median, years)	66.0			68.7
SEX				
Females	39	65%	23	43%
PERFORMANCE STATUS				
0	27	45%	22	42%
1	33	55%	31	58%
DURATION OF GEMCITABINE BASED THERAPY				
≤ 4 months	22	37%	20	38%
LIVER METASTASES				
Yes	39	65%	38	72%
NUMBER OFF PROTOCOL TREATMENT DUE TO:				
Adverse Event (AE)	6		13	
Refusal unrelated to AE	8		2	
Progression/relapse	37		36	
MEDIAN SURVIVAL (months)				
Progression-free	2.0		2.0	
Overall	7.5		4.0	

4120 Poster Session (Board #232), Mon, 8:00 AM-11:30 AM

Effectiveness and tolerability of maintenance capecitabine administrated to patients with metastatic pancreatic cancer treated with first line FOLFIRINOX. *First Author: Juliette Reure, Centre Antoine Lacassagne, Nice, France*

Background: Treating metastatic pancreatic cancer (MPC) remains a challenging issue. Significant improvement was achieved recently by combining 4 drugs with Folfirinox regimen at the cost of increased toxicities compared to Gemcitabine. Maintenance therapy is a growing concept used in many different types of cancer. Our retrospective analysis aims to evaluate effectiveness and tolerability of early maintenance capecitabine administrated to patients with MPC treated with first line Folfirinox. **Methods:** 103 patients treated for MPC between November 2009 and July 2014 were retrospectively identified. Among them, 31 patients initially treated with a minimum of 4 cycles of Folfirinox, without sign of progression, received maintenance therapy with capecitabine until progression. Upon first progression (PFS1), patients were retreated with Folfirinox until second progression (PFS2). Survival was estimated with Kaplan Meier method. **Results:** Median numbers of cycles achieved for Folfirinox and capecitabine were respectively 6 and 4.5. Initial median dose of capecitabine was 2000mg/m^2, we recorded dose reduction in 11 cases (35,4%), mostly due to cutaneous and digestive toxicities. Median overall survival (OS) was 19 months. Survival rates were 74% at 1 year (95% CI [0.59 to 0.91]) and 24% at 2 years (95% CI [0.12 to 0.47]). Median PFS1 was 11 months (95% CI [0.22 to 0.58]). 30 patients have relapsed during capecitabine treatment (96,7%). After disease progression, Folfirinox could be reintroduced in 14 cases. Other patients received FOLFIRI, Gemcitabine and Folfox due mainly to persistence of neuropathy and asthenia. Median PFS 2 was 16 months (95% CI [0.22 to 0.65]). **Conclusions:** Maintenance with capecitabine seems effective and safe without compromising Folfirinox efficacy and allows obtaining very promising overall and progression free survival. Role of maintenance therapy in MPC will soon be addressed in a French multicenter phaseII/III study. PANOPTIMOX/PRODIGE 35.

4121 Poster Session (Board #233), Mon, 8:00 AM-11:30 AM

A prospective, single-arm, phase I/II trial of RAS peptide vaccine TG01/GM-CSF and gemcitabine as adjuvant therapy for patients with resected pancreatic adenocarcinoma. *First Author: Daniel H. Palmer, University of Liverpool Cancer Research UK Centre, Liverpool, United Kingdom*

Background: TG01 targets oncogenic mutations in RAS genes that are present in 80-90% of pancreatic cancers. TG01 is a mixture of 7 RAS peptides and previously, as monotherapy in patients with pancreatic cancer, induced specific cellular immune responses in 100% of patients. This study evaluated safety and whether induced immune responses are maintained with standard adjuvant chemotherapy. **Methods:** Patients were eligible after an R0 or R1 pancreatic adenocarcinoma resection and expected to receive gemcitabine (1000 mg/m^2 for 3/4 weeks x 6 cycles) started within 12 weeks of surgery. For gemcitabine toxicity 5-FU/ leucovorin could be substituted. TG01 0.7 mg id was given on days 1, 3, 5, 8, 15, 22 and 2-weekly until end of chemotherapy, 4-weekly up to 1 year and 12-weekly thereafter. GM-CSF 0.03 mg id was given 15 minutes prior to TG01. TG01 was used for the DTH test. **Results:** 18 patients were included from 3 sites (Norway and UK). 6 patients are ongoing 3 to 50 weeks from the start of vaccinations. 5 patients were withdrawn due to recurrent disease, 1 for an unrelated death, 3 for related AEs and 2 for other reasons. 10 SAEs in 6 patients occurred; 3 related to gemcitabine (pulmonary infection and fever) and 2 related to TG01 (anaphylaxis) the others were unrelated to gemcitabine or GM-CSF/TG01. The main AEs related to GM-CSF/TG01 were local reactions in 4/18 patients (8 events), allergic reactions in 4/18 patients (6 events); one occurring before gemcitabine (Grade 1). Anaphylaxis only occurred after gemcitabine completion. Other adverse events were flu-like symptoms and single cases of fatigue, arthralgia, fever, nausea and vomiting. 14/16 patients (87.5%) had a positive DTH by week 11 persisting after gemcitabine and to date 7/8 patients (87.5%) generated positive T cell responses. **Conclusions:** TG01/ GM-CSF generated immune responses in 87.5% of patients with resected pancreatic cancer, these responses were maintained with chemotherapy and persisted with booster injections. The regimen was generally well tolerated although some late allergic reactions were seen. Clinical trial information: NCT02261714.

4122 Poster Session (Board #234), Mon, 8:00 AM-11:30 AM

DocOx (AIO-PK0106): A phase II trial with docetaxel and oxaliplatin as a second-line systemic therapy for patients with advanced and/or metastatic adenocarcinoma of the pancreas—Final results. *First Author: Thomas Jens Ettrich, Department of Internal Medicine I, University of Ulm, Ulm, Germany*

Background: Pancreatic ductal adenocarcinoma still remains a major cause of cancer related deaths in the western world. The current study was conducted to confirm the activity and feasibility of docetaxel/ oxaliplatin combination in 2nd-line treatment of advanced pancreatic ductal adenocarcinoma. **Methods:** Prospective single arm, non-randomized, multi-center, Simon's two stage phase II trial using docetaxel (75 mg/m2, 60 min, d 1) and oxaliplatin (80 mg/m2, 120 min, d 2) in 21-day cycles. Duration of the trial was scheduled up two 8 cycles. Primary endpoint was tumor response according to RECIST 1.0. Secondary endpoints were progression free survival, overall survival, safety/toxicity, QoL and clinical benefit. **Results:** Data represents the intention to treat analysis of 44 patients included between 2008 and 2012. The majority of patients received a gemcitabine based first-line chemotherapy (95.5%). The primary endpoint of tumor response was achieved in 15.9% (7 partial remissions, no complete remission), with a disease control rate of 48% after the first two treatment cycles. Median progression free survival was 7 weeks (CI 6-15.9 weeks) and overall survival 40 weeks (CI 20.4-56.4 weeks). No unexpected adverse events occured. The recorded AEs were mainly hematologic (neutropenia grade 3/4 63.6%, febrile neutropenia 4.6%), gastrointestinal (29.6% grade 3/4 AEs) and infectious (18.2% grade 3/4 AEs). **Conclusions:** In this single-arm 2nd-line trial for the treatment of advanced PDAC, the combination of docetaxel and oxaliplatin shows promising results comparable with other 2nd-line protocols such as OFF (oxaliplatin, 5-FU, leucovorin) or liposomal irinotecan (MM-398) plus 5-FU/leucovorin (NAPOLI 1-trial). Some patients seem to benefit particularly as indicated by long periods of treatment in this setting. Even after 8 cycles of treatment with DocOx, partial response was observed in 2 patients and stable disease in another 6 patients corresponding to a disease control rate of 18%. The toxicity profile was quite tolerable and comparable to other 2nd-line studies. Clinical trial information: NCT00690300 Clinical trial information: NCT00690300.

4123 Poster Session (Board #235), Mon, 8:00 AM-11:30 AM

Nab paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after failure of folfirinox: Results of an AGEO multicenter prospective cohort. *First Author: Alix Portal, Hopital Européen Georges Pompidou, Paris, France*

Background: Both Folfirinox and Nab-paclitaxel plus Gemcitabine showed a benefit in terms of survival in first-line treatment of metastatic pancreatic adenocarcinoma (MPA) when compared to gemcitabine. It could be of interest to use them consecutively, knowing that there is currently no standard for 2nd line treatments for MPA and that median Progression free survival (PFS) is consistently less than 4 months in this setting. The aim of this study was to evaluate the efficacy and tolerability of gemcitabine plus Nab-paclitaxel after Folfirinox failure in MPA. **Methods:** From February 2013 to July 2014, all consecutive patients (pts) from 12 French centers treated by Nab-paclitaxel plus Gemcitabine for a histologically proven MPA after failure of Folfirinox were prospectively recorded. Nab-paclitaxel plus Gemcitabine was delivered on days 1, 8, and 15 every 4 weeks, as previously reported, until disease progression, patient refusal or unacceptable toxicity **Results:** Nab-paclitaxel plus Gemcitabine was administered to 57 pts. They received a median number of 4 cycles (1–12). Disease control rate was 58% (n = 33) with a 18.5 % (n = 18) objective response rate (RECIST). Within the whole cohort, median overall survival (OS) was 8.8 months (95% CI: 6.2-9.7) and median PFS was 5.1 months (95% CI : 3.2-6.2). Since the start date of first line chemotherapy with Folfirinox, median OS was 18 months (95% CI: 16-21). No toxic death occured. Grade 3–4 toxicities were reported in 40% of patients and were neutropenia (12%), neurotoxicity (12%), asthenia (8%) and thrombocytopenia (8%). **Conclusions:** With median PFS and OS of respectively 5.1 and 8.8 months Nab-paclitaxel plus Gemcitabine seems promising with a manageable toxicity profile after folfirinox failure, in selected patients able to receive second line treatment for a MPA. These promising results have now to be confirmed in a phase III randomized trial.

4124 Poster Session (Board #236), Mon, 8:00 AM-11:30 AM

Multiplatform molecular profiling of pancreatic adenocarcinomas to identify BRCA1/2 mutations and PD-1/PD-L1 status with therapeutic implications. *First Author: Sherri Z. Millis, Caris Life Sciences, Phoenix, AZ*

Background: Pancreas adenocarcinoma (PAC) is a challenging disease with overall single digit 5-year survivorship. BRCA1 and BRCA2 germline mutations are associated with increased risk of PC. Recent retrospective studies have described response of BRCA patients to platinum agents and PARP inhibitors. Additionally, immune therapies targeting the programmed cell death pathway in other cancers have shown promise; evaluating the incidence of aberrations of these markers in PAC impact therapeutic decisions. **Methods:** 450 PAC's were evaluated at a commercial CLIA laboratory using a combination of sequencing (Sanger or next generation sequencing (NGS)) and protein expression (immunohistochemistry). BRCA1/2 mutations that could be germline or somatic, coincidence with other mutations identified in the tissue, and expression levels of PD-L1 and PD-1 tumor infiltrating lymphocytes (TIL's) were evaluated. **Results:** Mutations (MT) in BRCA1 and BRCA2 were identified in 5 and 17% percent of tissues, respectively. BRCA1 and BRCA2 MT had different rates of concurrence with other gene alterations, which was also different from the general PC population (table). Overexpression of PD-L1 and PD-1 TIL's were also identified in 7% and 37% of PAC cases, respectively. BRCA1 MT cases had a higher incidence of PD-1 TIL's, while BRCA2 MT cases had a higher percent of overexpressed PD-L1 than the overall population. **Conclusions:** The different frequencies of KRAS, TP53, PIK3CA and SMAD4 MT between the overall PAC population and BRCA MT populations may inform driver differences and may help select drugs and refine treatment decision making for certain patients. Evaluating the profiles of the BRCA MT populations with clinical outcomes will provide valuable insight into the clinical behavior in genomically defined subsets and may facilitate in developing rational combinations of targeted agents in PAC.

Biomarker MT	BRCA1 MT	BRCA2 MT	Overall PC Population
		% Coincidence	
APC	14	0	3
BRAF	0	0	1
KRAS	71	77	85
PIK3CA	14	0	3
SMAD4	0	10	16
TP53	43	60	59
PD-1	38	50	37
PD-L1	13	8	7

4125 Poster Session (Board #237), Mon, 8:00 AM-11:30 AM

A retrospective single institution review of 90 pancreatic adenosquamous cancer (PASC) patients (pts). *First Author: Jennifer Brooke Goldstein, The University of Texas MD Anderson Cancer Center, Medical Oncology Fellowship, Houston, TX*

Background: PASC is a rare and aggressive subset of pancreatic cancer. PASCs are more likely to have poorly differentiated histology and positive lymph nodes. No separate treatment guidelines exist for PASC, however platinum-based therapy (tx) is commonly used based on a few published case series. The molecular signature of PASC has been reported in small studies and mirrors that of pancreatic adenocarcinoma (PA), with genetic mutations commonly involving TP53, CDKN2A, KRAS and loss of SMAD4 and the recently reported UPF1. These genomic analyses have been limited to genes known to be important in PA. **Methods:** We retrospectively reviewed the medical records of pts with PASC that were seen at M.D. Anderson Cancer Center from 1990 to 2014. Pts were chosen based on a pathologic diagnosis of PASC either in the primary tumor or metastasis. Descriptive statistics and survival analysis were performed using Stata 13.1. **Results:** A total of 90 pts were identified as having PASC, 75 diagnosed from the primary tumor and 15 from a metastatic site. Median age was 65 years (40-86), 62% were male, and 67% had locally advanced or metastatic disease at presentation. The median overall survival (OS) was 8.8 mths [95%CI (6.8-10.3)]. Of 29 pts who underwent surgical resection, the median time to recurrence was 6.7 mths [95%CI (3.4-Not Estimable)]. First line platinum-based tx did not impact OS (HR 1.07, 95% CI 0.66-1.75, P=0.785). 6 pts had genomic testing performed. All 6 had mutations in codon 12 of KRAS (three G12D, two G12R, and one G12V), 4 had mutations in TP53, all at different loci. One pt had CDKN2A loss, while another had a point mutation in the gene. Additionally, 2 of 6 pts showed FGF 3 and 19 amplification. **Conclusions:** Our results demonstrate that PASC has a poor prognosis. Pts undergoing surgical resection are at a high risk for relapse and neoadjuvant tx may be utilized to stratify pts who would benefit from resection. Next generation sequencing of tumors show the classically described KRAS and TP53 mutations seen in PA, but a potentially novel amplification of FGF 3 and 19, which could play a role in tumorigenesis. Further molecular profiling may demonstrate potential targets for tx not traditionally seen in PA.

4126 Poster Session (Board #238), Mon, 8:00 AM-11:30 AM

A quantitative analysis of funding for pancreatic cancer research. *First Author: Andrew Eugene Hendifar, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Although pancreatic cancer is the fourth most common cause of cancer death, it only receives approximately 2.5% of federal dollars distributed by the NCI. Recognizing the need for research support, patient advocacy groups, private institutions, and public institutions are working together to correct this funding gap. **Methods:** The International Cancer Research Partnership (ICRP) is an alliance of governmental and charitable organizations funding regional, national and international cancer research. The ICRP maintains a database of grants and awards that its members have provided. We interrogated the ICRP database to review the number of grants and their monetary value for pancreatic cancer and liver cancer ($>$ 50% relevance) awarded from 2002 to 2012 in the United States. In addition, we received private funding data from the Pancreatic Cancer Action Network, Lustgarten Foundation, and the American Association for Cancer Research. We compared private and public funding for pancreatic cancer and then benchmarked against the funding for liver cancer. Wilcoxon-Mann-Whitney test was used to compare private and public funding from 2002 to 2012. **Results:** Between 2002 and 2012 total funding for pancreatic cancer has increased nearly ten-fold from $11 million (60 grants) to $92 million (347 grants). Private and charitable funding makes up 27% of the total funding and the mean difference per award (public minus private) has decreased from $139,425 to $6,396 ($p < 0.001$). Funding for liver cancer has also increased over this time period, from $10.5 million to $59.5 million; however, the contribution from private and charitable organizations is significantly less as compared to pancreatic cancer (13% vs 27% $p < 0.001$). **Conclusions:** Funding for pancreatic cancer has increased significantly from 2002-2012. Private and charitable contributions comprise an increasingly larger portion of these funds. As federal funding for research has become increasingly constrained, private and charitable organizations have assumed a growing role in the funding landscape and are helping fill the gap.

4127 Poster Session (Board #239), Mon, 8:00 AM-11:30 AM

Discovery of new potentially actionable mutations in pancreatic ductal adenocarcinoma by next generation sequencing. *First Author: Mariacristina Di Marco, "L & A Seràgnoli" Department of Hematology and Oncological Sciences, University of Bologna, Bologna, Italy*

Background: Advances in chemotherapy, represented by FOLFIRINOX and Gemcitabine plus Nab-paclitaxel regimens, have resulted in a modest outcome improvement and Gamcitabine-based chemotherapy remains the treatment of choice especially in metastatic disease. Therefore, there is an urgent need to develop accurate markers of pre-invasive pancreatic neoplasms in order to help disease diagnosis at an earlier stage and to apply the best treatment. We aimed to better understand PDAC biology and genomic alterations of invasive phenotype by whole genome sequencing (RNAseq and WES). **Methods:** We analyzed 27 PDAC samples together with their normal counterpart by HiScanSQ Illumina platform (15/27 by RNASeq and 12/27 by WES). All data were mapped with BWA on hg19, SNVs were called with either SNVMix2 (RNA-seq) or MuTect (WES) while Indels were called with GATK. All variants were filtered on dbSNP, 1000genomes and compared with Cosmic data base. Non-synonymous SNVs were analyzed with PROVEAN and SIFT to predict mutation effect on protein function. **Results:** Deleterious point mutations or Indels were found in *KRAS* (92%), *TP53* (63%), *SMAD4* (48%), and *CDKN2A* (52%) genes. Components of mTOR signaling pathway (*PTEN*, *MTOR*, *PIK3IP1*) were found mutated in 50% of patients with poor prognosis PDAC suggesting that mTOR signaling alterations might promote the development of metastatic PDACs. Furthermore, we found inactivating mutations in *PARP* and *ATM* genes (26%), that could confer sensitivity to DNA cross-linking agents and to poly(ADP-ribose) polymerase inhibitors. Moreover, it has been elsewhere reported that ATM mutant neoplasms may be more sensitive to PARP and protein DNA-PKcs inhibitors. **Conclusions:** Our results demonstrated that PDACs are tumors harboring an high number of mutations. Beyond conventional mutated genes, we identified shared mutations in mTOR signaling components as well as *PARP* and *ATM* genes. These are potentially targetable mutations. In particular, mTOR signaling inhibition is a promising strategy to increase the therapeutic efficacy of conventional chemotherapeutic drugs. In conclusion, our results provide novel insights into PDACs target therapy.

4128 Poster Session (Board #240), Mon, 8:00 AM-11:30 AM

Dendritic cells generated with PDL-1 checkpoint blockade for treatment of advanced pancreatic cancer. *First Author: Jan Nesselhut, Institut Fuer Tumortherapie, Duderstadt, Germany*

Background: The efficacy of immunotherapy with monocyte derived dendritic cells (MoDC) is controlled via immune checkpoints, among them the PD-1/PDL-1 pathway. PDL-1 expressed on DC delivers an inhibitory signal to T-cells upon binding to PD-1 expressed on activated T-cells. Blocking of PDL-1 on DC may lead to improved efficacy of DC therapy for pancreatic cancer. **Methods:** After isolating monocytes from peripheral blood of $n = 44$ patients with stage IV pancreatic cancer, who failed first-line chemotherapy, antigen primed MoDC were generated using standard protocols. Patients included in the follow-up analysis received a minimum of 3 vaccines. 10 patients received MoDC modified by PDL-1 blockade after failure of previous DC therapy. PDL-1 blockade was performed by adding soluble CD80 or anti-PDL-1 to MoDC. Cytokine release and T-cell activity were measured exemplary using a mixed lymphocyte culture (MLC). **Results:** Median survival after onset of DC-therapy was 8 months with MoDC alone (18 months after primary diagnosis) with longest follow up of 36 months (49 months after primary diagnosis). We could induce a secondary stabilisation (4 to 8 months) in 5 from 10 patients, who failed to respond to previous DC therapy by using MoDC modified by PDL-1 blockade. Cytokine measurement using MLC, which was exemplarily performed, shows a change in the cytokine release upon PDL-1 blockade. **Conclusions:** An effective immune response requires both the inhibition of inhibitory signals and the activation of an antigen specific T-cell response. The efficacy of dendritic-cell based therapy may be improved by blockade of PDL-1 on dendritic cells to avoid an inhibitory signal and thus improve the T-cell specific response. Further investigations are necessary to ascertain whether the combination of systemic anti PD1-therapy with DC therapy using MoDC modified with PDL-1 blockade may further enhance therapeutic efficacy in solid tumors.

4129 Poster Session (Board #241), Mon, 8:00 AM-11:30 AM

Targeting Sema3D in pancreatic cancer: A novel therapeutic strategy. *First Author: Adrian Murphy, The Sidney Kimmel Comprehensive Cancer Center Johns Hopkins, Baltimore, MD*

Background: Pancreatic ductal adenocarcinoma (PDA) is known for its chemotherapy resistance and dismal survival rates. Little is known about the mechanisms of metastasis in PDA. We identified Annexin A2 (AnxA2), an essential mediator of metastasis using sera from patients with prolonged survival after GVAX treatment. AnxA2 regulates secretion of semaphorin3D (Sema3D) promoting invasion and metastasis of PDA cells. Sema3D and other axon guidance genes have been shown to be the cellular pathways most frequently altered in PDA. **Methods:** KPC mice, which spontaneously develop PDA, were generated with KRAS/P53 mutations. KPCA$^{-/-}$ mice were created by crossing AnxA2 knockouts with KPC mice. Cell lines were developed from primary tumors of these mice and gene expression profiling performed comparing KPC and KPCA$^{-/-}$ cells. Sema3D secretion was measured from KPC and KPCA$^{-/-}$ cells by ELISA. Anti-AnxA2 antibodies were used to see the effect of AnxA2 inhibition on Sema3D secretion. Sema3D knockdown KPC cells were used in a hemi-spleen model of liver metastasis to evaluate metastasis *in vivo*. Immunohistochemistry (IHC) was used to analyze Sema3D expression in resected human PDA tissue. **Results:** While PDA tumors spontaneously developed in both KPC and KPCA$^{-/-}$ mice, metastases were only seen in KPC (16/17) but not in KPCA$^{-/-}$ mice (0/23). Sema3D expression was down-regulated in KPCA$^{-/-}$ cells compared to KPC cells and Sema3D secretion was significantly lower from KPCA$^{-/-}$ cells (0.25 ng/ml) than KPC cells (17.5 ng/ml) ($p = 0.01$). Antibody blockade of AnxA2 suppressed Sema3D secretion in KPC cells suggesting its role in Sema3D secretion. Animals injected with KPC cells transfected with Sema3D-targeting shRNA had fewer metastases (5/13) and longer survival than mice injected with control (11/12) ($p = 0.01$). IHC on human PDA tumors showed that 15/20 patients with DFS < 1 year abundantly expressed Sema3D. Sema3D secretion can be measured in 96 well plates after 24 hours of incubation and this platform is optimized for drug testing. **Conclusions:** Sema3D secretion, which is regulated by AnxA2, is crucial for PDA metastasis. Targeting this pathway may lead to increased therapeutic options in PDA. We have established a platform to detect drugs that reduce Sema3D secretion.

TPS4131 Poster Session (Board #243a), Mon, 8:00 AM-11:30 AM

A randomized, double-blind, placebo-controlled phase III study of cisplatin plus a fluoropyrimidine with or without ramucirumab as first-line therapy in patients with metastatic gastric or gastroesophogeal junction (GEJ) adenocarcinoma (RAINFALL, NCT02314117). *First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA*

Background: Ramucirumab, a human IgG1 monoclonal antibody directed to the ectodomain of VEGFR-2, prevents ligand binding to the receptor, blocking activation of downstream receptor-mediated pathways. Ramucirumab has demonstrated significant improvement in overall survival (OS) and progression-free survival (PFS) in 2 phase III registration studies (REGARD, RAINBOW) in patients in second-line treatment of gastric cancer. This global phase III trial will compare PFS in patients with HER2-negative, metastatic gastric or GEJ adenocarcinoma receiving ramucirumab with cisplatin/capecitabine (or 5-FU) versus placebo with cisplatin/capecitabine (or 5-FU) as first-line treatment. The trial is conducted in 139 sites in the Americas, Europe and Japan and is currently open to enrollment. **Methods:** Eligible patients will be randomized to receive a higher dose of ramucirumab (8mg/kg on days 1 and 8, based upon population pharmacokinetic modelling) or placebo with cisplatin/capecitabine every 21-day cycle until disease progression, unacceptable toxicity, or other withdrawal criteria are met. The primary endpoint is PFS; OS is the key secondary endpoint. Efficacy will be considered at 3 analysis points: futility analysis for PFS, primary analysis of PFS & final analysis of OS. A gatekeeping strategy will be used to assess PFS and OS. The OS endpoint will only be tested if the PFS test is significant to control Type I error at 5% across both endpoints. An exposure/safety analysis will be done after 30 patients in each cycle have started the 3rd cycle. The study has over 90% power to demonstrate a PFS advantage assuming HR = 0.70 and 80% power to demonstrate an OS advantage assuming HR = 0.77. Other secondary endpoints include PFS2 (the time from randomization to disease progression after the start of additional systemic anticancer treatment, or death from any cause, whichever occurs first), objective response rate, safety and quality of life. As of 1/28/2015, one patient has been enrolled in the US. Clinical trial information: NCT02314117.

TPS4132 Poster Session (Board #243b), Mon, 8:00 AM-11:30 AM

Perioperative chemotherapy and cytoreductive surgery with versus without HIPEC in gastric cancer with limited peritoneal metastases: A randomized phase III study (GASTRIPEC). *First Author: Beate Rau, Charite Campus Mitte University of Berlin, Berlin, Germany*

Background: Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) can improve prognosis of patients with peritoneal metastases (PM) in colorectal cancer. In gastric cancer (GC) patients with PM this concept is under debate. Perioperative chemotherapy has been shown to improve survival in gastric cancer. In patients with limited PM systemic chemotherapy, a palliative gastrectomy and CRS may prolong survival compared to chemotherapy alone (Sun) in selected patients. It is unclear whether HIPEC has an additional benefit in this setting. The GASTRIPEC trial (NCT02158988) will clarify the role of HIPEC. **Methods:** It is an open label, multicenter randomized phase III trial. 180 patients with histological proven GC or GE-junction and PM will be included. All patients will receive 3 cycles of pre- and postoperative chemotherapy, dependent on the HER 2 status (Her 2 + ve: cisplatin, capecitabine, trastuzumab (CCT); HER 2 –ve: epirubicin, oxaliplatin, capecitabine (EOX). All patients will receive gastrectomy and peritonectomy. Patients randomized into **group B will be treated with additional intraoperative HIPEC** with Mitomycin C and Cisplatin for 60 minutes at 41-43°C. Main inclusion criteria: Histological proven PM in GC including adenocarcinoma of the GE-junction, no evidence of distant metastases in CT scan chest and abdomen other than PM (exception of Krukenberg tumors), estimation of peritoneal cancer index via staging laparoscopy or laparotomy, possibility of 80% tumor reduction at CRS, Karnofsky Index $>$ 70%, written informed consent. We hypothesize a hazard ratio for overall survival as the primary endpoint of 0.65 (9 months in None-HIPEC versus 13.8 months in HIPEC arm). With an alpha error of 0.05 and a power of 80 percent 180 patients need to be enrolled. Secondary endpoints are 30 days complication-rate, time to progression, quality of life, toxicity, adverse events. 18 patients are included since March 2014. Conclusion**:** The GASTRIPEC trial may help to clarify the role of HIPEC in addition to systemic chemotherapy, gastrectomy and CRS in GC patients with limited PM. Clinical trial information: NCT02158988.

TPS4133 Poster Session (Board #244a), Mon, 8:00 AM-11:30 AM

Perioperative chemotherapy vs. adjuvant chemotherapy for potentially resectable gastric cancer: A randomized and multicenter phase III study in locally advanced gastric cancer with D2 dissection. *First Author: Qun Zhao, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China*

Background: The MAGIC and ACTS-GC/CLASSIC trials demonstrated benefit in resectable gastric cancer from both perioperative and postoperative adjuvant chemotherapy, although such management remains controversial for locally advanced gastric cancer (LAGC) after D2 lymph node dissection. **Methods:** A Phase III 1:1:1 randomized, open label, multicenter, trial comparing adjuvant (Arm A) or perioperative SOX (Arm B), and perioperative XELOX (Arm C) was initiated in February 2012, in T3/4, node+ gastric cancer patients after R0 resection. SOX included S-1 40 mg/m2 bid day 1-14, Oxaliplatin 130 mg/m2 on day 1, XELOX included Capecitabine 1000 mg/m2 bid day1-14, plus Oxaliplatin 130 mg/m2 on day, each cycle was 3 weeks, each patient received 8 cycles. Arm B and C patients received 2 cycles prior to surgery, and 6 cycles post op. Patients were stratified by tumor stage, ECOG PS and institution. The study was powered to show superiority of perioperative over adjuvant SOX, and non-inferiority of SOX to XELOX. Eligibility included histologically proven gastric cancer (including gastroesophageal junction), age 18-75, D2 or more extensive surgery with no residual disease, ECOG score ≤ 2, and no distant metastasis. Primary endpoint was R0-resection rate, secondary endpoints included overall survival, disease–free survival, safety. Up until January 2015, 638 subjects from 7 centers have been enrolled. Hematological toxicities included neutropenia, anemia, and thrombocytopenia. Non-hematological toxicities included fatigue, abnormal hepatic/renal function, neurotoxicity, and skin pigmentation, most adverse events were tolerable. No treatment related death was observed. Updated safety data will be presented. This study was registered with Clinicaltrials.gov, NCT01516944. Clinical trial information: NCT01516944.

TPS4134 Poster Session (Board #244b), Mon, 8:00 AM-11:30 AM

The Nationwide Cancer Genome Screening Projects for Gastrointestinal Cancer in Japan (SCRUM-Japan GI-SCREEN): Efficient identification of actionable cancer genome alterations in advanced colorectal and non-colorectal gastrointestinal cancer (GI Screen 2013-01-CRC and 2015-01-Non CRC). *First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Several cancer genome alterations have been identified as important targets for treatment. Example of possible candidates in gastrointestinal (GI) cancer include *BRAF* mutations in colorectal cancer (CRC) or MET amplification in gastric cancer, for which corresponding targeting agents showed attractive activity in early phase clinical trials. Efficient screening systems for these relatively minor cancer genome alterations are necessary for the successful development of targeted therapies. We initiated a nationwide screening project in Japan (GI-SCREEN) in February 2014 to detect rare mutations from CRC (GI-SCREEN 2013-01-CRC). The patient's population will be expanded to non-CRC GI cancer (SCRUM-Japan GI-SCREEN 2015-01-Non CRC). The objective of these consecutive projects is to evaluate the frequency of oncogenic genome alterations in advanced GI cancers and to facilitate the enrollment of patients in IND registration trials for targeted therapies as well as optimal individualized treatment. **Methods:** These prospective observational studies are designed to enroll patients with CRC or non-CRC GI cancer (gastric, esophageal, small-intestinal, appendiceal, anal carcinomas and neuroendocrine carcinoma) who are planned to receive systemic chemotherapy. Tumor samples from surgical or biopsy specimens have been examined by Luminex technology so far. Starting from February 2015, it will be redesigned to analyze more than 140 kinds of alterations in cancer genome, which included mutations, copy number variations, and gens fusions, using next generation sequencing of the Oncomine Cancer Research Panel (OCP) at a quality-controlled central laboratory. Patient characteristics and treatment outcome are also planned to be collected. The targeted sample size is 2000 patients with CRC and 1000 patients with non-CRC. As of January 26, 2015, a total of 844 CRC patients were enrolled and non-CRC study will be opened in April 2015 with planned participation of 18 major cancer centers in Japan. Clinical trial information: UMIN000016344.

TPS4135 Poster Session (Board #245a), Mon, 8:00 AM-11:30 AM

Multicohort phase II KEYNOTE-059 study of pembrolizumab (MK-3475) for recurrent or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. *First Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA*

Background: Many tumors suppress immune control via the programmed death receptor 1 (PD-1) pathway. Pembrolizumab is an anti–PD-1 monoclonal antibody designed to block the interaction of PD-1 with its ligands PD-L1 and PD-L2. In 39 patients (pts) with PD-L1–positive metastatic gastric cancer enrolled in the phase I KEYNOTE-012 trial, 67% of whom had $\geq$ 2 prior lines of therapy, pembrolizumab 10 mg/kg every 2 wk (Q2W) provided a 22% confirmed ORR (RECIST v1.1, central review) and an acceptable safety profile. KEYNOTE-59 (NCT02335411) is an ongoing, international, 3-cohort, phase II study designed to further assess pembrolizumab in pts with gastric cancer. **Methods:** All cohorts of KEYNOTE-059 will enroll pts with recurrent or metastatic gastric or GEJ adenocarcinoma, $\geq$ 1 measurable lesion, and ECOG PS 0 or 1. All pts must provide a newly collected (preferred) or archival tumor biopsy sample for immunohistochemical determination of PD-L1 expression at a central laboratory. In cohort 1, up to 180 pts with any PD-L1 status who progressed on $\geq$ 2 prior chemotherapy regimens that included a fluoropyrimidine and platinum doublet and, if $HER2^+$, trastuzumab, will receive pembrolizumab 200 mg Q3W. In cohort 2, approximately 20 non-Asian and 20 Asian treatment-naive, $HER2^-$ pts with any PD-L1 status will receive pembrolizumab 200 mg Q3W plus infusional 5-FU or capecitabine and 6 cycles of cisplatin. In cohort 3, approximately 50 treatment-naive, $HER2^-$ pts with PD-L1–positive tumors will receive pembrolizumab 200 mg Q3W. In all cohorts, pembrolizumab will be given for 24 mo or until disease progression, intolerable toxicity, or investigator decision; treatment may be discontinued for complete response. Eligible pts may continue pembrolizumab beyond initial RECIST-defined progression. AEs will be monitored. Response will be assessed at wk 9 and every 6 wk thereafter per RECIST v1.1 and RECIST adapted to account for response patterns observed with immunotherapies. Primary end point is ORR per RECIST v1.1 by central review; secondary end points include PFS, OS, disease control rate, and duration of response. KEYNOTE-059 enrollment began in February 2015. Clinical trial information: NCT02335411.

TPS4136 Poster Session (Board #245b), Mon, 8:00 AM-11:30 AM

A randomized phase III study of neoadjuvant chemotherapy with docetaxel(D), oxaliplatin(O), and S-1(S) (DOS) followed by surgery and adjuvant S-1 vs. surgery and adjuvant S-1 for resectable advanced gastric cancer (PRODIGY). *First Author: Yoon-Koo Kang, Department of Oncology, Asan Medical Center, Seoul, South Korea*

Background: Although adjuvant chemotherapy with S-1 is now considered a standard after D2 resection in stage II or III locally advanced gastric cancer (LAGC) in Asia, many patients still experience recurrence of disease. Addition of neoadjuvant chemotherapy can be one method to further improve outcomes in LAGC. A previous phase II study of neoadjuvant DOS triplet regimen followed by surgery and adjuvant S-1 in LAGC demonstrated promising outcome with 98% of R0 resection rate, 90% of 2-year disease-free survival and manageable toxicity (Park et al, Cancer Chemother Pharmacol. 2013;72:815). On this background, a phase III randomized study has been initiated. **Methods:** Since Jan 2012, patients with newly diagnosed resectable gastric or gastroesophageal junction(GEJ) adenocarcinoma at clinical stage T2,3/N(+) or T4/N(any) by AJCC 7th edition have been recruited. Key exclusion criteria are Eastern Cooperative Oncology Group (ECOG) performance status $\geq$ 2, history of any malignancy other than gastric or GEJ cancer, or patients who have difficulties in oral ingestion/digestion/absorption. Patients are randomized 1:1 in open label to neoadjuvant DOS chemotherapy, surgery and then adjuvant chemotherapy (CSC) arm vs surgery and chemotherapy (SC) arm. Neoadjuvant DOS regimen consists of D 50mg/m^2 i.v. on day 1, O 100mg/m^2 i.v. on day 1 and S 40mg/m^2 twice orally on days 1-14 every 3 weeks for 3 cycles. Surgical method is D2 dissection. Adjuvant chemotherapy is S 40mg/m^2 twice orally on days 1-28 every 6 weeks for 8 cycles. Primary endpoint is 3 year progression free survival (PFS). Secondary endpoints include overall survival (OS), pathologic stage, R0 resection rate and safety profiles compared in two arms. With power of 80% and two-sided α- level of 5%, 244 events are required to detect 70% of 3 year PFS in CSC arm compared to 60% in SC arm (HR = 0.698). Considering 10% of drop-out rate, target enrollment is 530 subjects from 17 sites in Korea until July 2016. The first Independent Data Monitoring Committee meeting was held in October 2014 and the committee recommended continuing the study as planned. NCT01515748 Clinical trial information: NCT01515748.

TPS4137 Poster Session (Board #246a), Mon, 8:00 AM-11:30 AM

A randomized phase III study of adjuvant capecitabine vs observation in curatively resected stage IB (by AJCC 6th edition) gastric cancer (CATALYSIS; KCSG ST14-05). *First Author: Min-Hee Ryu, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: In stage I (by AJCC 6thedition) gastric cancer (GC), recurrence rate is generally low, and long-term outcomes are considered very good after curative resection. For this reason, only limited number of stage I GC patients (pts) were included in most previous studies of adjuvant treatment, and no stage I GC pts were included in ACTS-GC and CLASSIC trials which compared adjuvant chemotherapy vs observation after D2 dissection. However, a large scale retrospective study (Park et al, Gastric Cancer. 2015 Jan 23 [Epub ahead]) demonstrated that pts with stage IB GC with other risk factors showed high recurrence rate more than 20%. Considering more than 30% risk reduction of recurrence by adjuvant chemotherapy in stage II GC, stage I GC pts at high risk of recurrence may also get benefit from adjuvant chemotherapy. Moreover, in Korea, more than 50% of GC pts have stage I disease, which is increasing due to nationwide screening program. Based on this background, a phase III randomized study has been initiated and here we present the progress. **Methods:** Since November 2013, pts with curatively resected gastric or gastroesophageal junction adenocarcinoma at stage IB have been recruited from 12 sites in Korean Cancer Study Group (KCSG). Other key eligibility criteria include ECOG performance status 0-2, age of 18-74 years, at least one more other risk factors for recurrence-free survival (RFS) (i.e., age $\geq$ 65 years, male gender, lymphovascular invasion, and/or perineural invasion). Three to 6 weeks after curative surgery (D1 beta or D2 dissection), pts are randomized 1:1 in open label to adjuvant capecitabine arm vs observation arm. In adjuvant chemotherapy arm, pts receive capecitabine 1,250 mg/m^2 p.o. twice daily on days1-14 every 3 weeks for 8 cycles. Primary endpoint is 5-year RFS rate. Secondary endpoints include overall survival, safety, compliance, and pharmacokinetic study of capecitabine. With power of 80% and two-sided α level of 5%, 174 events are required to detect 7% difference in 5-year RFS rate, i.e., 85% in adjuvant capecitabine arm vs. 78% in observation arm (HR = 0.654). Considering 10% of drop-out rate, target enrollment is 870 subjects. NCT01917552 Clinical trial information: NCT01917552.

TPS4138 Poster Session (Board #246b), Mon, 8:00 AM-11:30 AM

A phase III study to compare efficacy and safety of DHP107 (oral paclitaxel) versus IV paclitaxel in patients with metastatic or recurrent gastric cancer after failure of first-line chemotherapy (DREAM). *First Author: Sang Cheul Oh, Korea University Guro Hospital, Seoul, South Korea*

Background: Paclitaxel is an antineoplastic agent widely used for treating cancer patients. However, only IV paclitaxel is available on the market. DHP107, a novel oral formulation, is composed of edible oils. Also, it is able to safely and effectively absorb paclitaxel to body via intestine without concomitant use of P-glycoprotein inhibitors. In the first-in-human study, DHP107 showed no dose limiting toxicity (DLT) at a single dose-escalating schedule and was considered safe and feasible in patients with advanced malignancies. In a phase I-IIa study which included advanced gastric cancer or metastatic solid tumors, the recommended dose (RD) of DHP107 was determined as 200mg/m^2 bid on days 1, 8, 15 at 4-weekly interval. In the study, the pharmacokinetic profiles of DHP107 were similar to IV paclitaxel, and 3 out of 10 gastric cancer patients who failed first-line chemotherapy showed partial response at the RD. Based on this background, a phase III randomized study has been initiated in gastric cancer and the progress is presenting here. **Methods:** Since April 2013, patients with metastatic or recurrent gastric cancer in second-line setting have been enrolled. Patients are randomized as 1:1 in open label to Arm A (DHP107) vs Arm B (IV paclitaxel). Arm A regimen consists of 200mg/m^2 po bid on day 1, 8, 15, every 4 weeks. In arm B, paclitaxel 175mg/m^2 was infused on day 1, every 3 weeks. Key inclusion criteria are ECOG performance status $\leq$ 2, failure of first-line chemotherapy including fluoropyrimidine and/or platinum, at least 1 measurable lesion by RECIST version 1.1. Response evaluation is performed every 6 ($\pm$1) weeks. Primary endpoint is progression free survival (PFS). Secondary endpoints include overall response rate, overall survival and safety. With power of 80% and one-sided type I error rate of 2.5%, 204 events are required to observe non-inferiority of DHP107 compared with IV paclitaxel in PFS. With 10% of drop-out rate, target enrollment is 238 subjects from 12 sites in Korea. For the efficacy analysis, test for non-inferiority will be performed sequentially, first with non-inferiority margin of 1.48, and then 1.25. Clinical trial information: NCT01839773.

TPS4139 Poster Session (Board #247a), Mon, 8:00 AM-11:30 AM

The BRIGHTER trial: A phase III randomized double-blind study of BBI608 + weekly paclitaxel versus placebo (PBO) + weekly paclitaxel in patients (pts) with pretreated advanced gastric and gastro-esophageal junction (GEJ) adenocarcinoma. *First Author: Manish A. Shah, Weill Cornell Medical College, New York, NY*

Background: BBI608 is an orally-administered first-in-class cancer stemness inhibitor. By targeting Stat3, BBI608 blocks cancer stem cell (CSC) self-renewal and survival through suppressing stemness pathways, including Stat3, β-catenin as well as immune checkpoint gene expression. Potent anti-tumor and anti-metastatic activity was observed in preclinical models, with marked synergy between BBI608 and paclitaxel. Moreover, cancer stemness genes, such as Stat3 and β-catenin, two poor prognostic biomarkers in many cancer types, predict sensitivity to BBI608. Encouraging anticancer activity in refractory gastric and GEJ adenocarcinoma was observed in a phase Ib (Stephenson et al, ASCO 2014 abstr) and a subsequent phase II study including 39 gastric or GEJ adenocarcinoma pts. On the basis of these data, a phase III trial is being conducted in North America, South America, Europe, Australia, and Asia. **Methods:** This study (ClinicalTrials.gov NCT02178956) will assess the efficacy of BBI608+paclitaxel *vs* PBO+paclitaxel in pts with pre-treated, advanced gastric and GEJ adenocarcinoma (target n=680). Pts must have failed one prior line of therapy containing a fluoropyrimidine/platinum doublet for unresectable disease. Pts are randomized in a 1:1 ratio to receive BBI608 480 mg or PBO twice daily continuously plus paclitaxel 80 mg/m^2 IV, weekly, for 3 of every 4 weeks. Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Primary endpoint is overall survival (OS) in the general study population; secondary endpoints include progression free survival (PFS), OS and PFS in a predefined biomarker (β-catenin)-positive sub-population, objective response rate, disease control rate, and safety. In addition, blood, plasma, and archival tissue will be assessed for pharmacokinetic and biomarker analyses and quality of life will be measured. As of January 2015, 28 pts were randomized and recruitment is ongoing. Clinical trial information: NCT02178956.

TPS4140 Poster Session (Board #247b), Mon, 8:00 AM-11:30 AM

Adjuvant chemotherapy with gemcitabine and cisplatin compared to observation after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1): A randomized, multidisciplinary, multinational phase III trial. *First Author: Alexander Stein, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany*

Background: Despite complete resection, disease free survival (DFS) and overall survival (OS) of patients with cholangiocarcinoma (CCA) or muscle invasive gallbladder carcinoma (GBCA) is poor. Thus, evaluation of adjuvant chemotherapy (CTx) in biliary tract cancer (BTC) in a large randomized trial is warranted. **Methods:** ACTICCA-1 is a phase III investigator initiated trial (EudraCT No 2012–005078-70). With respect to ABC-02 trial, cisplatin and gemcitabine for 24 weeks were selected as investigational treatment. Based on adjuvant trials in pancreatic cancer with a comparable postoperative recovery time, inclusion of patients within a maximum interval of 16 weeks between surgery and start of CTx was chosen. Due to the different prognosis and treatment susceptibility of gallbladder carcinoma, two separate cohorts for CCA and GBCA were included. Randomization will be stratified for lymph node status for both cohorts and localization for CCA. The primary endpoint is DFS and secondary endpoints include OS, safety, tolerability and quality of life. For CCA, DFS 24 months post surgery (DFSR@24) is expected to be 40% without CTx. CTx should increase DFS@24 to 55% to be regarded as clinically relevant. With a power of 80% and a significance level of 5%, 271 evaluable study patients have to be followed for 24-28 months to observe 166 events. For GBCA, adjuvant CTx should increase DFSR@24 from 35% to 55% to be relevant; thus, 154 evaluable patients and 90 events are needed. In both cohorts, randomization will be 1:1 with adjuvant CTx for 24 weeks and imaging every 12 weeks. The ACTICCA-1 trial has been started in Germany (funded by the Deutsche Krebshilfe and supported by medac) in 2014 and recently in the Netherlands (funded by the Dutch Cancer Society and supported by medac). Furthermore, Australia, Denmark and the United Kingdom (funded by Cancer Research UK) will particpate within the next months. **Conclusion:** The randomized, multinational, multidisciplinary phase III ACTICCA-1 trial will establish the role of adjuvant gemcitabine and cisplatin in patients with BTC. Clinical trial information: NCT02170090.

TPS4141 Poster Session (Board #248a), Mon, 8:00 AM-11:30 AM

Randomised phase III study of gemcitabine, cisplatin plus S-1 (GCS) compared with gemcitabine plus cisplatin (GC) for unresectable or recurrent biliary tract cancer (KHBO1401-MITSUBA). *First Author: Tatsuya Ioka, Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan*

Background: Gemcitabine plus cisplatin (GC) therapy has been the standard palliative chemotherapy for patients with advanced biliary tract cancer (BTC). Our previous KHBO1002 trial, a single-arm phase II study of GC plus S-1 combination therapy (GCS), demonstrated a favorable survival benefit in BTC patients (Kanai M, et al. Cancer Chemother. Pharmacol. (2015) 75, 293-300). This phase III study aims to confirm the superiority of GCS to GC in terms of overall survival in patients with recurrent or unresectable BTC. **Methods:** Eligibility criteria include chemotherapy-naïve patients with recurrent or unresectable biliary tract adenocarcinoma (gallbladder, intrahepatic biliary tract, extrahepatic biliary tract, or ampulla of Vater), an Eastern Cooperative Oncology Group performance status of 0–2, and adequate organ function. Eligible patients are randomized into either GCS arm or GC arm. In the GCS arm, gemcitabine and cisplatin were administered intravenously at doses of 1,000 or 25 mg/m (2), respectively, on day 1, and oral S-1 was administered daily at a dose of 80 mg/m (2) on days 1-7 every 2 weeks. In the GC arm, 1000 mg/m2 of gemcitabine and 25 mg/m2 of cisplatin are infused on days 1 and 8 and repeated every 3 weeks. The primary endpoint is overall survival and the secondary endpoints are progression-free survival, %response rate, %planned dose, adverse events. The sample size was calculated to be 220 (110 patients per arm), assumed median survival time of 11.2 months in GC and of 16.2 months in GCS, an accrual period of 4 years, and a follow-up period of 1 year. Forty-nine institutions are participating in this study (NCT02182778□AUMIN 000014371). The study was activated in August 2014. Clinical trial information: NCT02182778.

TPS4142 Poster Session (Board #248b), Mon, 8:00 AM-11:30 AM

SWOG S1310: Randomized phase II trial of single agent MEK inhibitor trametinib vs. 5-fluorouracil or capecitabine in refractory advanced biliary cancer. *First Author: Richard D. Kim, Moffitt Cancer Center, Tampa, FL*

Background: No standard treatment options are available for patients with advanced biliary cancer (BC) who fail gemcitabine/platinum based regimen. The most commonly used second line regimens are 5-fluorouracil (5-FU) with leucovorin (LV), or capecitabine based on limited data. Trametinib is an orally bioavailable, potent, and specific allosteric inhibitor of MEK1/2. In cell lines, increased sensitivity to trametinib was observed especially in cells with mutations in the MAPK pathway. Aberrant activation of the Ras/Raf/MAPK pathway occurs in more than 60% of BC indicating the importance of these pathways. Furthermore other MEK inhibitors have been studied in advanced BC demonstrating promising results including complete responses (Bekkai-Saab et al JCO 2012, Finn RS GI ASCO 2011) **Methods: :** An open label phase II trial was designed to randomly assign patients to receive trametinib (2.0mg daily) versus 5-FU (400 mg/m^2 bolus and 2400 mg/m^2 infusion over 48 hours) with LV(400 mg/m^2) every 2 weeks or capecitabine (1000 mg/m^2 BID 14 days on 7 days off) in refractory BC. Eligible patients must have histologically or cytologically documented BC (excluding ampullary cancer) following progression of first line chemotherapy. The primary endpoint is overall survival. Secondary endpoints include progression-free survival and overall response rate. Additional endpoints will assess a 16 gene expression signature as a biomarker of MEK efficacy and to measure inflammatory cytokines. MRI or CT scan will also be obtained for all patients at the time of study entry and at 6 weeks into treatment to estimate lean soft tissue and fat mass weight gain according to treatment with trametinib. Analysis will compare randomized groups, stratified by 5FU/LV versus capecitabine and cholangiocarcinoma versus gall bladder. Assuming a one-sided type 1 error of 10%, 80% power, and 2 years of accrual with an additional year of follow-up, approximately 80 eligible patients (40 per arm) are needed to detect an improvement in median OS from 5 months to 8.25 months (corresponding to a 1.65 hazard ratio). As of Jan 2015, 33 of the planned 89 patients have been randomized. Clinical trial information: NCT 02042443.

TPS4143 Poster Session (Board #249a), Mon, 8:00 AM-11:30 AM

Randomized phase III study of etoposide plus cisplatin versus irinotecan plus cisplatin in advanced neuroendocrine carcinoma of the digestive system: A Japan Clinical Oncology Group study (JCOG1213). *First Author: Chigusa Morizane, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: According to the World Health Organization grading system for neuroendocrine neoplasms, neuroendocrine carcinoma (NEC) is a poorly differentiated, high-grade malignant tumor, including small and large cell carcinoma. The primary sites of NEC vary, and NEC arising in the digestive system accounts for 20%–68% of extra-pulmonary NEC. Treatment guidelines for advanced extra-pulmonary NEC recommend platinum-based chemotherapy regimens, which are suitable for small-cell lung carcinoma. We previously reported that etoposide plus cisplatin (EP) and irinotecan plus cisplatin (IP) are commonly used as community standard regimens for NEC of the digestive system in Japan (Yamaguchi et al. Cancer Sci. 2014;105(9)). However, no randomized controlled trial has ever been conducted, and it is unknown which is more effective. This phase III study compares EP and IP in terms of overall survival for patients with recurrent or unresectable NEC of the digestive system. **Methods:** Eligibility criteria include chemotherapy-naïve patients with recurrent or unresectable, histologically or cytologically confirmed NEC of the digestive system, an ECOG PS of 0-1, age of 20–75 years, and no history of platinum agents. Eligible patients are randomized into the EP arm or the IP arm. In the EP arm, 100 mg/m^2 of etoposide on days 1, 2, and 3 and 80 mg/m^2 of cisplatin on day 1 are infused every 3 weeks. In the IP arm, 60 mg/m^2 of irinotecan on days 1, 8, and 15 and 60 mg/m^2 of cisplatin on day 1 are infused every 4 weeks. The primary endpoint is overall survival. Due to scarcity of this disease, we set the sample size to be 140 (70 patients per arm), based on the assumption of median survival time (MST) of 8 months by the inferior regimen and 12 months by the superior regimen (6 years accrual, 1 year follow-up), with a two-sided alpha of 10%, a power of $\geq$ 70%. Seventy-eight institutions belonging to JCOG are participating in this study (UMIN000014795). This study was activated in Aug 2014 and the current enrollment is 17 as of Jan 2015. Clinical trial information: UMIN000014795.

TPS4144 Poster Session (Board #250a), Mon, 8:00 AM-11:30 AM

A randomized phase II trial of epigenetic therapy following adjuvant treatment in patients with resected pancreatic cancer and high risk for recurrence. *First Author: Kim Anna Reiss, Johns Hopkins Univ, Batimore, MD*

Background: Pancreatic ductal adenocarcinoma (PDAC) has the highest disease specific mortality-to-incidence ratio of any malignancy. Even patients who present with potentially curable disease have a median survival of $<$ 2 years. Those with positive nodes or margins at time of resection or with persistent CA 19-9 elevation have $>$ 90% chance of recurrence despite triple modality therapy. Epigenetic abnormalities in PDAC have been shown to increase malignant proliferation, metastasis and resistance to chemotherapy. Preclinical data has identified a number of specific genes that are commonly hypermethylated in PDAC and have an accompanying phenotypic change leading to a more aggressive tumor, greater chemotherapy resistance and increased epithelial mesenchymal transition. Methylation reversal with a DNA methyltransferase inhibitor (DNMTi) and subsequent gene retranscription has been preclinically demonstrated to result in a less aggressive PDAC phenotype. The effects of DNMTi therapy have been shown to persist even after the DNMTi exposure is removed and may prime for sensitization to chemotherapy, including gemcitabine and taxane therapies. We designed a randomized phase II study of oral 5-azacitidine (CC-486) for patients with resected PDAC and high risk of recurrence (node positive disease, margin-positive resection or rising CA 19-9 following resection). **Methods:** We have enrolled 11/60 patients. Patients must have completed adjuvant therapy (chemotherapy, radiation or a combination thereof) and have no evidence of recurrence at the time of enrollment. Patients are 1:1 randomized to receive standard-of-care (observation and surveillance) or CC-486 (300mg PO daily for days 1-21 of 28 day cycles) until there is evidence of recurrence. At recurrence, patients have fresh biopsies obtained. Correlative work evaluates for global methylation status as well as for the methylation status of a select group of genes known to be aberrantly methylated in PDAC and whose reversal may be associated with a phenotypic change in tumor behavior. These include: SLIT2/3, ROBO1/2, BRCA1, RAR-B, MGMT, hMLH1, EYA2, p16, RASF1A, FOXE1, NPTX2, Reprimo, ARID1B and Dkk3. Clinical trial information: NCT01845805.

TPS4145 Poster Session (Board #250b), Mon, 8:00 AM-11:30 AM

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). *First Author: Pamela L. Kunz, Stanford University School of Medicine, Stanford, CA*

Background: Patients with advanced pancreatic neuroendocrine tumors (NETs) have few treatment options that yield objective radiographic tumor regression. Somatostatin analogues and biologics yield prolonged progression-free survival (PFS) but minimal overall response rates (RRs). Historical studies reporting the highest RRs and longest PFS intervals include regimens with cytotoxic chemotherapy, such as streptozocin. Recent retrospective and small, prospective studies, suggest that temozolomide is similarly active but less toxic than streptozocin-based therapy. The proposed study will provide prospective data on response rates and progression-free survival associated with temozolomide or temozolomide in combination with capecitabine, and will also assess the relative efficacy of these two regimens. **Methods:** E2211 is a two-arm, multi-center, randomized phase II trial comparing temozolomide (200 mg/m2 PO QD days 1-5) vs. capecitabine (750 mg/m2 PO BID days 1-14) and temozolomide (200 mg/m2 PO QD days 10-14) in patients with advanced pancreatic NETs. Eligibility criteria include: metastatic or unresectable, low or intermediate grade pancreatic NETs, progression within preceeding 12 months, and no prior temozolomide, DTIC, capecitabine, or 5-FU therapy. Primary endpoint is PFS; secondary endpoints are Overall Survival (OS), RR, safety, and MGMT status as evaluated by immunohistochemistry and promoter methylation status. This study will require a minimum of 138 patients (or a maximum of 145 patients to allow for 5% ineligibility) to be accrued at the rate of 6 patients per month. With 23 months of accrual time and 13 months of follow-up (3 years total study time), this trial will have at least 81% power to detect a difference in median PFS between the treatment arms of 9 versus 14 months (hazard ratio of 0.64) using a two-sided log-rank test at the overall 0.20 significance level. First patient entered onto the study in August 2013. As of January 2015 a total of 67 (46% of target) patients have been recruited. Clinical trial information: NCT01824875. Clinical trial information: NCT01824875.

TPS4146 Poster Session (Board #251a), Mon, 8:00 AM-11:30 AM

JANUS 2: A phase III study of survival, tumor response, and symptom response with ruxolitinib plus capecitabine or placebo plus capecitabine in patients with advanced or metastatic pancreatic cancer (mPC) who failed or were intolerant to first-line chemotherapy. *First Author: Eileen Mary O'Reilly, David M. Rubenstein Center for Pancreatic Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The systemic inflammatory response characteristic of PC is mediated in part by JAK-STAT signaling and may contribute to local tumor growth and disease-related weight loss, decreased muscle mass, and poor performance status. In the phase II, randomized, double-blind RECAP study, the combination of the JAK1/JAK2 inhibitor ruxolitinib with capecitabine improved overall survival (OS) versus placebo + capecitabine in patients with mPC and elevated C-reactive protein (CRP) levels or a modified Glasgow Prognostic Score (mGPS) of 1 or 2 (Hurwitz et al. *J Clin Oncol*. 32:5s, 2014 [suppl; abstr 4000]). **Methods:** JANUS 2 is a phase III, randomized, double-blind, multicenter study. Eligible patients are ≥ 18 years of age and have histologically or cytologically confirmed pancreatic ductal adenocarcinoma, advanced and inoperable or metastatic disease; ECOG performance status of 0–2; only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy); no concurrent anticancer therapy; and an mGPS of 1 (CRP > 10 mg/L and albumin ≥ 35 g/L) or 2 (CRP > 10 mg/L and albumin < 35 g/L). Exclusion criteria are prior severe reaction to fluoropyrimidines, dihydropyrimidine dehydrogenase deficiency, or other sensitivity to 5-fluorouracil. Patients are randomized 1:1 to receive 21-day cycles of capecitabine 2000 mg/m^2/d (days 1−14) + ruxolitinib 15 mg twice-daily or capecitabine 2000 mg/m^2/d + placebo twice-daily. The primary endpoint is OS; secondary endpoints include progression-free survival, tumor response per RECIST 1.1, and duration of response. An exploratory endpoint is the assessment of change from baseline in PC symptoms using the Pancreatic Cancer Symptom Assessment Form electronic diary. Treatment will continue as long as it is tolerated and discontinuation criteria are not met. Patients who discontinue treatment will be followed for subsequent anticancer treatments and survival. Enrollment began in April 2014 and is ongoing. The planned enrollment is 270 patients. Clinical trial information: NCT02119663.

TPS4147 Poster Session (Board #251b), Mon, 8:00 AM-11:30 AM

JANUS 1: A phase 3, placebo-controlled study of ruxolitinib plus capecitabine in patients with advanced or metastatic pancreatic cancer (mPC) after failure or intolerance of first-line chemotherapy. *First Author: Herbert Hurwitz, Duke University Medical Center, Durham, NC*

Background: The systemic inflammatory response observed in PC is a negative prognostic factor and is mediated in part by JAK-STAT signaling. Treatment with the JAK1/JAK2 inhibitor ruxolitinib in combination with capecitabine was previously investigated as second-line therapy for patients with mPC and evidence of a systemic inflammatory response (elevated C-reactive protein [CRP] levels or a modified Glasgow Prognostic Score [mGPS] of 1 or 2) in the phase 2, randomized, double-blind RECAP study. Results showed improved overall survival (OS) relative to placebo + capecitabine (Hurwitz et al. *J Clin Oncol*. 32:5s, 2014 [suppl; abstr 4000]). Ruxolitinib has US Food and Drug Administration orphan drug status for the treatment of PC. **Methods:** JANUS 1 is a phase 3, international, multicenter, randomized, double-blind study. Eligible patients are ≥ 18 years of age with histologically or cytologically confirmed pancreatic adenocarcinoma that is advanced and inoperable or metastatic; have an ECOG performance status of 0–2; have received 1 prior chemotherapy regimen for advanced or metastatic PC not including neoadjuvant and/or adjuvant therapy; and have an mGPS of 1 (CRP > 10 mg/L and albumin ≥ 35 g/L) or 2 (CRP > 10 mg/L and albumin < 35 g/L). Patients are excluded for > 1 prior chemotherapy regimen for advanced or metastatic disease; radiation therapy; concurrent anticancer therapy; or prior severe reaction to fluoropyrimidines, dihydropyrimidine dehydrogenase deficiency, or other sensitivity to 5-fluorouracil. Patients are randomized 1:1 to receive 21-day cycles of capecitabine 2000 mg/m^2/d (days 1–14) + ruxolitinib 15 mg twice-daily or capecitabine 2000 mg/m^2/d + placebo twice-daily. The primary endpoint is OS. Secondary endpoints include progression-free survival, tumor response per RECIST 1.1, and duration of response. Treatment will continue as long as it is tolerated and discontinuation criteria are not met. Patients who discontinue treatment will be followed for subsequent anticancer treatments and survival. Enrollment was initiated in March 2014 and is ongoing. The planned enrollment is 310 patients. Clinical trial information: NCT02117479.

TPS4148 Poster Session (Board #252a), Mon, 8:00 AM-11:30 AM

Randomized phase II study of the safety, efficacy, and immune response of GVAX pancreas vaccine (with cyclophosphamide) and CRS-207 with or without nivolumab in patients with previously treated metastatic pancreatic adenocarcinoma (STELLAR). *First Author: Dung T. Le, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: A heterologous prime-boost vaccination strategy using GVAX pancreas vaccine and CRS-207 is showing promise in patients with pancreatic adenocarcinoma (PDA) (Le, JCO 2015). Furthermore, blockade of the immune checkpoint programmed death-1 (PD-1) is active in some cancers. Combinatorial strategies aimed at priming tumor antigen-specific T cells while simultaneously blocking negative checkpoints may be necessary to improve outcomes in PDA. GVAX is composed of allogeneic pancreatic cancer cells modified to express GM-CSF and induces a broad response against multiple tumor antigens. GVAX is given with low-dose cyclophosphamide (CY) to inhibit regulatory T cells. CRS-207 is live-attenuated *Listeria monocytogenes* engineered to express the tumor-associated antigen mesothelin. CRS-207 boosts responses against mesothelin and is unique in its capacity to stimulate both innate and adaptive immunity by activating T cells and NK cells. Nivolumab is an antibody against PD-1. **Methods:** This is a phase 2 study comparing CY/GVAX and CRS-207 with or without nivolumab in subjects with PDA who failed only one chemotherapy regimen for metastatic disease. Subjects are randomized in a 1:1 ratio to receive either 2 doses of CY/nivolumab/GVAX and 4 doses of nivolumab/CRS-207 (Arm A) or 2 doses of CY/GVAX and 4 doses of CRS-207 (Arm B). The primary objective is to compare OS between Arms A and B. Secondary/exploratory objectives include: assessment of safety and clinical responses (tumor assessments and CA19-9 levels) and correlation of *Lm*- and mesothelin-specific T cell and other immunological responses with OS, progression-free survival and best overall response. Clinical trial information: NCT02243371. Clinical trial information: NCT02243371.

TPS4149 Poster Session (Board #252b), Mon, 8:00 AM-11:30 AM

POLO: A randomized phase III trial of olaparib tablets in patients with metastatic pancreatic cancer (mPC) and a germline *BRCA1/2* mutation (g*BRCA*m) who have not progressed following first-line chemotherapy. *First Author: Hedy Lee Kindler, University of Chicago, Chicago, IL*

Background: Germline mutations in *BRCA1/2* define a molecular subgroup of PC that in some populations has a prevalence as high as 15%. g*BRCA*m-defective tumors are intrinsically sensitive to platinum and PARP inhibitors. In a Phase II trial (NCT01078662), 23 previously-treated g*BRCA*m mPC patients received the PARP inhibitor olaparib (Lynparza) as monotherapy. The tumor response rate was 22%, progression-free survival (PFS) was 4.6 months and overall survival (OS) was 9.8 months (Kaufman, JCO 2014). These data led to a double-blind, placebo-controlled Phase III trial (NCT02184195; POLO) of olaparib 'switch maintenance' monotherapy in patients with g*BRCA*m-associated mPC who have not progressed on first-line platinum chemotherapy. **Methods:** Eligible mPC patients must have documented disease control after completing at least 16 weeks of a first-line platinum-based regimen and must have a known or suspected deleterious g*BRCA*m, which will be confirmed by Integrated BRAC*Analysis* (Myriad Genetic Laboratories) during the trial. Patients are randomized (3:2) to olaparib (300 mg orally bid) or placebo. The primary endpoint is PFS, determined by blinded independent central review using RECIST 1.1. Disease will be assessed by CT scans at baseline, every 8 weeks for 40 weeks and every 12 weeks thereafter. Patients will receive treatment until objective disease progression unless toxicity is unacceptable. The primary PFS analysis will be performed after ~89 PFS events (~60% maturity) using a log-rank test. Secondary endpoints include OS, time from randomization to second progression (PFS2), HRQoL, safety and tolerability. Enrollment began in Q4 2014. The target number for randomization is ~145 patients across ~80 centers worldwide. Clinical trial information: NCT02184195.

TPS4150 Poster Session (Board #253a), Mon, 8:00 AM-11:30 AM

ACCEPT: Afatinib as cancer therapy for exocrine pancreatic tumors–An explorative randomized phase II trial. *First Author: Michael Haas, Department of Internal Medicine III and Comprehensive Cancer Center, Klinikum Grosshadern, Ludwig-Maximilians University of Munich, Munich, Germany*

Background: Metastatic pancreatic cancer still remains a disease difficult to treat. Since gemcitabine was established as a standard of care in the 1990s, the only targeted therapy which showed a moderate improvement in overall survival (OS) when applied along with gemcitabine was the tyrosine-kinase inhibitor erlotinib. Afatinib, a novel, oral irreversible ErbB family blocker has been approved for first-line-treatment in patients with non-small-cell lung cancer (NSCLC) bearing driver mutations of the epidermal-growth-factor-receptor (EGFR). Afatinib has shown superior progression-free survival and overall survival (in the prespecified subpopulation of Del 19 mutations) compared to standard of care chemotherapy. The combination of gemcitabine and afatinib was well tolerated with manageable adverse events (AEs) in patients with relapsed or refractory solid tumors in a phase I trial. **Methods:** ACCEPT is an open-label, controlled, randomized phase II trial for patients with histologically proven pancreatic adenocarcinoma previously untreated for metastatic disease. Patients are randomized in a 2:1 ratio to receive either gemcitabine 1000mg/m^2 intravenously over 30 minutes on days 1, 8 and 15 of a 28 day cycle in combination with oral afatinib, flat dose of 40mg daily, continuously (Arm A, experimental arm) vs. gemcitabine alone (Arm B). The study is designed to demonstrate a benefit in OS for the combination of gemcitabine and afatinib vs. gemcitabine alone. Estimating a hazard ratio (HR) of 0.60 for OS in favor of the experimental arm and expecting a drop-out rate of 15%, a total number of 117 patients to be recruited was calculated. The first patient was included in April 2013 and currently thirty high-volume centers are open for recruitment in Germany. The current recruitment status is 49/117 patients. The study has an explorative endpoint: tumor samples and peripheral blood are prospectively collected and centrally stored from all study participants. As part of this translational program analyses regarding tumor- and blood samples will focus on potential prognostic and predictive biomarkers associated with the EGFR pathway.Clinical trial information: NCT01728818 Clinical trial information: NCT01728818.

TPS4151 Poster Session (Board #253b), Mon, 8:00 AM-11:30 AM

Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus surgery-first for resectable pancreatic carcer (Prep-02/JSAP05). *First Author: Michiaki Unno, Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan*

Background: Despite the improvements in the surgery and postoperative adjuvant therapy for resected pancreatic adenocarcinoma (PDAC), its prognosis remains poor. Surgery-first and adjuvant increases survival for resected PDAC, but this strategy cannot be offered to a significant proportion of patients due to the unresectable cases found at laparotomy or postoperative morbidity. Neoadjuvant chemotherapy (NAC) with gemcitabine (GEM) and S1 is safe and effective strategy and has been reported 45.7% of 2-year survival rate in an intention-to-treat analysis. **Methods:** This is a prospective randomized phase II/III trial. Patients who planned resection with cytologically or histologically proven PDAC are eligible for this study. All patients must be at least 20 and under 80 years old with written informed consent. Abutment of major visceral arteries on radiological finding is considered exclusion criteria. Eligible patients will be randomized to surgery followed by adjuvant S1 (80 mg/m2/day for four weeks, repeated similarly every six weeks for a total of four courses) for 6 months or NAC (GEM 1000 mg/m2/week, S1 80 mg/m2/day) followed by surgery and the same adjuvant treatment. NAC is given a total of 4 doses of GEM and 4 weeks of S1 within 8 weeks. The primary study endpoint is resection rate for phase II (n = 80) and overall survival for phase III (n = 280). The secondary endpoints are adverse events and response of NAC, and recurrence-free survival. According to the sample size calculation, 180 patients in total need to be randomized to each treatment arm. For quality control, radiological staging and resected specimen will be centrally reviewed by dedicated radiologists and pathologists, respectively. In phase II part, no more than 14 cases of non-resection (90%CI: 22.6%-49.2%) in each arm (n = 40) is required to transit from phase II to phase III. Enrollment to cohort began in January 2013. **Discussion:**The Prep-02/JSAP05 study will provide the unbiased overall survival of all PDAC patients who were planned resection. Furthermore, this trial will determine the efficacy of NAC in PDAC and offers a potential for translational research. Clinical trial information: UMIN000009634.

TPS4152 Poster Session (Board #254a), Mon, 8:00 AM-11:30 AM

Randomized multicenter phase II/III study with adjuvant gemcitabine versus neoadjuvant/adjuvant FOLFIRINOX in resectable pancreatic cancer: The NEPAFOX trial. *First Author: Wael Hozaeel, Frankfurt A.M. Nordwest Krankenhaus GMBH, Frankfurt Am Main, Germany*

Background: The outcome of pancreatic cancer remains poor. Few patients (pts) can be assigned to surgery and 80% of resected pts experience a relapse. Currently, adjuvant ctx with gemcitabine is standard, but prognosis remains poor, with 5-year survival rates around 25%. FOLFIRINOX is superior to gemcitabine in the metastatic setting and may represent a valuable option in resectable stages. Therefore, we initiated this multicenter phase II/ III trial (NEPAFOX) to explore the efficacy of neoadjuvant FOLFIRINOX. **Methods:** This is a randomized phase II/III trial. Pts with locally limited, curatively resectable or borderline resectable adenocarcinoma of the pancreas without metastases are eligible. Eligible pts are randomized to (arm A) surgery followed by adjuvant gemcitabine (1000 mg/m^2) for 6 months or (arm B) perioperative FOLFIRINOX (irinotecan 180 mg/m^2, oxaliplatin 85 mg/m^2, 5-FU 400mg/m^2 bolus, 5-FU 2400 mg/m^2, sodium folinate 400 mg/m^2) with 6 cycles (12 weeks) pre and further 6 cycles post surgery. Staging includes CT of chest and abdomen and will be repeated after 3 cycles of neoadjuvant chemotherapy, before surgery and every 3 months after surgery. Follow-up will be two years for disease recurrence. As prophylaxis for neutropenia, pts will obtain Filgrastim (Nivestim) ($\leq$ 70 kg KG 30MioU/0,5 mL and $>$ 70 kg KG 48 MioU/0,5 mL) s.c. 1-0-0 d 5-7). The primary endpoint is median OS. Secondary endpoints are median PFS, perioperative morbidity and mortality, R0 resection rate, pathological complete remission and prevalence of iron deficiency anemia. 126 pts will be randomized 1:1. After an interims analysis, the trial can be continued as phase III (310 pts). Recruitment of the trial started in Nov 2014. Clinical trial information: NCT02172976.

TPS4153 Poster Session (Board #254b), Mon, 8:00 AM-11:30 AM

***nab*-paclitaxel (*nab*-P) plus gemcitabine (Gem) vs Gem alone as adjuvant treatment for resected pancreatic cancer (PC) in a phase III trial (APACT).** *First Author: Margaret A. Tempero, UC San Francisco Pancreas Center, San Francisco, CA*

Background: Adjuvant chemotherapy for resected PC has been shown to decrease recurrence and increase survival. Gem alone is a standard adjuvant therapy option. *nab*-P + Gem was superior to Gem alone as first-line treatment in a phase III trial in patients (pts) with metastatic PC, including the primary endpoint of overall survival (median, 8.5 vs 6.7 months; HR 0.72; $P < 0.001$). Toxicities were manageable. Based on these findings in the metastatic setting, the APACT trial will compare *nab*-P + Gem vs Gem alone in the adjuvant setting. **Methods:** Pts with histologically confirmed PC who underwent macroscopic complete resection (R0 or R1) within 12 weeks of randomization, with no evidence of metastasis at screening, are eligible for enrollment. Other eligibility criteria include staging of T1-3, N0-1, M0; Eastern Cooperative Oncology Group performance status of 0 or 1; acceptable hematologic function; CA19-9 $<$ 100 U/mL prior to randomization; and no prior neoadjuvant therapy or radiation for PC. Pts with neuroendocrine tumors, any other malignancy within 5 years of randomization, infection with HIV or hepatitis B or C, or prior neoadjuvant treatment or radiation therapy for PC are ineligible. The planned enrollment of $\approx$ 800 pts will allow 90% power to detect an HR for disease-free survival (DFS) of 0.74 at a 2-sided significance level of 0.05. One interim safety analysis and 2 interim efficacy analyses (the first for futility and the second for futility and efficacy) will be performed. Pt enrollment is ongoing. Clinical trial NCT01964430. Clinical trial information: NCT01964430.

Planned N	**$\approx$ 800**
Investigational arm	*nab*-P 125 mg/m^2 plus Gem 1000 mg/m^2 on days 1, 8, and 15 of each 28-day cycle $\times$ 6 cycles
Control arm	Gem 1000 mg/m^2 on days 1, 8, and 15 of each 28-day cycle $\times$ 6 cycles
Randomization	1:1
Stratification factors	Resection status (R0 vs R1) Nodal status (lymph node + vs lymph node −) Geographic region (North America vs Europe vs Australia vs Asia Pacific)
Primary endpoint	DFS (independently assessed)
Secondary endpoints	OS, safety
Exploratory endpoints	Molecular profiling of tumor tissue to correlate tumor heterogeneity with clinical outcome Quality of life as assessed by the EORTC questionnaires QLQ-C30 and QLQ-PAN26

4500 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma (mRCC): Association of biomarkers with clinical outcomes. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

Background: This prospective biomarker study in patients (pts) with mRCC treated with the programmed death-1 (PD-1) inhibitor antibody nivolumab assessed baseline (BL) and changes in serum chemokines, tumor T cell infiltrates (TIL), gene expression, T cell repertoire (TCR), and other biomarkers potentially associated with clinical outcomes (NCT01358721). **Methods:** Pts treated with 1–3 prior therapies received nivolumab 0.3, 2, or 10 mg/kg IV Q3W; treatment-naïve pts received 10 mg/kg IV Q3W. Biopsies were obtained at BL and cycle 2 day 8. Overall survival (OS) parameters were estimated by Kaplan-Meier method. Tumor PD-L1 expression was measured by immunohistochemistry (28-8 antibody; Dako). PD-L1 positivity was defined as ≥ 5% tumor membrane staining in ≥ 1 biopsy; tumor burden response as ≥ 20% reduction. Gene expression data were obtained on Affymetrix U219. **Results:** 91 pts were treated. Of 56 evaluable BL biopsies, 32% were PD-L1+. Median OS (95% CI) was 16.4 mo (10.1–not reached [NR]) for 0.3 mg/kg, NR for 2 mg/kg, 25.2 mo (12.0–NR) for 10 mg/kg, and NR for treatment-naïve pts. 1-yr and 2-yr OS rates (95% CI) were 75% (64–83) and 58% (46–68), respectively. OS by PD-L1 status is summarized (table). Pts with tumor burden response (n = 13) had ≥ 1.3-fold differential BL expression of 311 genes ($P < 0.01$, false discovery rate < 16%). Cell-mediated immune transcripts were elevated, including effector cell markers GZMB, NKG7, and CD7, NK/CD8-activating ligand MICB, inflammasome component AIM2, and activated macrophage marker IL-1a. Analysis of association between OS and serum chemokine levels, TCR and TIL is ongoing. **Conclusions:** Association of immune markers at BL with subsequent tumor burden response suggests that infiltrating immune activating cells may mediate response to nivolumab in mRCC pts. Consistent with the randomized phase II study of nivolumab in mRCC, OS appears longer in PD-L1+ pts but promising in both PD-L1+ and PD-L1– pts, especially when treatment-naïve. Clinical trial information: NCT01358721.

	PD-L1+ n = 18	PD-L1– n = 38
Median OS, mo (95% CI)		
Overall	NR	23.4 (13.1–33.3)
Previously treated	NR	22.3 (12.0–27.0)
Treatment-naïve	NR	33.3 (2.0–NR)
OS rate, % (95% CI)		
1-yr	71 (44–87)	71 (52–83)
2-yr	64 (37–82)	48 (30–64)

4501 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

A phase Ia study of MPDL3280A (anti-PDL1): Updated response and survival data in urothelial bladder cancer (UBC). *First Author: Daniel Peter Petrylak, Yale Cancer Center, New Haven, CT*

Background: PD-L1 may contribute to immune escape in UBC, a disease of high mutational complexity and immunogenicity. MPDL3280A was designed to restore T cell–mediated antitumor activity by blocking PD-L1 binding to PD-1 and B7.1 receptors. **Methods:** Previously treated, metastatic UBC pts were enrolled in an expansion cohort and received 15 mg/kg or 1200 mg IV MPDL3280A q3w. Efficacy-evaluable pts had ≥ 12 wk of follow-up (dosed by Jun 9, 2014; Sep 2, 2014 cutoff). ORR was assessed by RECIST v1.1 (unconfirmed), and archival biopsies were centrally evaluated for PD-L1 tumor-infiltrating immune cell (IC) expression by IHC. In-tumor gene expression and peripheral biomarkers were assessed as exploratory analyses in a subset of pts. **Results:** Updated analyses include 85 efficacy-evaluable, selectively enrolled UBC pts; 46 were PD-L1 IHC 2/3, 38 were IHC 0/1 and 1 had unknown IHC status. Median age was 66 y (36-89 y), and 75% were male. Baseline visceral mets were present in 77% of pts; 98% received ≥ 1 prior therapy (eg platinum in 93%). The ORR for IHC 2/3 pts was 46% (95% CI 31-61%; 6 CRs, 15 PRs), and for IHC 0/1 pts was 16% (95% CI 6-31%; 6 PRs) with median response durations not yet reached (IHC 2/3 pts, 0+ to 54+ wk; IHC 0/1 pts, 4+ to 33+ wk). Median PFS was 24 wk (95% CI 12-NE) for IHC 2/3 pts and 8 wk (95% CI 6-12 wk) for IHC 0/1 pts. 24-wk OS rates for IHC 2/3 and 0/1 pts were 85% (95% CI 74-96%) and 71% (95% CI 54-88%), respectively, with the medians not yet reached (3 to 72+ wk and 2+ to 51+ wk, respectively). Pts with visceral mets had ORRs of 32% (IHC 2/3: 3 CRs, 7 PRs; n = 31) and 12% (IHC 0/1: 4 PRs; n = 33). Median safety follow-up was 16 wk (3-73 wk). Drug-related AEs occurred in 64% of 87 safety-evaluable pts (most often fatigue, asthenia, nausea); 8% had a related G3-4 AE. 12% of pts had an immune-related AE. No related deaths were seen. Responders had lower myeloid gene expression at baseline (eg *Cox-2, IL8; IL1B*) and decreased circulating inflammatory and tumor markers (eg CRP; HCG, CA 19-9, CA-125) by cycle 2. **Conclusions:** MPDL3280A was well tolerated and had durable activity in UBC pts. Response, PFS and OS data are promising for IHC 2/3 and IHC 0/1 UBC pts vs historic controls. Response also correlated with in-tumor and blood-based biomarkers. Clinical trial information: NCT01375842.

4502 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012. *First Author: Elizabeth R. Plimack, Director, Genitourinary Clinical Research Fox Chase Cancer Center, Philadelphia, PA*

Background: Pembrolizumab, an anti–PD-1 antibody, demonstrated antitumor activity and acceptable safety in patients with recurrent or metastatic PD-L1–positive urothelial cancer enrolled in the phase 1b KEYNOTE-012 study (NCT01848834). We present updated efficacy and safety data for these patients, as well as an analysis of the relationship between PD-L1 expression and ORR. **Methods:** Eligible patients had recurrent, metastatic, or persistent urothelial cancer of the bladder, renal pelvis, ureter, or urethra. Patients received pembrolizumab 10 mg/kg every 2 weeks until complete response, progression, or unacceptable toxicity. PD-L1 expression was evaluated in baseline tumor samples at a central laboratory. Patients were enrolled if there were ≥1% PD-L1–positive cells in tumor nests or a PD-L1–positive band in stroma by a prototype immunohistochemistry assay. Samples were also analyzed with the clinical trial immunohistochemistry assay. Response was evaluated every 8 weeks per RECIST v1.1 by central review. **Results:** Thirty-three patients were enrolled (median age, 70 years; ≥3 prior therapies, 33%; visceral or osseous metastases, 66%). Median follow-up duration was 13 months (range, 1-16). Grade 3-4 drug-related adverse events occurred in 5 (15%) patients. In the 28 patients with measurable disease at baseline, ORR was 25% (95% CI 11-45), with 3 (11%) complete and 4 (14%) partial responses per central review. At the time of analysis, median duration of response had not been reached (range, 16-50+ weeks). The 12-month PFS rate was 19%. ORR in patients with tumors positive for PD-L1 expression as assessed with the clinical trial assay was 38%. **Conclusions:** Pembrolizumab demonstrates durable antitumor activity in patients with advanced urothelial cancer. A higher response rate was seen in patients with PD-L1 expression. Further analysis of the relationship between response and predictive biomarkers is ongoing. Clinical trial information: NCT01848834.

4503 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

First-line randomized phase II study of gemcitabine/cisplatin plus apatorsen or placebo in patients with advanced bladder cancer: The International Borealis-1 trial. *First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Heat shock protein 27 (Hsp27) is over-expressed in bladder cancer (BC) and postulated to increase tumor growth, metastasis, and chemotherapy resistance. Apatorsen (A; OGX-427), a novel antisense oligonucleotide, inhibits Hsp27 production and can potentially enhance the efficacy of chemotherapy. This trial was designed to evaluate efficacy and safety of A in combination with gemcitabine and cisplatin (GC) in patients (pts) with advanced BC. **Methods:** Chemotherapy naïve pts with advanced BC were randomized to GC+A 600 mg, GC+A 1000 mg, or GC + placebo. Pts were stratified by Karnofsky performance status (KPS) and visceral disease. The primary endpoint was overall survival (OS). Prognostic sub-groups were retrospectively evaluated using multiple variable modeling and hierarchical step down. A post hoc analysis was performed to explore the hypothesis that Hsp27 inhibition might be relevant to OS in poor prognosis disease. **Results:** A total of 179 pts were randomized/treated. Median OS was 15.2 months (m). When compared to GC + placebo, GC+A 600 demonstrated improved OS and PFS (OS HR = 0.856 and PFS HR = 0.830) versus GC+A 1000 (OS HR = 0.898; PFS HR = 0.927). Results from the post hoc model revealed that KPS, liver mets, alk phos, and hemoglobin were prognostic. A median prognostic score dichotomized pts into poor and good prognosis groups (50% each group). Pts with poor prognosis treated with GC+A 600 had a greater reduction in risk of death (HR = 0.717) than pts with good prognosis (HR = 1.44). The most significant prognostic factor was KPS ≤ 80% (35% pts in GC+A 600 vs GC) resulting in HR = 0.50 in favor of GC+A 600. Overall treatment was well tolerated. Most common Grade ≥ 3 adverse events (AEs) were neutropenia, anemia, thrombocytopenia and hypertension. Frequency of ≥ 3 Grade toxicities were: 89% (GC), 93% (GC+A 600) and 95% (GC+A 1000). GC+A 1000 had a higher treatment discontinuation rate due to AEs. **Conclusions:** Advanced BC pts with poor prognosis benefited from apatorsen 600mg combined with first line GC. Apatorsen may be impacting the intrinsic biology of patients with poor risk factors. Further evaluation is warranted in this pt population. Clinical trial information: NCT01454089.

4504 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Eribulin in advanced urothelial cancer (AUC) patients (pts): A California Cancer Consortium trial—NCI/CTEP 7435. *First Author: David I. Quinn, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: There is an unmet need for new agents in AUC. We previously reported that eribulin, a microtubule modulator derived from black Pacific sea sponge toxin, is highly active against metastatic UC in frontline and previously treated settings (ASCO 2010; ECC 2013). Here we report composite results of 150 AUC pts treated in a single phase II trial. **Methods:** Eligible pts with AUC, calculated CrCl ≥ 20mL/min were treated in 3 cohorts of first line, 2nd line with or without tubulin exposure. Eribulin 1.4mg/m2 IV on d1 & 8, q3 wks. In each cohort RR > 20% considered promising; 41 pts in a Simon 2-stage design. PFS & OS were secondary endpoints. **Results:** Pt characteristics: Median age 68 yrs (range: 25-90); Males: 71%; KPS ≥ 90%: 57%; Transitional cell histology: 90%; Lower tract 88%, Visceral mets 67%, Bajorin risk groups: 0: 30%, 1: 61%, 2: 9%. Bajorin risk group, visceral mets +/- KPS associated with OS & PFS ($p < 0.01$) while renal fn, age, line of therapy & prior tubulin exposure did not. Toxicities included Gr3/4 neutropenia: 57%, FN: 4%, Gr3 Hb: 13%, Gr1/2 sensory neuropathy: 45%. Age > 70 associated with Gr3+ neutropenia, no factors including tubulin exposure predicted neuropathy, developing any Gr3+ toxicity associated with age > 70 & KPS. **Conclusions:** Eribulin exceeded the prespecified benchmark in all strata with highly encouraging single agent activity in AUC. Phase III evaluation of eribulin in AUC is warranted. (NCT00365157; UM1 CA186717; U01 CA062505; P30 CA014089; P30 CA033572). Clinical trial information: NCT00365157.

Endpoint summary.

	Overall (n = 150)	Normal renal fn# (n = 121)	Moderate renal dysfn (n = 17)	Severe renal dysfn (n = 12)	First line (n = 52)	Tubulin naïve (n = 53)	Tubulin exposed (n = 45)
Median OS months (95%CI)	9.6 (7.6, 2.4)	9.2 (7.1,11.9)	16.8 (4.3,40.0)	11.3 (5.1,27.4)	11.3 (7.2,40.1)	9.6 (6.2,12.6)	8.7 (6.0,14.0)
Median PFS months (95%CI)	4.1 (3.5, 5.0)	4.0 (3.0, 5.0)	4.2 (2.8, 8.3)	6.1 (1.5,17.0)	4.2 (3.1, 5.6)	4.2 (2.8, 6.4)	3.9 (2.8, 5.1)
% Responded (95%CI)	32 (24, 40)	31 (22, 39)	41 (15, 67)	33 (2, 65)	42 (28, 56)	28 (16, 41)	24 (11, 38)
Median Stable disease wks	13.9	13.6	12.5	17.3	12.7	14.9	17
Stable disease > 12 wks/# pts with SD	42/60	31/47	6/8	5/5	13/21	16/24	13/15

Normal renal fn: serum creat < 1.5 ULN or calc crcl > 60, Moderate 40-60, Severe 20-40

4505 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

A phase II/III, double-blind, randomized trial comparing maintenance lapatinib versus placebo after first line chemotherapy in HER1/2 positive metastatic bladder cancer patients. *First Author: Thomas Powles, Barts Cancer Institute, Barts Health and the Royal Free NHS Trust, London, United Kingdom*

Background: First-line chemotherapy for metastatic transitional cell carcinoma (TCC) is associated with clinical benefit. Further therapies are largely ineffective. The purpose of this trial was to establish if maintenance lapatinib after first-line chemotherapy was associated with clinical benefit in HER1/HER2 positive TCC patients. **Method:** During first-line chemotherapy, patients were screened for their HER1/HER2 status by centralised immunohistochemistry (IHC). HER1/2 positive patients with advanced/metastatic TCC who achieved clinical benefit after completing first-line chemotherapy (4-8 cycles) were potentially eligible for randomisation (1:1). The primary endpoint was to compare progression free survival (PFS). Secondary endpoints included adverse events (AE), overall survival (OS) and subset analysis for HER status. **Results:** Between 2007-2013, 455 patients were screened and 232 HER 1 or 2 positive patients were randomised to lapatinib (L) (n = 116) or placebo (P) (n = 116). 71.2% had visceral metastasis. 64.1% received cisplatin based chemotherapy. The median number of chemotherapy cycles was 6. The progression free survival for L and P was 4.6 months (95% CI: 2.8 – 5.4) and 5.3 months (95% CI: 3.0 – 5.9) respectively [HR: 1.04 (95% CI: 0.79 – 1.39) p = 0.77]. The overall survival for L and P was 12.6 months (95% CI: 9.5 – 16.2) and 11.9 months (95% CI: 10.6 – 15.8) respectively [HR = 0.98 (95% CI: 0.71 – 1.35) p = 0.89). The best response rate for L and P was 13.8% vs 7.8% (p = 0.14). The rate of grade 3-4 AEs for L and P was 24.3% vs. 15.5% (p = 0.09). Subset analysis of i) HER1/HER2 3+ positive patients on IHC ii) HER1 positive patients iii) HER2 positive patients showed no significant benefit in PFS (HR 0.94, 0.99 and 1.19 respectively: p > 0.05 for each) or OS (HR 0.76, 0.92 and 1.03 respectively: p > 0.05 for each) for lapatinib. A model predicting outcomes was constructed. **Conclusion:** This is the first personalised randomised trial in metastatic TCC. It shows maintenance lapatinib does not improve outcomes in HER1 or HER2 positive individuals. Clinical trial information: NCT00949455.

4506 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC). *First Author: Robert Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lenvatinib (LEN), an oral tyrosine kinase inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT, in combination with EVE had manageable toxicity and antitumor activity in a phase 1 mRCC trial (*CCP* 2013;73:181). This phase II, open-label, multicenter study compared LEN, EVE, and LEN+EVE in pts with mRCC. **Methods**: Pts with progressive clear cell mRCC following 1 VEGF-targeted therapy were randomized 1:1:1 to LEN (24 mg/d), EVE (10 mg/d), or LEN+EVE (18+5 mg/d) in 28d cycles. The primary objective was progression-free survival (PFS) of LEN+EVE or LEN vs EVE. Secondary objectives included overall survival (OS), objective response rate (ORR), and safety. Primary analysis data cutoff was June 13, 2014. **Results**: One hundred and fifty-three pts were enrolled: 99% had one prior VEGF-targeted therapy, 1% had two; 18% had prior immunotherapy. LEN+EVE prolonged PFS vs EVE (Table; hazard ratio [HR] 0.40; 95% confidence interval [CI] 0.24–0.68; P < 0.001). LEN alone also prolonged PFS vs EVE (HR 0.61; 95% CI 0.38–0.98; P = 0.048). LEN+EVE and LEN improved ORR vs EVE (P < 0.001 and P = 0.007, respectively). Median duration of response (months) was longest in LEN+EVE, 13.1; LEN, 7.5; EVE, 8.5. OS analysis showed a trend favoring LEN+EVE vs EVE (HR 0.55; 95% CI 0.30–1.01; P = 0.062); this reached significance (HR 0.51; 95% CI 0.30–0.88; P = 0.024) in an updated analysis on Dec 10, 2014. For LEN+EVE, most common any-grade treatment-emergent adverse events (TEAEs) were diarrhea (84%), decreased appetite (51%), and fatigue (47%). Most common grade ≥ 3 TEAEs were diarrhea (20%), hypertension (14%), and fatigue (10%). **Conclusions**: LEN+EVE improved PFS and ORR versus EVE alone in this phase II trial of pts with mRCC following prior VEGF-targeted therapy. Updated OS also showed improvement with LEN+EVE. A phase III randomized trial of the combination in mRCC is planned. Clinical trial information: NCT01136733.

Primary analysis	LEN+EVE n = 51	LEN n = 52	EVE n = 50
Median survival, months (95% CI)			
PFS	14.6 (5.9–20.1)	7.4 (5.6–10.2)	5.5 (3.5–7.1)
OS	25.5 (20.8–25.5)	18.4 (13.3–NE)	17.5 (11.8–NE)
ORR, n (%)	22 (43)	14 (27)	3 (6)
Median duration of response, months (95% CI)	13.1 (3.8–NE)	7.5 (3.8–NE)	8.5 (7.5–9.4)
Median # of cycles, (range)	9.0 (1–25)	8.5 (1–25)	5.0 (1–22)

NE, not evaluable

4507 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Final clinical results of a randomized phase II international trial of everolimus vs. sunitinib in patients with metastatic non-clear cell renal cell carcinoma (ASPEN). *First Author: Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC*

Background: Limited evidence exists to guide therapeutic decisions in patients (pts) with metastatic non-clear cell RCC (NC-RCC). **Methods:** ASPEN was an international, randomized trial of pts with metastatic papillary, chromophobe, or unclassified histology; any MSKCC risk group, and no prior systemic therapy. Pts were randomized 1:1 to either everolimus (E) or sunitinib (S) until progression, stratified by histology and risk group. The primary endpoint was radiographic PFS by RECIST 1.1. With an expected 90 PFS events, there was 83% power to detect a 38% decrease in the hazard rate of progression/death assuming a two-sided type I error of 0.20 using a stratified log-rank statistic. **Results:** Between September 2010 and October 2013,we enrolled108 subjects across 17 sites and 3 countries. Median age was 63, 75/25% male/female, 66% papillary, 15% chromophobe, 19% unclassified; 27/59/14% good/intermediate/poor risk; 57 vs. 51 were randomized to E vs S. Treatment arms were well balanced at baseline. With 87 PFS events, 53 deaths, and 2 pts remaining on study treatment, S improved overall PFS, meeting the primary endpoint. S improved PFS in good/intermediate risk and papillary/unclassified pts, but E improved PFS in poor risk and chromophobe pts (**Table**). No unexpected safety signals emerged. **Conclusions:** Sunitinib prolonged rPFS as compared with everolimus in patients with NC-RCC, but resulted in higher rates of severe toxicity. This is the largest trial to date in NC-RCC and the first to demonstrate an mTOR-sensitive subgroup of NC-RCC pts as compared with VEGF inhibition in the front-line setting, including chromophobe and poor risk RCC pts. Clinical trial information: NCT01108445.

Endpoint	E (n=57)	S (N=51)	HR (80% CI) S as Reference	p-value
Median PFS (mo)	5.6	8.3	1.41	0.16
(80% CI)	5.5-6.0	5.8-11.1	(1.03-1.92)	
Papillary	5.5	8.1	1.52 (1.05-2.20)	
Chromophobe	11.4	5.5	0.71 (0.31-1.65)	
Unclassified	5.6	11.5	2.55 (1.01-6.45)	
Risk: Good	5.7	14.0	3.07 (1.51-6.28)	
Intermediate	4.9	6.5	1.38 (0.96-2.00)	
Poor	6.1	4.0	0.21 (0.06-0.69)	
Median OS (mo, 95% CI)	13.2	31.5	1.17 (0.65-2.14)	0.60
Objective Response Rate (%)	5	4	-	-
CR+ PR %	12	31		
SD %	67	61		
PD %	16	4		
Missing %				
>Grade 3 Treatment-Related AEs (%)	47%	65%	-	-

4508 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Dose analysis of ASSURE (E2805): Adjuvant sorafenib or sunitinib for unfavorable renal carcinoma, an ECOG-ACRIN-led, NCTN phase 3 trial. *First Author: Naomi B. Haas, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: E2805 is a phase III trial of sunitinib (SU), sorafenib (SOR) or placebo (PB) in patients (pts) with completely resected locally advanced renal cell carcinoma (RCC). There was no difference in DFS between the arms. Midway through the trial, starting doses were reduced. We analyzed the effect of this approach on drug dosing, toxicity and outcome. **Methods:** 1,943 pts stratified by risk, histology, ECOG PS, and nephrectomy type, were randomized to SU daily (4 of 6 wk cycle), SOR daily, or PB, for $\leq$ 1 yr. The primary endpoint was disease-free survival (DFS). After 1322 pts, starting doses of SU and SOR were reduced from 50 to 37.5 mg (25%) and from 800 to 400mg (50%), respectively, to mitigate the impact of pt discontinuation (DISC). Escalation to full dose after the first 2 cycles was mandatory when tolerated. Total dose of each agent over the entire yr, relative dose (actual/intended x 100), and number (no.) of cycles were related to DFS. **Results:** The redesign reduced the 3-month DISC rate from adverse events or refusal from 25%/30% in pts starting at full dose to 17%/11% in pts starting at reduced dose on SU/SOR (Gray's p = 0.01/0.0001). Total dose did not differ between groups on either SOR (p = 0.41) or SUN (p = 0.83). Most common grade $\geq$ 3 adverse events were hypertension, hand-foot reaction, rash and fatigue. There was no relationship between no. of cycles received or dose intensity and DFS. **Conclusions:** Dose titration reduced the DISC rate but not the total dose, with no impact on overall DFS by arm. Decreased DFS with reduced-dose SOR raises concern about the differential effects of multi-kinase inhibitors across a range of doses. Clinical trial information: NCT00326898.

	SU		SOR		PB	
Randomized	647		649		647	
Treated	629		630		632	
DFS Events	265		272		270	
Median DFS (yrs)	5.8		5.8		6.0	
Hazard Ratio	1.01		0.98		(ref)	
97.5% CI	0.83 – 1.23		0.81 – 1.20			
Starting Dose Grp	Full	Red	Full	Red	Full	Red
Pts	438	191	441	189	443	189
SOR/PB, rel dose, % (sd)	85 (22)	91 (18)	84 (42)	91 (22)	92 (14)	93 (14)
SU/PB, rel dose, % (sd)	90 (18)	93 (16)	87 (42)	93 (18)	95 (13)	95 (13)
Cycles, median[range]	8 [1 –9]	9 [1 –9]	7 [1 –9]	9 [1 –9]	9 [1 –9]	9 [1 –9]
5-yr DFS (%)	55.1	56.0	56.6	29.2	55.0	55.8
97.5% CI	49.7 – 61.2	46.7 – 67.1	51.2 – 62.6	15.0 – 56.7	49.7 – 61.0	45.5 – 68.3
Hazard Ratio	0.92	1.13	0.86	1.44	ref	ref

4509 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM

Identification of efficacy biomarkers in a large metastatic renal cell carcinoma (mRCC) cohort through next generation sequencing (NGS): Results from RECORD-3. *First Author: James Hsieh, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Several large genomic analyses of RCC have recently identified prevalent mutations in epigenetic regulators with prognostic significance. However, the impact of these novel mutations on clinical outcomes of different classes of targeted therapies is unknown. We explored the potential correlations between somatic mutations and treatment efficacy in RECORD-3, a randomized phase 2 trial comparing 1st-line everolimus (EVE) then sunitinib (SUT) with 1st-line SUT then EVE at progression in 471 treatment-naïve mRCC patients (pts)(JCO 32:2764-72). **Methods:** Somatic mutations in exons of 341 cancer related genes were identified by an NGS assay (MSK IMPACT platform) at ~530X coverage on tumor (archival tissues, 260 pts) and matched germline (181 pts) DNA. Association between genotypes and 1stline PFS was assessed by Cox PH models and log-rank tests. **Results:** PBRM1 mutations were associated with longer PFS within EVE (median PFS [mPFS] 11.1 vs 5.3 months; unadjusted p=0.0031). Pts with PBRM1 mutations (41% of the cohort) derived comparable PFS benefit from EVE vs. SUT. KDM5C mutations were associated with longer PFS within SUT (mPFS 20.6 vs 8.4 months; unadjusted p=0.0511). Profiles of 227 clear cell RCC (ccRCC) pts showed a SETD2 mutation rate of 29%, substantially higher than the 10% seen in random tumor sample cohorts (842 pts, Nature Genetics 45:849-50), suggesting SETD2's role in ccRCC metastasis. **Conclusions:** Mutations in epigenetic regulators PBRM1 and KDM5C may represent novel mechanisms associated with sensitivity to EVE or SUT. These candidate predictive biomarkers could be considered as molecular entry criteria for prospective clinical studies in selecting mTORC1 or VEGFR inhibitors for genomically distinct mRCC pts. Clinical trial information: NCT00903175.

		EVE		SUT		Hazard Ratio (95% CI)
Genes	**Genotype**	**events/ pts**	**mPFS (95% CI) months**	**events/ pts**	**mPFS (95% CI) months**	**RAD/SUT**
PBRM1	MT	35 / 49	11.5 (8.1, 16.2)	41 / 57	11.0 (8.4, 13.4)	1.07 (0.66, 1.74)
PBRM1	WT	64 / 79	5.3 (3.1, 8.3)	48 / 75	8.3 (7.1, 13.9)	1.85 (1.25, 2.75)
KDM5C	MT	10 / 11	9.8 (2.2, 16.6)	11 / 21	20.6 (12.4, 27.3)	2.35 (0.96, 5.72)
	WT	89 / 117	8.1 (5.4, 10.5)	78 / 111	8.4 (8.1, 11.3)	1.38 (1.00, 1.90)

4510 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM

Association of genomic alterations with cisplatin resistance (cisR) in advanced germ cell tumors (aGCT). *First Author: Darren Richard Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: 20% of patients (pts) with aGCT progress after initial chemotherapy (chemo), displaying at least partial cisR. We sought to characterize the genetic alterations in aGCT and identify markers of cisR. **Methods**: aGCT pts with available tumor tissue (except pure teratoma or malignant transformation) were eligible. Cisplatin sensitive (cisS) pts had a CR to chemo +/- surgery (if pathology = necrosis or teratoma) or PR + negative tumor markers lasting one year or more. CisR pts had non-teratoma GCT at post-chemo surgery or at relapse. Cis status was inevaluable (IE) if followup (f/u) was too short (without progression) or standard initial chemo was not given. Whole exome sequencing (WES) in 19 pts (10 cisR, 9 cisS) identified several mutations and copy number changes, which we confirmed by targeted exon-capture sequencing of 341 cancer-related genes (MSK-IMPACT). MSK-IMPACT was then preformed for 69 additional pts. Results on all 88 pts were analyzed for associations with clinicopathologic features using Fisher's exact test and for progression-free survival (PFS) using Cox regression multivariable analysis (MVA). **Results:** Of 88 pts (65 nonseminoma [NS], 23 seminoma [SEM]), 23 (26%) were cisS, 59 (67%) cisR, and 6 (7%) IE. Primary site was testis in 77, mediastinum in 10, and retroperitoneum (RP) in 1. IGCCCG risk group was good in 39, intermediate in 9, and poor in 36 (4 IE). Forty-two primary and 46 metastatic tumors were sequenced; 47 were obtained pre- and 41 post-chemo. With median follow-up of 25 months, 59 pts progressed, with 10 dying from aGCT. On WES, cisR samples had more nonsynonymous mutations than cisS samples (mean 49 vs 15, p = 0.03). On MSK-IMPACT, *TP53* mutations were more common for pts with a mediastinal vs testis/RP primary (60 vs 3%, p < 0.0001) and KRAS mutations more common in SEM vs NS (26 vs 6%, p = 0.018). *TP53* mutations and *MDM2* amplifications were mutually exclusive and both occurred only in cisR pts (25 vs 0%, p = 0.008). On MVA adjusted for IGCCCG group, *TP53/MDM2*alteration independently predicted PFS (HR 2.6, 95%CI 1.4-4.8, p = 0.002). **Conclusions:** Genomic changes in aGCT differ by histology and primary site. As *TP53/MDM2* alterations correlate with cisR and predict PFS independent of IGCCCG risk, they may aid prognostic assessment.

4511 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM

Molecular drivers of the non-T cell-inflamed tumor microenvironment in urothelial bladder cancer. *First Author: Randy F. Sweis, University of Chicago, Chicago, IL*

Background: A T cell-inflamed tumor microenvironment is linked to response to immunotherapies and survival in malignancies including urothelial bladder cancer (UBC). We recently identified tumor-intrinsic β-catenin activation in melanoma as causally related to T cell exclusion. However, molecular mechanisms that prevent T cell infiltration in other cancers are incompletely defined. Using gene expression profiling and exome sequencing, we pursued targetable pathways associated with absence of T cells in UBC. **Methods:** RNA sequencing and exome somatic mutation data from 267 UBC samples in the cancer genome atlas were downloaded. Unsupervised hierarchical clustering was performed on 16,197 filtered genes. A 725-gene cluster contained 12 genes from a previously described T cell signature and was used to segregate samples. Differential gene expression was detected using ANOVA with a false discovery rate q < 0.01 and fold change > 2.0. Enriched pathways were identified by Ingenuity Pathways Analysis. Somatic variants were converted to VCF format and analyzed according to immune phenotype. **Results:** Expression of CD8A was positively correlated with inhibitory molecules PDL1, IDO1, FOXP3, TIM3, and LAG3 (all p < 0.0001). Based on a signature of T cell inflammation, 36% of bladder tumors showed a T cell-inflamed phenotype, 33% were non-inflamed, and the remainder intermediate. The non-inflamed group contained 730 over-expressed genes. Pathway analysis revealed the most significantly activated regulators were Wnt/β-catenin and peroxisome proliferator-activated receptor gamma (PPARG) (both p = 0.003). Exome mutation analysis revealed no difference in mutation number per patient for each group (p = 0.80). Genes mutated in two or more samples included 891 occurring only in non-inflamed tumors. FGFR3 was the most common mutation exclusive to non-inflamed tumors (p < 0.0001). Expression of WNT7B, PPARG, and FGFR3 were inversely correlated with CD8A (all p < 0.0001). **Conclusions:** Bladder tumors are characterized by T cell-inflamed and non-inflamed phenotypes. Mutational burden does not vary between these subsets. Activation of β-catenin, PPARG, and FGFR pathways are strongly correlated with T cell exclusion in UBC.

4512 Poster Discussion Session; Displayed in Poster Session (Board #182), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Association of p53-ness with chemo-resistance in urothelial cancers treated with neoadjuvant gemcitabine plus cisplatin. *First Author: Roland Seiler, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada*

Background: Recent genomic analyses demonstrated that muscle-invasive bladder cancers can be grouped into intrinsic basal and luminal subtypes. Within the luminal subtype, tumors with "p53-like" gene expression were resistant to neoadjuvant chemotherapy (NAC) with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). We investigated the response of these subtypes to gemcitabine plus cisplatin (GC), the other major frontline NAC regimen in this disease setting. **Methods:** Fifty-two bladder cancer patients received neoadjuvant GC followed by cystectomy. At diagnosis 44 (85%) and 36 (69%) patients had extravesical extension of the primary tumors and were clinically node-positive, respectively. At cystectomy, 37 (71%) patients did not respond to NAC (ypT $\geq$ 2 or any ypN1-3). RNA was isolated from pre-NAC transurethral resection (TUR) specimens and post-NAC cystectomy specimens using the RNeasy FFPE kit (Qiagen), amplified with the Ovation WTA FFPE system (NuGen) and hybridized to GeneChip Human Exon 1.0 ST microarrays (Affymetrix). A one nearest neighbor (oneNN) prediction model was used with the RNA normalized gene expression values to assign the tumors to intrinsic subtypes. **Results:** Unsupervised hierarchical clustering separated the tumors into clusters characterized by non-overlapping expression of basal or luminal biomarkers. Assignment of pretreatment TUR tumors to subtypes yielded the expected ratios of basal, p53-like, and luminal tumors. Rates of pathological down staging ($<$ ypT2), disease specific ($p = 0.013$), and overall survival ($p = 0.003$) were lower in the p53-like tumors compared to the other subtypes. An immune signature was enriched in the basal tumors that responded to NAC, although this did not reach statistical significance. Analyses of matched tumors before and after therapy revealed enrichment for p53-like tumors at cystectomy. **Conclusions:** Patterns of response and resistance to neoadjuvant GC appear to be very similar to those observed with MVAC, with p53-like tumors displaying chemo-resistance. If these results are confirmed prospectively, patients with p53-like tumors should not be treated with cisplatin-based chemotherapy.

4513 Poster Discussion Session; Displayed in Poster Session (Board #183), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Whole exome sequencing to reveal chemotherapy-driven evolution of platinum-resistant metastatic urothelial cancer. *First Author: Bishoy Faltas, Weill Cornell Medical College, New York, NY*

Background: First line platinum-based chemotherapy is the standard of care for metastatic urothelial carcinoma (UC). While a subset may achieve long-term disease control, the majority of patients will die of metastatic platinum-resistant UC (PRUC). Our objective was to understand chemotherapy-driven molecular evolution of metastatic PRUC by sequencing matched pairs of treatment-naive primary UC and metastatic PRUC from each patient. **Methods:** Following informed consent, 50 UC samples from 23 patients were analyzed (23 metastases, 37 PRUC and 18 trios of matched primary, metastatic and germline samples including 2 rapid autopsy cases yielding tumor samples from multiple sites).Germline samples were prospectively collected and matched archival formalin-fixed paraffin-embedded primary tumors from the same patients were retrieved. Whole exome sequencing was conducted. Data was analyzed using an integrated analysis of somatic single nucleotide variants and somatic copy number alterations (SCNA), and CLONET to estimate tumor purity and ploidy and to quantify corrected SCNAs for the inference of the clonal hierarchy of genomic aberrations; allele-specific SCNAs analysis was conducted with a focus on 9p21 locus across the cohort. **Results:** 414 recurrently mutated genes were identified, the most common in TP53 (45%), FOXD2 (33%), NIN (28%), TSC1 (19%) and PIK3CA (11%). Frequent SCNA included CDKN2A deletions (33%), E2F3 amplifications (10%) and ERBB2 amplifications (7%). Reconstructed phylogenetic trees from matched primary, metastatic and germline trios revealed evidence of divergent clonal evolution. Paired pre-chemotherapy and post-chemotherapy tumors from the same patients shared only an average of 33% of the total number of mutations. Allele-specific SCNA analysis revealed significant inter and intra-patient heterogeneity in the 9p21 region. **Conclusions:** This study generates a detailed molecular profile of the genomic landscape of PRUC revealing extensive heterogeneity and clonal selection underlying evolution of platinum-resistance and metastatic spread.

4514 Poster Discussion Session; Displayed in Poster Session (Board #184), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Defects in DNA repair genes and sensitivity to cisplatin based neoadjuvant chemotherapy (NAC) for bladder cancer. *First Author: Yu-Ning Wong, Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA*

Background: Cisplatin based NAC prior to cystectomy is standard of care for MIBC, with 40-50% expected to respond with $\leq$ pT1N0M0. Biomarkers predictive of response are lacking. **Methods**: MIBC pts who received 3 cycles of cisplatin based NAC on 1 of 2 prospective multicenter clinical trials were included. Pts treated with accelerated methotrexate, vinblastine, doxorubicin + cisplatin (AMVAC) provided the discovery set [n = 34, 15/34 (44%) $\leq$ pT1N0M0]. Pts treated with dose dense gemcitabine + cisplatin (DDGC) provided the validation set [n = 24, 11/24 (46%) $\leq$ pT1N0M0]. DNA from pre-treatment tumor tissue underwent sequencing for all coding exons of 287 cancer-related genes and was analyzed for presence of base substitutions, indels, copy number alterations, and selected re-arrangements. The mean number of variants and variant status for each gene were correlated with response using two-sample t-test and Fisher's exact tests. Variant data were used to create a classification tree to discriminate responders vs. non-responders in the AMVAC discovery cohort. The resulting decision rule was then tested in the independent DDGC validation set. Overall survival analysis was performed using Kaplan-Meier. **Results**: Pts with pT0 had significantly more alterations than those with residual tumor in both the AMVAC discovery ($p = .024$) and DDGC validation ($p = 0.018$) set. In the AMVAC discovery set, alteration in $\geq$ 1 of the three DNA repair genes *ATM*, *RB1* or *FANCC* predicted for $\leq$ pT1N0M0 ($p < 0.001$, 87% sensitivity, 100% specificity) and improved overall survival (OS) ($p = 0.007$). This test remained predictive for $\leq$ pT1N0M0 in the DDGC validation set ($p = 0.033$), with a trend towards improved OS ($p = 0.055$) at short median follow up of 16.75 mo. **Conclusions**: Alterations in $\geq$ 1 of *ATM*, *RB1* and *FANCC* predict response to cisplatin based chemotherapy defined as $\leq$ pT1N0M0 in both our AMVAC discovery and DDGC validation sets. We hypothesize that defects in these genes, which are important for maintenance of chromatin structure and DNA repair, confer sensitivity to DNA damaging chemotherapy and explain the accumulation of alterations seen among pts with pT0. Further validation is planned.

4515 Poster Discussion Session; Displayed in Poster Session (Board #185), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase Ib/II study of an IL-2/T-cell receptor fusion protein in combination with gemcitabine and cisplatin in advanced or metastatic chemo-refractory urothelial cancer (UC). *First Author: Mayer N. Fishman, Moffitt Cancer Center, Tampa, FL*

Background: Although UC is sensitive to platinum-based chemotherapy such as gemcitabine (G) + cisplatin (C), patients who are refractory to GC have limited therapeutic options. ALT-801 is an IL-2/single-chain T-cell receptor fusion protein previously tested in various murine models. ALT-801 demonstrated potent activity against syngeneic and xenograft UC, suggesting sensitivity of this disease to IL-2 based immunotherapy. **Methods:** We report efficacy and safety results of co-administration of G (1000 mg/m^2/dose, d 1 & 8) + C (70 mg/m^2/dose, d 1) with ALT-801 (0.06 mg/kg/dose, d3, 5, 8, 12) on a 21 day schedule for 3 cycles in patients with advanced/metastatic chemo-refractory UC. The initial ALT-801 dose escalation and expansion study included chemo-naïve or refractory subjects of group 1. Group 2 are patients in a 2-armed Phase II dose expansion study of only chemo-refractory subjects receiving either 0.06 mg/kg ALT-801 + GC or 0.06 mg/kg ALT-801 + G based on the renal function. Those with at least stable disease (SD) after 3 cycles may receive addition cycles of study treatment. **Results:** To date, 62 were enrolled of whom 34 were chemo-refractory receiving ALT-801+GC (group 1, n = 17; group 2, n = 17). They were 82% male, had median age 62 y (47-74); 47% were ECOG PS = 1, and 76% had visceral metastases. Favorable responses including complete response (CR) were seen in both groups 1 and 2 with an overall response rate of 35% (95% CI: 20 - 54%) (3 CR, 9 PR, 6 SD, 12 PD, 4 non-evaluable). Median OS was 12.3 months for group 1; the group 2 results are pending follow-up. Grade 3/4 toxicities observed (n = 31) include thrombocytopenia (62%), neutropenia (48%), anemia (39%), lymphopenia (26%), hypophosphatemia (19%) and low WBC (13%). Evaluation of treatment-induced immune responses is ongoing. **Conclusions:** Based on responses seen in both groups, we conclude that ALT-801+GC has clinical activity in advanced/metastatic chemo-refractory UC patients. Observed toxicities are consistent with GC and with ALT-801 known pharmacological effects. Further evaluation of this regimen in randomized trials is warranted. Clinical trial information: NCT01326871 Clinical trial information: NCT01326871.

4516 Poster Discussion Session; Displayed in Poster Session (Board #186), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Expanded cohort results from CheckMate 016: A phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). *First Author: Hans J. Hammers, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: Nivolumab (N), a fully human IgG4 immune checkpoint inhibitor antibody, has shown durable response and encouraging overall survival (OS) in mRCC. Previously in CheckMate 016, N + ipilimumab (I) demonstrated manageable safety and promising antitumor activity in mRCC. Here, we report results from expansion cohorts in this study (NCT01472081). **Methods:** Patients (pts) with mRCC were randomized to N 3 mg/kg + I 1 mg/kg (N3 + I1), N 1 mg/kg + I 3 mg/kg (N1 + I3) or N 3 mg/kg + I 3 mg/kg (N3 + I3) IV Q3W for 4 doses, then N 3 mg/kg IV Q2W until progression or toxicity. Primary endpoint: safety. Other endpoints: objective response rate (ORR), duration of response (DOR), OS. DOR and OS were assessed by Kaplan-Meier method. **Results:** Pts randomized to N3 + I1 and N1 + I3 cohorts were expanded to 47 pts per arm; N3 + I3 (n = 6) arm showed early toxicity and did not proceed to expansion. 53% and 47% of pts were treatment naive and previously treated in N3 + I1; 45% and 55% were in N1 + I3. Median (range) follow-up was 34.3 (15.4 – 80.1) wks in N3 + I1 and 31.3 (4.6 – 79.9) wks in N1 + I3. Treatment-related AEs were seen in 88% of pts. Discontinuations for any grade AE occurred in 16% of pts. Grade 3-4 treatment-related AEs occurred in 34% and 64% of pts in N3 + I1 and N1 + I3, respectively; most common: ↑ lipase (13% and 26%), ↑ ALT (4% and 19%), diarrhea (2% and 15%), colitis (0 and 13%), ↑ AST (4% and 9%), and ↑ amylase (4% and 9%). Most common grade 3-4 select AEs were GI and hepatic (N3 + I1, N1 + I3); GI: 2%, 23%; hepatic: 4%, 21%. Efficacy is summarized in the table below. **Conclusions:** Updated results from expanded cohorts in CheckMate 016 confirm initial safety findings and promising antitumor activity for N + I in pts with mRCC. OS results for N + I in mRCC appear encouraging and support further development of this combination in the first-line setting. Clinical trial information: NCT01472081.

	N3 + I1 n = 47	N1 + I3 n = 47
OS, mos (range)	NR (3.5 – 18.4+)	NR (1.1 – 18.4+)
Overall ORR[a], n (%)	18 (38)	20 (43)
Stable disease, n (%)	19 (40)	18 (38)
Median DOR[b], wks (range)	NR (4.1+ – 67.1+)	53.9 (6.1+ – 66.0+)
Median PFS, wks (range)	30.3 (4.7+ – 72.6+)	36.0 (4.1+ – 77.9+)
PFS, 24 wks, % (95% CI)	53 (37 – 67)	64 (47 – 77)

[a]Confirmed response + unconfirmed response; [b]Confirmed response. NR, not reached.

4517 Poster Session (Board #197), Mon, 1:15 PM-4:45 PM

Effectiveness of adjuvant chemotherapy (AC) versus observation in patients with ≥ pT3 and/or pN+ bladder cancer (BCa). *First Author: Matt D. Galsky, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Though Level I evidence supports the use of neoadjuvant chemotherapy in BCa, the data supporting AC has been mixed. Experience suggests an adequately powered trial to definitely assess the role of AC is unlikely to be completed. Alternative approaches to evidence development are necessary. **Methods:** Patients undergoing cystectomy for ≥ pT3 and/or pN+ M0 BCa were identified from the National Cancer Database. Patients who received neoadjuvant chemotherapy and/or diagnosed after 2006 (most recent year with survival data) were excluded. Logistic regression was used to calculate propensity scores representing the predicted probabilities of assignment to observation versus AC based on: age, demographics, year of diagnosis, pT stage, margin status, lymph node density, distance to hospital, hospital cystectomy volume, and hospital type and location. Missing data were handled by multiple imputation. A propensity score-matched (1:1) cohort of AC versus observation patients was created using these variables. Stratified Cox proportional hazards regression was used to estimate the hazard ratio (HR) for the matched sample. Sensitivity analyses examined the impact of an alternative adjustment approach and comorbidities. **Results:** 4360 patients undergoing cystectomy alone and 1293 patients undergoing cystectomy plus AC met inclusion criteria.Patients receiving AC were significantly more likely to: be younger, have more lymph nodes examined and involved, have positive margins, reside in the Northeast, and have private insurance. HR are shown in the Table. Subset analyses explored the impact of nodal status [pN+ HR = 0.63 (0.56-0.70), pN- HR = 0.76 (0.63-0.90)] and age [<70 HR = 0.80 (0.72-0.88), ≥ 70 HR = 0.71 (0.61-0.82)]. The results were robust to sensitivity analysis for comorbidities. **Conclusions:** AC was associated with improved survival in patients with ≥ pT3 and/or pN+ BCa in this large comparative effectiveness analysis.

HR for overall survival with AC versus observation.

Model	HR [95% CI]
Matched Sample – Cox Model Stratified	0.71 [0.63-0.80]
Cox Model Weighted by Inverse Probability of Treatment Weight	0.78 [0.74-0.81]

4518 Poster Discussion Session; Displayed in Poster Session (Board #188), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

RECORD-4: A multicenter, phase II trial of second-line everolimus (EVE) in patients (pts) with metastatic renal cell carcinoma (mRCC). *First Author: Robert Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the pivotal RECORD-1 trial, EVE was superior to placebo in pts with mRCC previously treated with sunitinib, sorafenib, or both; prior treatment with cytokines, bevacizumab, and chemotherapy was permitted (*Cancer* 2010; 116:4256). The RECORD-4 study assessed EVE in pts with mRCC who progressed after 1 prior anti-VEGF or cytokine. **Methods:** RECORD-4 enrolled pts with clear cell mRCC into 3 cohorts based on prior first-line therapy: sunitinib, other anti-VEGF, or cytokines. Pts received EVE 10 mg/d until progression of disease (PD; RECIST, v1.0) or intolerance. Primary endpoint was PFS per investigator review. Data cutoff was Sept 1, 2014. **Results:** Enrolled pts (N = 134) previously received sunitinib (n = 58), other anti-VEGF therapy (n = 62: 23 sorafenib, 16 bevacizumab, 13 pazopanib, 10 other), or cytokines (n = 14). Demographics were balanced among cohorts; overall 90% of pts had good/intermediate MSKCC prognosis; most were white (56%) or Asian (41%). At data cutoff, 88% of pts had discontinued, mainly due to PD (54%). Median duration of exposure was 5.8 mo. Median overall PFS (95% CI) was 7.8 (5.7-11.0) mo, 5.7 (3.7-11.3) mo with prior sunitinib, and 7.8 (5.7-11.0) mo with prior other anti-VEGFs (Table). Overall response rate (ORR) was 7.5% (95% CI, 3.6-13.3%); most pts achieved stable disease (67%) as best overall response. Overall rate of grade 3 or 4 adverse events (AEs) was 56%. **Conclusions:** RECORD-4 results reinforce the clinical benefit of EVE in the second line setting after sunitinib and other first-line therapies. EVE safety profile was consistent with previous experience. (ClinicalTrials.gov ID, NCT01491672). Clinical trial information: NCT01491672.

Key efficacy and safety results.

	Prior therapy			
	Overall population N=134	Sunitinib N=58	Other anti-VEGF N=62	CytokinesN=14
Median PFS (95% CI), mo	7.8 (5.7-11.0)	5.7 (3.7-11.3)	7.8 (5.7-11.0)	12.9 (2.6-NE)
ORR, % (95% CI)	7.5 (3.6-13.3)	6.9 (1.9-16.7)	4.8 (1.0-13.5)	21.4 (4.7-50.8)
Safety set	N=133	N=58	N=61	N=14
Grade 3/4 AEs[a], n (%)				
Anemia	17 (13)	6 (10)	7 (11)	4 (29)
Stomatitis/mouth ulceration	10 (8)	4 (7)	4 (7)	2 (14)
Hyperglycemia	6 (5)	2 (3)	4 (7)	0 (0)
Hypertriglyceridemia	6 (5)	3 (5)	3 (5)	0 (0)

NE, not evaluable. [a]Commonly reported (incidence ≥ 4%).

4519 Poster Discussion Session; Displayed in Poster Session (Board #189), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Activating genomic mutations in the mTOR pathway to predict responses to everolimus and temsirolimus in patients with metastatic renal cell carcinoma (mRCC): Results from a large multi-institutional cohort. *First Author: Andre Poisl Fay, Oncology Service and Oncology Research Unit, HSL/PUCRS, Porto Alegre, Brazil*

Background: Mammalian target of rapamycin (mTOR) inhibitors are approved in mRCC, but only a subset of patients derives clinical benefit. Recently, case reports have suggested that mutations in mTOR pathway genes might be associated with response to everolimus and temsirolimus in several malignancies, including mRCC. **Methods:** We amassed a large international cohort of mRCC patients with available tumor specimens who received mTOR inhibitors and had distinct clinical outcomes: responders were defined as complete response (CR), partial response (PR) or stable disease with any tumor shrinkage or no tumor growth for at least 6 months (R); non-responders were defined as disease progression within the first 3 months of therapy (NR). Tumor DNA from 94 patients was analyzed using a targeted next-generation sequencing panel covering 504 cancer genes. We performed a blinded analysis to investigate the correlation between mutations in mTOR pathway genes and response status. **Results:** Samples from 79 of 94 patients were successfully sequenced and were included in the analysis. Mutations are summarized in **Table 1**. Mutations in *MTOR*, *TSC1* or *TSC2* were more common in R (12/43) than NR (4/36) (OR: 3.05; *p = 0.06; primary hypothesis*). Similarly, mutations in *TSC1* or *TSC2* were more common in R (9/43) than NR (2/36) (OR: 4.42; *p = 0.05; secondary hypothesis*). In an exploratory analysis, 5/12 with PR/CR had mutations in *MTOR*, *TSC1* or *TSC2* vs 4/35 NR (OR: 5.28; *p = 0.04*). **Conclusions:** In this large cohort of mRCC patients, mutations in *MTOR*, *TSC1* or *TSC2* were more common in patients with clinical benefit from everolimus or temsirolimus than in NR. Mutations in those 3 genes were associated with PR/CR to mTOR inhibitors. In contrast, neither PTEN nor PIK3CA mutations showed any association with response. These findings suggest that a personalized medicine approach has value for selection of mTOR inhibitors in mRCC.

Gene Mutation	NR(n = 36) n(%)	R(n = 43) n(%)	Total(N = 79) n(%)
MTOR(activating)	2(6)	3(7)	5(6)
PTEN(inactivating)	5(14)	5(12)	10(13)
TSC1(inactivating)	2(6)	8(19)	10(13)
TSC2(inactivating)	0	1(2)	1(1)
PIK3CA(activating)	0	1(2)	1(1)

4520 Poster Discussion Session; Displayed in Poster Session (Board #190), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Comprehensive genomic profiling of 443 patients with advanced renal cell carcinoma (RCC) to reveal clinically relevant genomic alterations and to aid in classification of rare subtypes. *First Author: Sumanta Kumar Pal, City of Hope, Duarte, CA*

Background: Large scale genomic sequencing studies in RCC (e.g., TCGA) have classically focused on localized disease, which is often curable. Advanced RCC represents a unique disease setting in which novel therapeutic targets may have a clinical impact. **Methods:** CGP for genomic alterations (GAs) was performed prospectively in 443 consecutive patients with advanced RCC (relapsed RCC or metastatic RCC at presentation). DNA was extracted from 40 microns of FFPE sections. CGP was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 646X for 3,230 exons of 182 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer (Frampton et al, Nat Biotechnol 2013). The CGP assay included base substitutions, INDELs, copy number alterations and fusions/rearrangements. Clinically relevant genomic alterations (CRGAs) were defined as alterations for which a selective inhibitor of the target or pathway is available. **Results:** There were 73% male and 27% female patients with a mean age of 56 years. 198 (44.6%) of the sequenced RCC cases were derived from metastatic sites. 400 patients (89%) had at least 1 GA with a mean 3.1 GA/case. Of the 400 RCC harboring GA, 396 (99%) had at least 1 CRGA involving 111 individual genes with a mean of 1.32 CRGAs/RCC case. The most common CRGA in order of frequency were: *ATM* (11%), *PTEN* (8.5%), *TSC1* (8.3%), *mTOR* (7%), *MET* (6.5%), *AR* (5.3%), *DNMT3A* (5%) and *TSC2* (5%). Other GAs such the ones with prognostic value in RCC included *CDKN2A* (21%) and *BAP1* (12%). Collecting duct carcinomas (CDCs) harbored an enrichment of *NF2* truncating alterations (>40%), distinct from renal medullary carcinoma (RMC). Multiple CDC cases harbored *SMARCB1* alterations suggesting these cases could be construed as RMC if a genomic criterion of *SMARCB1* loss of function is used for diagnosis. **Conclusions:** CGP can uncover a wide variety of CRGAs in advanced RCC with the potential to direct use of targeted therapies based on the tumor genotype. CGP can also refine the diagnosis of renal epithelial neoplasms.

4521 Poster Discussion Session; Displayed in Poster Session (Board #191), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Distinct MET alterations to induce a common phenotype and to define a MET-driven subset of papillary RCC: Results from the Cancer Genome Atlas (TCGA) Kidney Renal Papillary (KIRP) Working Group. *First Author: Laurence Albiges, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Papillary Renal Cell carcinomas (pRCC) are the most frequent non-clear cell RCC, commonly classified as type I and type II. *MET* oncogene mutations have been reported predominantly in type I. MET overexpression is a common feature in pRCC and correlates with copy number alteration (CNA). We aim to report the distinct molecular alterations of *MET* and their impact within the TCGA KIRP dataset. **Methods:** KIRP TCGA provides a comprehensive molecular evaluation of pRCC tumors. **Results:** Genomic analysis of 161 TCGA pRCC tumors revealed recurrent mutations in *MET* in 18 cases (11.2%): 3 germline and 15 somatic, and 72 cases (46%) with gain of chromosome 7. Analysis of RNA-Seq identified a new recurrent splicing isoform of *MET* in 8 cases (5%) skipping exons 1-2 (encoding the ligand binding domain) with inclusion of a new transcription start site prior to exon 3. Two new fusions (1.2%) involving the *MET* kinase domain and predicted to be constitutively activated were also identified. We further defined *MET* alterations as either a *MET* mutation, a splice variant or a *MET*-fusion. These alterations were mutually exclusive but tended to co-occur with CNA ($p < 0.001$). *MET* expression by RNA-seq was significantly elevated compared to the rest of the cohort ($p < 0.001$) when the alteration co-occurred with chromosome 7 gain. The *MET*-altered tumors exhibited a common phenotype associated with lower grade ($p < 0.001$), lower stage ($p < 0.001$), and better overall survival (log-rank $p < 0.001$) relative to all other pRCC. *MET* alterations were mostly observed in type I pRCC ($p < 0.001$). **Conclusions:** Overall, at least 17% of pRCC tumors included in the TCGA KIRP dataset present a *MET* alteration and display a common phenotype. A new splice variant is identified and may constitute a mechanism of ligand-independent *MET* activation. This report provides a survey of the diverse mechanisms of activation of the *MET* oncogene. Ongoing clinical trials of MET inhibitors in pRCC will hopefully help characterize the functional relevance of each proposed mechanism of activation involving *MET* in pRCC. *Funded in part by FNLCR Contract HHSN261200800001E.*

4522 Poster Discussion Session; Displayed in Poster Session (Board #192), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A phase II trial of everolimus (E) and bevacizumab (B) in advanced non-clear cell renal cell cancer (ncRCC) to show efficacy in patients (pts) with papillary features. *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: VEGF- and mTOR-directed therapies achieve inferior outcomes in pts with advanced ncRCC compared to clear cell RCC. Limited benefit from monotherapy supports study of combination regimens, prompting this phase II trial of E + B in pts with metastatic ncRCC. **Methods:** Treatment-naïve pts received concurrent E + B at standard doses until disease progression or intolerance to therapy. The primary endpoint was 6 month (mo) progression-free survival (PFS) with a planned sample size of 34 pts. Correlative analyses included ultra-deep next generation sequencing (NGS) from tumor and germline across 341 genes of interest. **Results:** 34 pts are evaluable (median follow-up 13.6 mo). The most common histologic subtype was unclassified RCC (URCC, n=23), the majority of which had papillary growth as a major component (n=14). 60% of pts achieved 6mo PFS; PFS varied significantly by histology ($p<0.001$). Objective response rates (ORR) were high in pts with significant papillary (7 of 18 pts) or chromophobe (2 of 5 pts) elements. Presence of a major papillary component was associated with treatment benefit across the entire cohort (table), particularly in pts with URCC, where this feature correlated with ORR (43 vs. 11%), median PFS (12.9 vs. 1.9 mo) and median OS (23.2 vs. 9.3 mo) (logrank $p<0.001$). NGS, performed on 33 cases, provides insight into the molecular background of disease phenotypes (e.g. frequent loss of chromosome 1p in tumors with papillary elements) and of treatment response (e.g. clonal convergence of activating alterations within the PI3K/mTOR pathway). **Conclusions:** Promising activity of E + B was seen in specific subtypes of ncRCC, particularly those with papillary features, justifying further study in a more defined population. The correlative analysis presented provides insight into the molecular basis of histologic phenotypes and response. Clinical trial information: NCT01399918.

	n	ORR (%)	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
Full cohort	34	29	11.0 (3.8 – NR)	17.3 (14.6 – NR)
Cases with major papillary component	18	39	12.9(10.9 – NR)	19.7 (16.7 – NR)
Cases without major papillary component	16	19	1.9 (1.6 – NR)	10.3 (7.9 – NR)

CI: confidence interval; NR: not reached.

4523 Poster Discussion Session; Displayed in Poster Session (Board #193), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

SWOG 1107: Parallel (randomized) phase II evaluation of tivantinib (ARQ-197) and tivantinib in combination with erlotinib in patients (Pts) with papillary renal cell carcinoma (pRCC). *First Author: Przemyslaw Twardowski, City of Hope, Duarte, CA*

Background: pRCC is associated with activation of MET signaling pathway and less favorable responses to VEGF inhibition than clear cell RCC. In SWOG 0317, the EGFR inhibitor erlotinib yielded a response rate (RR) of 11% and median overall survival (OS) of 27 months in pRCC pts. Tivantinib is a non-ATP competitive inhibitor of MET. In a preclinical pRCC model, combination erlotinib and tivantinib showed synergistic activity. A randomized multicenter phase II trial of tivantinib alone or with erlotinib was conducted in pts with either type I or II pRCC. **Methods:** Pts with histologically-confirmed advanced or metastatic pRCC and 0-1 prior systemic therapy were randomly assigned to tivantinib 360 mg BID (Arm 1) or tivantinib 360 mg BID plus erlotinib 150 mg daily (Arm 2). A RR of $\geq$ 30% was to be considered a promising outcome. Target accrual was 70 pts (35 per arm) with interim analysis planned after enrollment of 40 pts. Robust accrual resulted in 55 pts registered by the time of interim closure. **Results:** Of 55 pts enrolled, 50 were eligible: 25 in each arm. Median age was 64 years; most pts were male (68%). 33 pts (66%) had no prior systemic therapy; 6% of pts had type 1 pRCC, 42% had type 2, and 52% had no subtype assigned. The study was permanently closed at interim analysis when both arms yielded RR of 0%. Median progression free survival (PFS) was 2.0 and 5.4 months, and OS was 10.3 and 11.3 months in Arms 1 and 2 respectively. Most frequent adverse events: Arm 1- fatigue, nausea and anemia; Arm 2-rash, nausea, fatigue and diarrhea. Deep exome sequencing of archival tumor specimens is ongoing. **Conclusions**: Tivantinib - either alone or in combination with erlotinib has no clinical activity in pts with advanced pRCC. The addition of tivantinib to erlotinib may have reduced the latter's previously reported efficacy (although wide confidence intervals preclude a definite conclusion); this was not predicted by preclinical modeling. Although MET remains a reasonable therapeutic target in PRCC, more careful credentialing of proposed MET inhibitors, biomarkers, and patient subsets most likely to benefit would be required. (NIH/NCI NCTN CA180888;CA180819;CA180820). Clinical trial information: NCT01688973.

4524 Poster Session (Board #194), Mon, 1:15 PM-4:45 PM

Adjuvant chemotherapy for residual disease after neoadjuvant chemotherapy for muscle invasive urothelial cancer (MIUC). *First Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA*

Background: Neoadjuvant cisplatin-based chemotherapy (Neo) improves outcomes in MIUC. However, the benefit achieved with Neo correlates with pathologic downstaging and patients with residual disease (RD) remain at high risk for metastatic recurrence. The optimal management of such patients is unknown. We evaluated whether adjuvant chemotherapy (Adj) improves time to recurrence (TTR) in pts with RD after Neo. **Methods:** Data were captured from 23 sites participating in the Retrospective International Study of Cancers of the Urothelium (RISC). Pts with RD after Neo for UC were identified. Median (med) TTR was estimated by Kaplan-Meier method from 2 mo post-surgery to minimize lead time bias in non-Adj pts. The association between Adj and TTR was assessed using a multivariate Cox regression model. **Results:** From 11/1989 to 4/2013, 185 pts were identified who had RD despite Neo and had adequate follow-up time for data on Adj. Med follow-up time was 30 mo. 25 pts received Adj while 160 proceeded with surveillance. Both groups had similar performance status and med age at time of Neo. Med time to Adj was 1.5 mo. The majority changed regimens between Neo and Adj. Gemcitabine/cisplatin and dose dense MVAC were the most common regimens used in either setting. Use of Adj significantly correlated with higher path stage (p = 0.003). Med TTR was 17 mo with 95/185 experiencing relapse. After adjusting for path stage, type of Neo and age, Adj pts had a significantly decreased risk of relapse (HR = 0.35, 95% CI: 0.17,0.74). A subset analysis (Adj = 19, surveillance = 50) of pts with residual pathologic T4 and/or N+ after Neo also revealed a significant improvement with Adj: median TTR of 20 mo versus 9 mo, p = 0.02 (HR = 0.43, 95% CI: 0.21,0.89). **Conclusions:** In this international series, the use of Adj chemo for RD after Neo was rare. While limited by small numbers and the potential selection bias inherent to retrospective analyses, Adj may delay recurrence in pts with residual pT4 or N+ disease despite Neo. Overall survival analysis will be presented.

4525 Poster Session (Board #195), Mon, 1:15 PM-4:45 PM

JEVTCC: Phase II trial of cabazitaxel (Cbz) in patients (pt) with advanced or metastatic transitional-cell carcinoma (mTCC), who progressed before 12 months after cisplatin-based chemotherapy—A Spanish Oncologic Genitourinary Group (SOGUG) study. *First Author: Jose Angel Arranz Arija, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Background: Treatment of mTCC progressing to cisplatin is an unmet need. Prognostic factors (PF) for worse overall survival (OS) are ECOG >0, Hb <10 g/dL and liver metastases (Bellmunt, JCO 2010). Taxanes are active as 2nd-line in mUC. Cbz, a semi-synthetic taxane, is a poor substrate for the multidrug resistance system. **Methods:** Phase II study of Cbz 25 mg/m2/3w until progression, death or unacceptable toxicity, in each of the 3 subgroups of mTCC: very good, good or poor prognosis (VGP, GP, PP), defined by 0, 1 or > 1 of the above PF respectively. Primary endpoint of response rate ≥ 20% (RR, RECIST 1.1), required 35 pt in each group. Multinomial response and early progressions method (MREP, $\alpha = 0.05$, $\beta = 0.2$), and 2-stage Simon's optimal design (SOD, $\pi 0 = 10\%$, $\pi 1 = 30\%$ $\alpha = 0.05$, $\beta = 0.1$), were used for early stopping rules in an intermediate analysis (IA) in each group, after 15 and 18 evaluable pt respectively. Secondary endpoints: PFS, OS, and toxicity. Recruitment was not stopped until IA were available. **Results:** 71 pt were included (ITT population), 59 eligible and evaluable: 16/21 VGP, 28/34 GP, 15/16 PP. Mean age 65 y, 85% male, 94% ECOG 0-1, 77% bladder mTCC. Metastatic sites: 69% lymph nodes, 41% lung, 32% bone, 24% liver, 30% others. Toxicity is described in a separate abstract. Response (R), stable disease (SD), progression (PD), % RR, PFS and OS (months, with CI 95%) are summarized in the table below. **Conclusions:** In the IA, a RR ≥20% of Cbz after cisplatin in mTCC could be excluded in all prognostic subgroups, and the study was stopped. However, PFS and OS seem to be similar to those obtained with other active drugs in 2nd-line mTCC. EUDRACT 2011003498-27. Funding: Sanofi. Clinical trial information: 2011003498-27.

Group	N	# R	# SD	# PD	% RR (CI 95%)	Median PFS (CI 95%)	Median OS (CI 95%)
VGP	16	1	6	8	6.25 (1.1 – 28.3)	2.3 (1.9 - 3.9)	11.6 (4.5 - 20.1)
GP	28	0	11	17	0%	2.1 (1.9 - 4)	7.1 (3.6 - 8.3)
PP	15	1	2	12	6.7 (0.3 – 34)	2 (1.8 - 2.3)	3.7 (2.3 – 5.2)
ITT	71				4.9 [1.7 - 13.5]	2.1 (1.9 - 2.4)	5.3 (4.1 - 8.3)

4526 Poster Session (Board #196), Mon, 1:15 PM-4:45 PM

Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the urinary bladder to reveal frequency of clinically relevant genomic alterations. *First Author: Matthew J. Hawryluk, Foundation Medicine Inc., Cambridge, MA*

Background: Clinically advanced metastatic urothelial carcinoma (UC) is a devastating disease lacking effective systemic therapies. Herein, we present a comprehensive genomic profile-based (CGP) study of UC designed to detect clinically relevant genomic alterations (CRGA) that could inform the selection of established and novel targeted therapies. **Methods:** DNA was extracted from 295 consecutive cases of relapsed/metastatic UC. CGP was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 688X for 236 cancer-related genes. The CGP assay included base substitutions (SUB), INDELs, copy number alterations (CNA) and fusions/rearrangements. CRGA were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials. **Results:** There were 75% male and 25% female patients with a mean age of 66 years. 295/295 (100%) of UC were high grade and advanced stage (III and IV). 294/295 (99.7%) UC had at least 1 GA on CGP with a mean of 6.4 GA/UC with 61% SUB + INDEL, 37% CNA and 2% fusions. 275 (93%) UC had at least 1 CRGA involving 75 individual genes with a mean of 2.6 CRGA/UC. The most common CRGA involved *CDKN2A* (34%), *FGFR3* (21%), *PIK3CA* (20%) and *ERBB2* (16%). *FGFR3* GA were of diverse type and included 10% fusions. *ERBB2* GA were equally divided between amplifications (CNA) and SUB. *ERBB2* SUB were predominantly in the extracellular domain and were highly enriched in the micropapillary UC subgroup. Multiple clinical antitumor responses to therapies targeting *FGFR3* and *ERBB2* will be presented. **Conclusions:** Using a CGP assay capable of detecting all classes of GA simultaneously, an extraordinary high frequency of CRGA were identified in a large series of patients with clinically advanced UC. More than one-third of these relapsed/refractory cases of UC harbored alterations in *FGFR3* and *ERBB2* that are showing active responses to targeted therapies. Continued evaluation of CGP for UC and the development of genomic driven clinical trials designed to employ targeted agents potentially in combination with cytotoxic drugs for this challenging disease appears warranted.

4527 Poster Session (Board #198), Mon, 1:15 PM-4:45 PM

Externally validated improved 5-factor prognostic model in patients (pts) receiving salvage systemic therapy for advanced urothelial carcinoma (UC). *First Author: Guru Sonpavde, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

Background: Prognostic factors in pts receiving salvage systemic therapy for advanced UC include performance status (PS), liver metastasis (LM), hemoglobin (Hb) and time from prior chemotherapy (TFPC). We investigated the impact of neutrophil count (N), lymphocytes (L), platelets (PLT) and albumin (Alb). **Methods:** Patient level data from phase II trials of salvage therapy on N, L, PLT and Alb were required in addition to TFPC, Hb, PS and LM status. Cox proportional hazards regression was used to evaluate their association with overall survival (OS). An optimal regression model was constructed using forward stepwise selection and risk groups defined using number of adverse factors. Trial was a stratification factor. External validation of significant factors was conducted in a separate dataset of 5 salvage phase II trials including 167 pts. **Results:** Data for discovery was obtained from 10 trials accruing 708 pts. After adjustment for TFPC < 3 months (mo), Hb < 10 g/dl, PS > 0 and LM status, PLT > ULN (upper limit of normal) and Alb < LLN were significant poor prognostic factors (Table). Only the addition of Alb < LLN was externally validated. Based on the 5 factor risk model, the median OS (mo) is 8.9, 6.4, 4.5 for 0-1, 2, 3+ risk factors (n = 207, 171, 113) in discovery dataset (n = 491), and 10.6, 10.0, 7.0 with n = 73, 47, 47 in the validation dataset (n = 167). The c-index improved from 0.631 to 0.638 in the discovery set and from 0.601 to 0.632 in the validation set by adding Alb < LLN to the previously identified 4 factors. **Conclusions:** A 5-factor model including TFPC < 3 mo, Hb < 10 g/dL, PS > 0, LM status and Alb < LLN was externally validated and enhanced the Bellmunt prognostic model in pts receiving salvage systemic therapy for advanced UC. Table

	Discovery (n = 491)		Validation (n = 167)	
Factor	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
TFPC < 3 months	1.49 (1.19, 1.87)	< 0.001	1.35 (0.87, 2.08)	0.18
ECOG PS > 0	1.39 (1.16, 1.67)	< 0.001	1.58 (1.06, 2.35)	0.023
Liver Metastases	1.45 (1.16, 1.81)	< 0.001	1.26 (0.83, 1.90)	0.27
Hb < 10 g/dl	1.73 (1.27, 2.35)	< 0.001	1.35 (0.94, 1.96)	0.10
Alb < LLN	1.61 (1.20, 2.15)	0.002	1.90 (1.27, 2.85)	0.002

4528 Poster Session (Board #199), Mon, 1:15 PM-4:45 PM

Molecular characterization of bladder cancer in smokers versus non-smokers. *First Author: Monika Joshi, Penn State Hershey Medical Center, Harrisburg, PA*

Background: Bladder cancer (BC) is one of the most common malignancies of the urinary tract and is 4thmost common cancer among men. It is estimated that by the end of 2015, the US will have approximately 74,000 new BC cases, accounting for 16,000 cancer related deaths. Smoking is considered an important risk factor for BC; recent data demonstrate an increase in BC incidence in non-smokers as well. Molecular characterization of BC in non-smokers has not been well studied. To the best of our knowledge, no retrospective or prospective study examining the correlation between smoking status (smokers vs non-smokers) and specific genetic alterations in BC has been published to date. **Methods:** 676 consecutive BC profiled at a CLIA certified laboratory were evaluated for differences in molecular characterization between smokers and non-smokers. Smoking status, patient characteristics, age, sex and survival data were collected on a subgroup; compilation of etiology is ongoing for additional patients. **Results:** 30 patients were confirmed lifetime nonsmokers (NS) and 39 were confirmed smokers or reformed smokers (R/S). Identified trends included differences in the PI3 kinase, WNT and EGFR pathways. Percentage of PIK3CA mutations was higher in NS (43%) vs. R/S (11%), whereas the WNT pathway aberration (CTNNB1 and APC mutations) occurred more frequently in R/S. EGFR amplification occurred in 22% NS and 11% in R/S, while HER2 was amplified only in R/S (23% vs. 0%, $p = 0.05$). Additionally, 3 of 8 R/S had an ALK 2p23 rearrangement, found in ~5% non-small cell lung cancers. TP53 did not differ between the populations. Survival data for 31 patients (14 NS, 17 R/S) showed overall average survival in the NS cohort was 175 days longer than in the R/S cohort. **Conclusions:** The difference in molecular biology between R/S and NS with BC suggests a different oncogenesis with potentially different treatment options. Increased incidence of PIK3CA mutations in NS may inform therapeutic options in this select group of BC patients with no smoking history. The results will need further verification in a larger group of BC patients in a prospective clinical study; more studies also need to be conducted to identify other mutational abnormalities between smokers vs. lifetime non-smokers.

4529 Poster Session (Board #200), Mon, 1:15 PM-4:45 PM

Maintenance vinflunine post cisplatin chemotherapy (CT) in patients with advanced urothelial carcinoma (UC): Preliminary analysis of a randomized placebo controlled phase II trial (MAJA trial)—SOGUG 2011-02. *First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Vinflunine (VFL) is a microtubule inhibitor approved by EMA as treatment after platinum progression, in metastatic bladder cancer. We evaluated whether maintenance VFL delays progression after response to CT. **Methods:** Patients (pts) with measurable disease, locally recurrent/metastatic UC and adequate organ function with radiological response or stabilization after 4-6 cy of a cisplatin/gemcitabine chemotherapy (carboplatin allowed after cy 4) were randomized 1:1 to receive VFL 320 mg/m^2 or 280mg/m^2(in case of PS 1, age $\geq$ 75 years, prior pelvic radiotherapy or CrCl $<$ 60ml/min) every 21 days vs best supportive care (BSC), until disease progression. The primary endpoint was progression free survival (PFS). With a median PFS considered unacceptable for the experimental arm 4 months (p0) and a very acceptable 6.5 (p1). 39 eligible pts per treatment arm were required to select better therapy with a type I error of 0.05 (α, one-tailed test), and a type II 0.1 (β) error. **Results:** 88 patients from 21 institutions of SOGUG cooperative group have been randomized between 04/2012 and 01/2015. At the time of present analysis 77 have confirmed eligibility and 66 pts (33 in the VFL arm and 33 in the BSC arm) have received at least 2 cy. Preliminary results based on these 66 pts are presented. Median age 63 years (range 42-78); PS 0/1, 50%/50%; CrCl $<$ 60 ml/min 24%; liver metastasis 25%; prior pelvic RT 10%. Primary location: bladder 82%. Metastatic/locoregional disease 77%/23%. Pure transitional 87%. 242 cy given in the VFL arm with a median of 4 cycles per patient (1–28). Most common G 3/4 (% pts) AEs were constipation (17.6%), neutropenia (17.6%), fatigue (11.7%), and 1 febrile neutropenia (2.9%). 2 deaths due to pneumonia not related to the treatment. With a median follow-up of 7.2 months (0.1-29.9), the median PFS was 10.4 months (0-24.6) in the VFL arm and 4.6 months (1.7-7.4) in the BSC arm ($p = 0.058$). **Conclusions:** Preliminary results indicate that maintenance VFL post CT has an acceptable tolerability profile in advanced UC pts and is associated with clinical activity. Further follow-up with mature results are needed. Clinical trial information: NCT01529411.

4530 Poster Session (Board #201), Mon, 1:15 PM-4:45 PM

Role of *miR-21*, *miR372*, and *E2F1* as biomarkers predicting outcome in cisplatin-treated bladder cancer patients. *First Author: Chensheng Willa Zhou, Dana-Farber Cancer Institute, Boston, MA*

Background: Cisplatin based chemotherapy is the gold standard for first line metastatic/locally advanced urothelial carcinoma (aUC). Variant expression of selected miRNAs and transcription factors (TF) are shown to correlate with and predict cisplatin efficacy in many types of cancers. In this study we aimed to confirm the role of selected miRNAs and TFs in patients receiving first line cisplatin combination therapy in aUC **Methods:** 82 clinically annotated patients with aUC (including N1 resected patients), with available tumor tissue, were identified, and total RNA was extracted from FFPE specimen. MicroRNA (miR21, miR106b, miR10b, miR146a, miR146b, miR371, miR372, miR373, miR1224, miR1248, miR200c, Let7i, miR27b, and miR26b) and TF panels (RELA, SMAD4, FOXO3, E2F1 and TWIST1) were identified using in silico data mining based on their roles in UC or in cisplatin response. Time to progression (TTP) was defined as time from chemotherapy start date to date of progression or censored on the last known without progression. For the TTP analysis, median miRNA expression levels were dichotomized and a cox regression model was used. For the extreme TTF phenotype, correlations were assessed by Wilcoxon's test ($P < 0.05$). Multivariate analysis was performed for all miRNAs, adjusting for ECOG status and visceral disease. **Results:** The median TTP was 12 mo, with 43 patients experiencing disease progression. In the TTP multivariate analysis, increased levels of E2F1 [$p = 0.02$, HR:0.49, (0.27, 0.89)], miR21 [$p = 0.03$, HR:0.53, (0.29, 0.97)] and miR372 [$p = 0.02$, HR: 0.49, (0.26, 0.90)], were associated with a shorter TTP. For the extreme phenotype, only miR21 and E2F1 were shown to be associated with TTP ($p = 0.055$). **Conclusions:** In this retrospective cohort of patients treated with cisplatin based therapy, higher levels of E2F1, miR21, and miR372 correlated with a shorter TTP. Biological validation of cisplatin effect on 6 bladder cancer cell lines that express different miR21 levels, from Cancer Cell Line Encyclopedia, is ongoing and results will be presented.

4531 Poster Session (Board #203), Mon, 1:15 PM-4:45 PM

The basal subtype to predict clinical benefit from neoadjuvant chemotherapy: Final results from a phase II clinical trial of DDMVAC + bevacizumab. *First Author: Arlene O. Siefker-Radtke, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Gene expression profiling (GEP) suggests 3 main subtypes of urothelial cancer: basal, which historically has the worst prognosis with high proliferation and HIF-1 expression; p53-like, with decreased proliferation and increased markers of extracellular matrix (ECM); and luminal which has increased proliferation compared to p53-like tumors. We hypothesized that GEP of transurethral resections (TUR) and cystectomy specimens from patients on a neoadjuvant trial would predict benefit from chemotherapy **Methods:** Sixty patients enrolled on a neoadjuvant trial of DDMVAC+B. TUR and cystectomy specimens were available for gene expression profiling in 39 and 33 patients, respectively, with matched specimens in 23 patients. The validation set consisted of 49 patients treated with perioperative MVAC on a previously published clinical trial **Results:** Chemotherapy was quite active with pT0N0 and $\leq$ pT1N0 down-staging rates of 38% and 53%, respectively. Basal tumors had improved survival compared to luminal and p53-like (5-year OS 91%, 73% and 36%, $p = 0.015$). A validation cohort of patients treated with perioperative MVAC confirmed this survival benefit (5-year OS basal, luminal, and p53-like 77%, 57%, and 57%, respectively, $p = 0.027$). The use of bevacizumab in basal tumors did not confirm evidence of significant benefit in these small numbers of patients (5-year OS bevacizumab: 91% vs MVAC: 77%, $p = 0.68$) Bone metastases within 2 years associated exclusively with the p53-like subtype (p53-like: 100%, luminal: 0%, basal 0%, $p \leq 0.001$). The p53-like subtype was enriched at cystectomy (basal to p53-like in 3/5 (60%), luminal to p53-like in 5/7 (71%), suggesting chemo-resistance in p53-like tumors **Conclusions:** In contrast to historical expectations, the basal subtype was predictive of clinical outcomes from neoadjuvant chemotherapy, reflecting the impact of chemotherapy on highly proliferative tumors. Bone metastases were associated with the p53-like subtype which is enriched for ECM. We can no longer think of urothelial cancer as one disease; subtyping should be considered for all tumors, and may have implications on selecting therapy Clinical trial information: NCT00506155.

4532 Poster Session (Board #204), Mon, 1:15 PM-4:45 PM

Association of somatic mutations in DNA damage repair (DDR) genes with efficacy of platinum-based chemotherapy in advanced urothelial carcinoma. *First Author: Richard Martin Bambury, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Platinum-based chemotherapy (PBC) is standard of care in the neoadjuvant and metastatic UC settings. Recent work identified mutations in *ERCC2*, *RB1*, *FANCC* and *ATM* as potential predictive biomarkers of response. We assessed response to PBC among patients with locally advanced or metastatic UC who underwent pre-treatment tumor genomic sequencing. **Methods:** 72 patients treated with PBC had exon sequencing of > 200 tumor suppressor/oncogenes using the MSK-IMPACT next generation sequencing assay. Deletions, truncations, frameshift, splice-site and missense alterations were recorded among 33 genes involved in the nucleotide excision repair, homologous repair and Fanconi anemia pathways (Table). Inactivating alterations in *RB1* and *TP53* were also investigated as potential predictive biomarkers. Baseline clinical parameters, investigator-assessed radiologic response and PFS were recorded. **Results:** 31(43%) patients had alterations in DDR genes and these were associated with improved PFS (median 11.3 v 6.1 months, HR 0.51, p 0.01). Among 65 evaluable patients, radiologic response was observed in 81% of those with DDR gene alterations vs. 58% in those without (p 0.06). DDR alterations remained a significant predictor for PFS on multivariate analysis (HR 0.45, p 0.004) after adjusting for ECOG performance status, visceral vs nodal metastases, chemotherapy type (cisplatin v carboplatin) and prior perioperative cisplatin. Among 9 patients with deletion, truncation, frameshift or splice-site alterations of DDR genes, 8 achieved PFS >11 months. There was no association between PFS and *RB1* (HR 1.37, p 0.32) or *TP53* (HR 0.93, p 0.79) alterations. **Conclusions:** Alteration of DDR genes is associated with improved efficacy in patients receiving 1st line PBC for advanced UC. Further refinement and validation could lead to prospective identification of patients who will respond to PBC, as well as identify patients unlikely to benefit and for whom alternative approaches are warranted.

ATM	ERCC2	PARP1
ATRX	ERCC3	PMS1
BAP1	ERCC4	PMS2
BARD1	ERCC5	POLE
BLM	FANCA	RAD50
BRCA1	MLH1	RAD51
BRCA2	MRE11A	RAD51B
BRIP1	MSH2	RAD51C
CHEK1	MSH6	RAD51D
CHEK2	NBN	RAD52
FANCC	PALB2	

4533 Poster Session (Board #206), Mon, 1:15 PM-4:45 PM

Germ cell cancer and multiple relapses: Toxicity and survival. *First Author: Jakob Lauritsen, Rigshospitalet, Copenhagen, Denmark*

Background: A small fraction of patients with germ-cell cancer (GCC) receive more than one line of systemic treatment. The purpose of this study was to evaluate late-toxicity and survival in an unselected cohort of patients who relapsed after initial systemic treatment for disseminated disease. **Methods:** Based on the Danish DaTeCa database we identified all patients who received two or more lines of systemic treatment. Information on late-effects and mortality in GCC-survivors was obtained through linkage to national registers. Prognostic factors for relapse and death were identified and compared to the International Prognostic Factors Study Group (IPFSG). **Results:** In total, 268 patients received two or more lines of systemic treatment for disseminated GCC. Approximately half of the patients died of their disease (n = 136). The surviving patients (n = 132) had highly increased risk of death of other causes hazard ratio (HR): 2.5 (95% CI: 1.6-4.1), second cancer HR: 3.4 (2.0-5.7), major cardiovascular disease HR: 1.9 (1.0-3.3), pulmonary disease HR: 2.4 (1.3-4.4), gastrointestinal disease HR: 7.1 (3.5-14.3), renal impairment HR: 9.2 (3.4-25.5), and neurological disorders HR: 5.4 (2.7-10.8) compared to patients treated with orchiectomy only. We found a dose-response relationship with increasing number of treatment lines within most toxicities. The IPFSG-classification was confirmed in our population; however, we could not confirm primary site and hCG as independent factors. We identified increasing age as a possible new prognostic factor for treatment failure, hazard ratio (HR): 1.2 (1.2-1.5) per 10 years. **Conclusions:** GCC-survivors after second-line systemic treatment have a highly increased risk of severe late-toxicity and death, and should be candidates for life-long follow-up. The IPFSG-classification was confirmed in this unselected population.

4534 Poster Session (Board #207), Mon, 1:15 PM-4:45 PM

Wilms' tumor gene 1 (WT1) aberrations in testicular germ cell tumors (TGCTs). *First Author: Ludmila Boublikova, Department of Pediatric Hematology and Oncology, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic*

Background: Wilms' tumor gene 1 (WT1) is a transcription factor essential for normal development of the urogenital system and male gonadal formation. Its alterations have been found in Wilms' tumor, other malignancies and testicular dysgenesis syndromes. We studied WT1 aberrations to address its role in the pathogenesis of testicular germ cell tumors (TGCT). **Methods:** In fresh-frozen samples of 85 TGCT (48 seminomas, 37 non-seminomas), 3 stromal tumors and 88 non-neoplastic controls, expression of total WT1 and its four main isoforms was quantified by qPCR. WT1 mutations were detected by direct and next-generation sequencing (NGS). The presence of WT1 protein was evaluated by standard immunohistochemistry. **Results:** The total WT1 expression was significantly lower (1 log) in TGCT than in the controls and stromal tumors (Kruskal-Wallis $p < 0.0001$), and was lower in seminomas than non-seminomas. Testicular tissue surrounding TGCT and containing *in situ* lesions expressed similar WT1 levels like other controls. WT1 isoforms lacking the exon 5 ([EX5-] isoforms A and C) were highly overexpressed in TGCT and stromal tumors in comparison with controls (Kruskal-Wallis, $p < 0.0001$). The isoform D, containing both main splice sites, was down-regulated in the tumors and this altered expression pattern was independent of total WT1 expression. Direct sequencing of exon 7 and 9 (with clustered hot-spots) could identify only 2 types of SNPs – synonymous rs16754 (31% of TGCT) and intronic rs5030274 (2%). By NGS however, 1 – 3 mutations in WT1 newly occurring in TGCT and not present in the paired controls were found in 59% of 22 analyzed cases. Staining for WT1 protein was positive in controls and undetectable in TGCT cells. **Conclusions:** The finding of total WT1 down-regulation in TGCT with the difference between seminomas and non-seminomas, the alteration of the isoform pattern with a pronounced shift to [EX5-] variants in TGCT independent of total WT1 levels, and the new occurrence of WT1 mutations in a high proportion of TGCT samples support the role of WT1 as a local tumor-suppressor gene in testicular tissues. *Supported by grants IGA NT/12414-5, GAUK56413, UNCE204012 and CDRO00064203FNM*

4535 Poster Session (Board #208), Mon, 1:15 PM-4:45 PM

Impact of response to induction chemotherapy (CT) and prior paclitaxel (TXL)-based CT on the outcome of salvage high-dose chemotherapy (HDCT) for relapsed germ-cell tumors (GCT) in the modern era: An EBMT Solid Tumors Working Party study. *First Author: Andrea Necchi, Istituto Nazionale Tumori of Milan, Milano, MI, Italy*

Background: The prognostic impact of response to induction CT preceding salvage HDCT courses, and prior TXL-therapy for advanced GCT is unknown. This knowledge can inform trial design, stratification and eligibility criteria to HDCT. **Methods:** 23 European centers contributed data. Eligibility included adult male patients (pts) with GCT, and treatment with salvage HDCT between the years 2002 and 2012. Both TXL used in prior CT lines of therapy and in induction-mobilization regimens pre-HDCT were considered. Multivariable Cox analyses (MVA) evaluated the association of prespecified factors (prior TXL therapy, line of HDCT, primary site, prognostic category, response to induction CT and chemosensitivity), with progression-free (PFS) and overall survival (OS). **Results:** Since 10/2013, 324 of 442 registered pts were suitable for present analysis. 165 pts (51%) received HDCT in second-line, 102 (31%) in third and 57 (18%) beyond the third-line. 76 (23%) HDCT regimens were taxane-containing. 192 pts (59.3%) have received prior TXL-regimens. 61 pts (19%) had a progression (PD) to induction CT, 234 (72%) a response (29 [9%] missing or GCSF only). Median follow up was 36 months (IQR: 19-70). PD to induction CT and prior TXL were significantly associated with shorter OS in the univariable model ($p < 0.001$ and $p = 0.032$). However, on MVA while PD to induction CT was significantly prognostic for PFS and OS (HR: 1.92, 95%CI, 1.24-2.98, $p = 0.003$, and HR: 2.09, 95%CI, 1.27-3.42, $p = 0.003$), prior TXL-therapy was not: HR: 1.10 (95%CI, 0.70-1.73, $p = 0.674$) and HR: 1.09 (95%CI, 0.64-1.86, $p = 0.739$). Also, line of HDCT was not significant ($p = 0.338$ and $p = 0.340$ for PFS and OS). A separate model evaluated the interaction between prior TXL-therapy and taxane-containing HDCT: no significant interaction was found ($p = 0.221$ and $p = 0.077$ for PFS and OS). **Conclusions:** While PD to induction CT was independently prognostic for PFS and OS, prior TXL-regimens did not affect the outcome of HDCT. Stratification of trials for the latter factor did not appear to be required when accounting for the other clinical predictors.

4536 Poster Session (Board #209), Mon, 1:15 PM-4:45 PM

Prognostic significance of thromboembolic events in chemotherapy-treated germ cell tumors. *First Author: Enrique Gonzalez-Billalabeitia, Hosp G Universitario Morales Meseguer, Murcia, Spain*

Background: To evaluate the incremental prognostic value of thromboembolic events (TEE) in combination with the International Germ Cell Cancer Collaborative Group (IGCCCG). **Methods:** Patients with germ-cell cancer receiving first-line platinum-containing chemotherapy (CT-GCC) between 2000-2014 were pooled from the Spanish Germ-Cell Cancer Group (Grupo Germinal)/Spanish Oncology Genitourinary Group (SOGUG) registry and another 3 tertiary hospitals. We used the Cox-proportional hazard model with bootstrap resampling to identify prognostic factors for both overall survival (OS) and progression-free survival (PFS). Good risk IGCCCG was used as the reference category. **Results:** We included 683 consecutive patients from 17 centers. With a median follow-up of 50 months TEE were observed in 8% of the patients (n=65), of which 86% were venous and 14% were arterial. Venous TEEs (VTE) occurred before, during and after chemotherapy in 27%, 57% and 16%. All arterial thrombosis (ATE) ensued during or after chemotherapy. On Cox regression analysis, the IGCCCG risk category, as well as pre-chemotherapy venous and arterial events were independent prognostic variables (Table 1). Bootstrap bias-corrected Harrell's C-index was 0.74 (95% CI, 0.692-0.794) and 0.880 (95%CI, 0.837-0.922) for PFS and OS in the model combining the IGCCCG score and the presence of VTE and ATE. **Conclusions:** Thromboembolic events are clinically significant in CT-GCC. The classification of germ-cell tumors might be improved by incorporating surrogate variables of hipercoagulable states, such as the presence of early venous thromboembolisms and arterial thrombosis.

Explanatory covariates included in the Cox-Proportional Hazard Model for PFS and OS.

	Progression-Free Survival			Overall Survival		
Variable	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
IGCCCG risk score						
· Intermediate	2.41	1.40-4.16	0.002	8.61	3.48-21.3	<0.001
· Poor	8.58	5.34-13.80	<0.001	39.27	16.89-91.30	<0.001
Venous thrombosis						
· Pre-CT	3.13	1.42-6.89	0.005	3.61	1.40-9.29	0.008
· On-CT	1.13	0.54-2.40	0.744	1.39	0.61-3.19	0.432
· Post-CT	3.36	1.50-7.52	0.003	0.98	0.26-3.70	0.972
Arterial thrombosis	5.11	2.05-12.75	<0.001	4.40	1.52-12.74	0.006

4537 Poster Session (Board #210), Mon, 1:15 PM-4:45 PM

Clinical outcomes of late relapse in stage I seminoma. *First Author: Ali Hosni, Princess Margaret Cancer Center, Toronto, ON, Canada*

Background: This study aimed to identify characteristics associated with late relapse (LR) in stage I seminoma and determine clinical outcomes according to timing of relapse. **Methods:** Between 1981 and 2011, 949 stage I seminoma patients were managed at our institution. Of these, 254 were treated with adjuvant radiotherapy (aRT) and 695 were managed by active surveillance (AS). LR was defined as tumor recurrence more than 2 years after orchiectomy. Treatment at relapse was dependent on initial treatment and disease extent at relapse. Progression free survival (PFS) from end of treatment of first relapse and overall survival (OS) were calculated. **Results:** At median follow-up of 10.9 years, 129 patients relapsed at median of 12 months; 14 after aRT and 115 on AS. There was no significant difference between the proportion of patients with LR for aRT (3/14; 25%) vs. AS (29/115; 21%) with no specific clinicopathological features were associated with LR. Paraaortic node(s) was the most common relapse site in AS patients either in LR (n = 28, 97%; median size: 2.1 cm) or early relapse (n = 79, 92%; median size: 2 cm), whereas in aRT patients; all LR were in mediastinum, and early relapse was inguinal (n = 4), scrotal (n = 3) and distant (n = 4). Most LR occurred between 2-3 years (n = 14, 44%; 13 of them were AS patients), and 8 of 9 patients who had LR beyond 5 years were on AS. Treatment of first relapse for aRT group consisted of chemotherapy (n = 10), RT (n = 3) and surgery (n = 1); and for the AS group: RT (n = 87), chemotherapy (n = 26) and surgery (n = 2).Only 1 aRT patient developed second relapse. Nine AS patients had second relapse (7 after RT and 2 after chemotherapy) at a median (range) time of 13 (2–48) months. Second relapse was predominantly distant (9/10), however all were successfully salvaged with chemotherapy. The 5-year PFS from end of treatment of first relapse for the whole, aRT and AS groups were similar, 93%. Among AS group, there was no significant difference between early and late relapse in 5-year PFS (91% vs 100%, p= 0.1) or 10-year OS (96%, for both). **Conclusions:** In stage I seminoma, the extent and pattern of LR is similar to that for early relapse. For AS patients, selective use of RT/chemotherapy for relapse results in excellent outcomes regardless of timing of relapse.

4538 Poster Session (Board #211), Mon, 1:15 PM-4:45 PM

Perioperative morbidity and mortality with bleomycin in primary mediastinal non seminomatous germ cell tumor (PMNSGCT). *First Author: Praveen Ranganath, Indiana University School of Medicine, Indianapolis, IN*

Background: PMNSGCT represents one of the most challenging subsets of malignant germ cell tumors. PMNSGCT has a distinctly worse prognosis and is appropriately categorized as poor risk disease. A phase III intergroup study in patients with poor risk germ cell tumors, including PMNSGCT demonstrated equivalent survival in patients with Etoposide, Ifosfamide and Cisplatin (VIP) compared to standard Bleomycin, Etoposide and Cisplatin (BEP) regimen. We have demonstrated that the magnitude of post chemotherapy surgery required for PMNSGCT is higher with potential for serious pulmonary complications including post operative pulmonary failure and death. This retrospective study from 1978-2013 compares perioperative morbidity and mortality associated with Bleomycin (BEP) vs. non Bleomycin (VIP) containing regimens. **Methods:** From 1978-2013, 221 PMNSGCT patients (mean age, 29 years; ranging from 12- 50 years) who underwent post chemotherapy surgery were reviewed. **Results:** Of the 221 patients who underwent post chemotherapy surgery, 55 were treated with VIP and 166 with BEP chemotherapy. Among patients who received BEP, 83% had ≥ 3 cycles of Bleomycin. Both groups were well balanced in respect to the number of patients requiring pulmonary resection, extent of pulmonary resection and surgical approach. Post operative complications including acute respiratory failure and/or pneumonia (22 vs. 0, p value 0.004) and prolonged ventilator requirement > 48 hrs (30 vs. 2, p value 0.004) were significantly higher in patients who received BEP compared to VIP chemotherapy respectively . There were 11 post operative deaths reported- 10 patients with post operative respiratory failure and 1 death from pulmonary embolism. All deaths were in BEP chemotherapy group and 0 post operative deaths were reported in patients who received VIP chemotherapy (p value 0.05). **Conclusions:** Bleomycin containing chemotherapy regimens have traditionally been the standard of care for patients with poor-risk NSGCTs, including PMNSGCTs. Given the high rate of post-operative pulmonary failure after BEP, these results support our present policy of preferring VIP in PMNSGCT patients prior to major thoracic surgical procedures.

4539 Poster Session (Board #212), Mon, 1:15 PM-4:45 PM

A retrospective analysis of patients with metastatic germ cell tumor (GCT) treated at Indiana University (IU) from 2000 to 2012. *First Author: Kimberly Ku, Indiana University School of Medicine, Indianapolis, IN*

Background: Metastatic GCT's have been classified by the International Germ Cell Cancer Collaborative Group (IGCCCG) in 1997 into good, intermediate, and poor risk with 5-year progression free survival (PFS) of 88, 75 and 41%, respectively and 5-year survival rate of 91, 79 and 48%, respectively. **Methods**: We conducted a retrospective analysis on outcomes of all patients with GCT who were diagnosed and received initial chemotherapy at IU between 2000-2012. We limited our analysis to patients with > 1 year of f/u. 5 years PFS and OS were analyzed using Kaplan Meier methods. **Results**: 403 patients were evaluable. 240 (58%) good, 46(11%) intermediate and 127 (30%) poor risk. Median time of f/u 5 years. Median age at diagnosis 29. The 5-year PFS of good, intermediate, and poor risk groups were 91, 80 and 52% (P value < 0.01) and 5-year survival rates were 95, 89 and 71%, (P value < 0.01) respectively. **Conclusions**: There was improvement in OS for men with poor risk metastatic GCT in this contemporary cohort of patients, possibly due to improved salvage chemotherapy compared to patients treated from 1975-1990 reported by the IGCCCG.

		Good (N = 240)	Int (N = 46)	Poor (N = 127)
Primary	Testis	235 (97.9%)	44 (95.6%)	80 (63.0%)
	Retroperitoneum	4 (1.7%)	1 (2.2%)	12 (9.4%)
	Mediastinal	0	1 (2.2%)	35 (27.6%)
Primary histology	Seminoma	51 (21.6%)	6 (13%)	0
	NSGCT	185 (78.4%)	37 (86.1%)	111 (100%)
AFP Pre Chemo	Median (range)	7.0 (0.2-871.7)	1912 (1.0-9653)	291.0 (0.9-280000)
hCG Pre Chemo	Median (range)	6.4 (0.4-4982)	5000 (0.0-41000)	16000 (0.6-1300000)
Chemo	BEPx3	183 (79.2%)	3 (6.5%)	5 (3.9%)
	BEPx4	3 (1.3%)	18 (39.1%)	62 (48.8%)
	BEPx3+EPx1	12 (5.2%)	19 (41.3%)	13 (10.2%)
	EPx4	14 (6.1%)	1 (2.2%)	0
	VIPx3	0	1 (2.2%)	3 (2.4%)
	VIPx4	0	1 (2.2%)	35 (27.6%)
	Other	19 (8.2%)	3 (6.5%)	9 (7.1%)
pcRPLND pathology	GCT	4 (1.7%)	2 (4.4%)	5 (3.9%)
	Teratoma	44 (18.3%)	9 (19.6%)	26 (20.5%)
	Malignant Transformation	4 (1.7%)	0	2 (1.6%)
	of Teratoma	27 (11.3%)	6 (13.0%)	35 (27.6%)
	Necrosis			
Salvage chemo		23 (10%)	7 (18.0%)	43 (34%)

4540 Poster Session (Board #213), Mon, 1:15 PM-4:45 PM

Bleomycin-induced pulmonary changes on restaging CT scans: Frequency and correlation with fibrosis markers. *First Author: Nico-Derk L. Westerink, University Medical Center Groningen, Groningen, Netherlands*

Background: Bleomycin-induced pneumonitis (BIP) is a well-known, potentially fatal, side-effect in metastatic testicular cancer (mTC). We prospectively investigated I: prevalence of lesions suspect for bleomycin-induced pulmonary changes on restaging CT scans; II: whether early changes of fibrosis markers Transforming Growth Factor β1 (TGF-β1) and Growth Differentiation Factor 15 (GDF-15) were predictive for these radiological changes. **Methods:** mTCpatients (pts), 18-50 years of age, treated with BEP (bleomycin, etoposide, cisplatin) chemotherapy were included from 2006 till 2012. Restaging CT scans were analyzed for bleomycin-induced pulmonary changes by 2 blinded radiologists and graded as minor, moderate or severe. Plasma samples were collected before, during and after chemotherapy and quantified for TGF-β1 and GDF-15. **Results:** 66 Pts were included. 45 Pts (68%) showed signs of bleomycin-induced pulmonary changes. 37 pts were classified as minor and 8 as moderate. Treatment and disease characteristics did not differ between the groups. 3 Pts had clinical signs of BIP (for which bleomycin was halted). Although there was a vast induction of both TGF-β1 and GDF-15 plasma levels (table), this was not different between pts with no and minor vs. pts with moderate radiological signs of bleomycin-induced pulmonary changes. **Conclusions:** Bleomycin-induced pulmonary changes are very common after BEP chemotherapy for mTC. TGF-β1 and GDF-15 plasma levels before and during treatment were not different between pts with and without radiological signs of bleomycin-induced pulmonary changes and therefore not helpful as predictive markers.

Biomarker levels in relation to bleomycin-induced pulmonary changes on restaging CT scan.

			No and minor changes (n=58)		Moderate changes (n=8)		
			Median	Range	Median	Range	P-value*
Cumulative dose bleomycin (USP)			270	150-360	270	240-360	.231
Biomarker	Course	Day					
TGF-β1	1	1	4788	550-24369	5268	2052-13361	.582
(pg/mL)	3	1	7889	1484-49897	8512	3878-20372	.765
	C	C	5275	595-18839	5116	3223-14207	.527
GDF-15	1	1	383	198-1935	413	187-1876	.397
(pg/mL)	3	8	5222	1439-14400	7246	4130-18959	.087
	C	C	840	299-2023	1089	442-2601	.073

* Mann-Whitney U test. C= 4 weeks after last course.

4541 Poster Session (Board #214), Mon, 1:15 PM-4:45 PM

Early changes in renal function and late cardiovascular disease risk in testicular cancer survivors with 25 years follow-up. *First Author: Sjoukje Lubberts, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

Background: Cisplatin-based chemotherapy (CT) for testicular cancer (TC) leads to an increased cardiovascular disease (CVD) risk, related to endothelial damage by circulating platinum levels of which renal function is the main determinant (J Clin Oncol 30, 2012 (suppl- abstr 4528)). Aim was to investigate the role of pre-CT renal function and early treatment-related decrease of renal function in relation to late CVD development. **Methods:** We performed a retrospective study in TC patients (pts) treated with cisplatin-based CT from 1980-1989. Renal function was determined before and after completion of at least 1 course CT with ^{125}I-iothalamate clearance which is the gold standard for glomerular filtration rate (GFR). Follow-up regarding CVD was collected in 5-yr survivors from hospital records and via general practitioners. **Results:** 50 pts, median age of 28 yrs (17-53) at start of CT, were eligible. All pts started with a normal renal function (GFR $\geq$ 90 ml/min/1.73m^2), median GFR was 129 ml/min/1.73m^2 (93-185). After start of CT median GFR decrease was 43 ml/min/1.73m^2 (-90-+11). 52% ended up with GFR impairment classified as chronic kidney disease (GFR $<$ 90 ml/min/1.73 m^2). There were 38 5-yr survivors with a median follow-up of 20 yrs (6-32). 8 (21%) developed CVD median 14 yrs (8-26) after CT (3 strokes, 2 myocardial infarctions, 1 coronary artery disease, 2 peripheral artery disease). Pts with late CVD had lower pre-CT GFR. Pts who ended up with a GFR $<$90 ml/min/1.73m^2 developed more frequently CVD (7/19 (37%) vs 1/19 (5%); p=.042). **Conclusions**: A GFR $<$ 90 ml/min/1.73 m^2 after CT is associated with an increased risk of late CVD after median 14 yrs. Patients with impaired renal function after treatment should be monitored closely regarding (risk factors for) CVD.

Characteristics of 5-year survivors, n=38.

		CVD (n=8)	No CVD (n=30)	P*
Age pre-CT (yrs)	median	30 (24-53)	26 (17-52)	.037
Cum cisplatinum dose (mg/m^2)	(range)	400 (375-800)	400 (350-800)	.688
GFR pre-CT (ml/min/1.73m^2)		104 (93-154)	132 (100-185)	.013
Change in GFR (ml/min/1.73m^2)		-38 (-76-+11)	-49 (-77- -6)	.299
After CT GFR < 90 ml/min (n,%)		7/8 (88%)	12/30 (40%)	.042

* Mann-Whitney U / Fisher exact test.

4542 Poster Session (Board #215), Mon, 1:15 PM-4:45 PM

Bevacizumab (Bev) alone or in combination with TRC105 for metastatic renal cell cancer (mRCC): A California Cancer Consortium clinical trial. *First Author: Tanya B. Dorff, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Inhibition of vascular endothelial growth factor (VEGF) pathway is effective in mRCC, but resistance inevitably develops. CD105 (endoglin) is highly expressed on endothelial cells and has been shown in preclinical models to mediate resistance to VEGF pathway inhibitors, in part due to TGF-beta signaling. TRC105 is a monoclonal antibody against CD105 which has been shown to be tolerable in combination with Bev at full doses. **Methods:** Eligible mRCC patients (pts) with any histologic subtype may have received 1-4 prior systemic therapies including cytokines, VEGF, or mTOR agents. Bev was administered at 10 mg/kg IV on day 1 and 15 of 28-day cycles as a single agent (Arm A) or with TRC105 10 mg/kg IV on days 1, 8, 15, and 22 (Arm B). Primary endpoint was progression-free survival (PFS). A total of 88 pts were to be randomized to detect a halving of PFS with 80% power and α = 0.1. An interim analysis for futility was conducted after 44 pts had PFS evaluated. **Results:** Enrollment was halted after interim analysis with 61 pts randomized; 45 were men. Median age was 60 (24-83). 20 (32%) of pts had received 3 or more prior lines of therapy (median = 2 on both arms). 44 patients had clear cell RCC and 15 had non-clear cell histology. One subject on each arm had a confirmed PR (3%) and 2 patients on each arm had stable disease lasting $>$ 9 cycles. For the 56 evaluable pts, the PFS (including early treatment termination as progression) at 12 weeks was 48% +/- 9% on Bev compared to 50% +/- 9% on Bev + TRC105. Survival did not differ significantly (p = 0.5) between arms, being 81% at 24 weeks for both arms. Grade $>$ 3 toxicities were more common in Arm B and included anemia (8 vs 2 pts), electrolyte abnormalities (6 vs 2 pts), dyspnea (4 vs 2 pts), nausea/vomiting (4 vs 0 pts), hyperglycemia (2 vs 0 pts) and infusion reaction (2 vs 0 pts); hemorrhage, hypertension, and proteinuria were more common in Arm A. **Conclusions:** TRC105 failed to prolong PFS when added to Bev. Further analysis will examine biomarkers of potential TRC105 benefit in this population. TRC105 is being studied in combination with VEGF receptor tyrosine kinase inhibitors in mRCC to determine whether there is an additive effect on PFS. Clinical trial information: NCT01727089.

4543 Poster Session (Board #216), Mon, 1:15 PM-4:45 PM

HIF inhibition in metastatic renal cell carcinoma (mRCC): Final results of a phase Ib /IIa clinical trial evaluating the nanoparticle drug conjugate (NDC), CRLX101, in combination with bevacizumab (bev). *First Author: Stephen Michael Keefe, Hospital of the University of Pennsylvania, Philadelphia, PA*

Background: *VHL* inactivation occurs in most clear cell RCCs and results in expression of the HIF hypoxia response program and tumor angiogenesis. Antiangiogenic therapies are central to therapy for mRCC, but resistance develops in all patients (pts). We hypothesized that a dual inhibition strategy focused on HIF would be active in the refractory setting. CRLX101 (Cerulean Pharma, Inc., Cambridge, MA, USA), an NDC with a camptothecin payload, has been shown in preclinical models to durably inhibit both HIF1a and HIF2a. Synergy has been observed in the pre-clinical setting between this NDC and antiangiogenic agents including bev. **Methods**: Pts with refractory mRCC were treated every 2 weeks with bev (10 mg/kg) and escalating doses of CRLX101 (12 mg/m^2, 15 mg/m^2) in a 3+3 phase I design. A phase IIa expansion cohort of 10 pts was treated at the RP2D. Pts were treated until progressive disease (PD) or prohibitive toxicity. Adverse events (AEs) were assessed using CTCAE v 4.0 and clinical outcome using RECIST v1.1. Correlative assays, designed to translate clinical results in terms of HIF expression and inhibition, were performed in parallel with the clinical investigation on baseline tumor material and on pre- and post-treatment bone marrow and plasma. **Results**: 22 response-evaluable pts were enrolled on study at two AMCs (12 clear cell, 5 papillary, 3 unclassified, 2 chromophobe). Pts had a median of 2 prior therapies, and all had at least 1 prior standard (std) therapy. No dose-limiting toxicities were observed. CRLX101 at its RP2D (15 mg/m^2) combined safely with std bev. Grade 3 treatment-related AEs were observed - non-infectious cystitis (4) and hypertension (4). All other AEs were grade 1 or 2. The median PFS was 9.9 months. Overall response rate (ORR) was 23%, and 85% experienced either a PR or SD as best response. The 5 pts with a PR included 3 with clear cell and 2 with papillary RCC. The primary efficacy endpoint of this study was met. **Conclusions**: CRLX101 can be safely combined with std bev in mRCC. This two-drug combination demonstrated provocative PFS and ORR signals. A randomized phase II clinical trial in mRCC is enrolling pts. Clinical trial information: NCT01625936.

4544 Poster Session (Board #217), Mon, 1:15 PM-4:45 PM

Cardiovascular toxicity following anti-angiogenic therapy in persons over age 65 with advanced renal cell carcinoma. *First Author: Sekwon Jang, Inova Comprehensive Cancer and Research Institute, Fairfax, VA*

Background: Sunitinib and sorafenib are oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) approved for treatment of patients with renal cell carcinoma (RCC) in 2005-2006. We conducted a population-based observational cohort study on the cardiovascular effects of VEGFR TKI therapy in elderly RCC patients. **Methods:** We analyzed patients with RCC diagnosed from 2000-2009 ages 66 and older using data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. We examined the incidence of cardiovascular adverse events through December 2010 including congestive heart failure and cardiomyopathy (CHF/CM), acute myocardial infarction (AMI), stroke, and cardiovascular deaths. We performed Cox-proportional hazard model to estimate the risk of these events associated with sunitinib or sorafenib adjusting for age, sex, comorbidity, and use of other systemic therapy. **Results:** A total of 171 out of 670 patients who received either sunitinib or sorafenib had cardiovascular events. The incidence rates for CHF/CM, AMI, stroke, and cardiovascular death in those who received one of the two drugs were 0.87, 0.14, 0.14, and 0.05 per 1000 person-days, respectively. Sunitinib or sorafenib use was associated with an increased risk of stroke (adjusted HR = 2.72, 95% CI: 1.49 -4.97) compared with 788 patients diagnosed with advanced RCC from 2007-2009 eligible for Part D but did not receive either agent. There were no statistically significant increased risks of CHF/CM, AMI, or cardiovascular deaths. **Conclusions:** Sunitinib or sorafenib are significantly associated with an increased risk of stroke, and clinicians should be aware of these rare adverse events.

4545 Poster Session (Board #218), Mon, 1:15 PM-4:45 PM

Overall survival analysis from a randomized phase II study of axitinib with or without dose titration for first-line metastatic renal cell carcinoma. *First Author: Brian I. Rini, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Background: In a randomized phase II trial in treatment-naïve patients with metastatic renal cell carcinoma (mRCC), objective response rate (ORR) was significantly higher with axitinib versus placebo titration; the hazard ratio (HR) for progression-free survival (PFS) favored axitinib titration but was not statistically significant. Analysis of overall survival (OS; as of Nov 4, 2014) is reported. **Methods:** Previously untreated patients with mRCC (N = 213) received axitinib 5 mg twice daily (BID) for a 4-week lead-in period. Patients with 2 consecutive weeks of blood pressure ≤ 150/90 mmHg, no grade > 2 axitinib-related toxicities, no dose reductions, and ≤ 2 antihypertensive medications were randomized (double-blind) to axitinib 5 mg BID + dose titration to a maximum of 10 mg BID with axitinib or placebo (n = 56 each). Those ineligible for randomization continued the axitinib 5 mg BID dose (n = 91); 10 patients discontinued prior to randomization. Primary endpoint was ORR; PFS and OS were secondary endpoints. **Results:** As of the data cut-off date, 90 of 213 patients (42%) were censored for survival (45% in the axitinib titration arm vs 30% in the placebo titration arm; 46% in the nonrandomized arm); at least 75 censored patients were alive. Median OS (95% confidence interval [CI]) from first dose was 42.7 months (24.7–not estimable [NE]) in the axitinib titration arm versus 30.4 months (23.7–45.0) in the placebo titration arm (HR 0.785; 95% CI 0.485–1.272; *P*= 0.1616). Median OS (95% CI) in the nonrandomized arm was 41.6 months (33.0–NE). In all patients, median OS (95% CI) was 39.3 months (32.7–45.8). Safety data were consistent with previous reports. Following treatment periods > 3.5 years, 9 (16%), 1 (2%), and 10 (11%) patients remain on treatment in axitinib titration, placebo titration, and nonrandomized arms, respectively. **Conclusions:** Median OS exceeded 3 years in patients with mRCC treated with first-line axitinib. Median OS was numerically longer in patients receiving axitinib titration compared with placebo titration but did not reach statistical significance. A substantial percentage of patients remain on axitinib, and no new important safety signals were observed. Clinical trial information: NCT00835978.

4546 Poster Session (Board #219), Mon, 1:15 PM-4:45 PM

Analysis of real world treatment compliance in a cohort of 2,395 patients with metastatic renal cell carcinoma (mRCC). *First Author: Jay Margolis, Truven Health Analytics, Bala Cynwyd, PA*

Background: Given recent European data highlighting the importance of real world dose intensity, we sought to examine real world compliance in patients with mRCC from a US perspective (Cancer Med 2014; 3(6): 1517-26). **Methods:** In this retrospective cohort study, we used MarketScan Commercial and Medicare Supplemental administrative claims databases to select patients newly diagnosed with mRCC (index event) during 1/1/2006 to 3/31/2014. First line therapy (1L) was defined by first prescription record post-index for any approved mRCC therapy and a change in line of therapy was defined by therapy switch. Compliance was measured using the medication possession ratio (MPR) during each and all lines of therapy. MPR was defined as total days of supply during the treatment period divided by the total treatment period until the start of the last treatment. **Results:** A total of 2,395 mRCC patients were identified as initiating 1L therapy. Across all treatments the mean MPR was 0.77 ± 0.20, which increased over time from 0.73 in 2006 to 0.81 in 2013. More than 50% of patients were noncompliant, defined as MPR < 80%. During 1L, patients treated with sunitinib had significantly lower mean MPR compared with most other treatments (table). Compliance was found to increase during 2L (0.85 ± 0.18) vs 1L (0.80 ± 0.19). A larger proportion of patients who initiated therapy with temsirolimus were compliant compared with those who initiated with sunitinib (62% vs 38%). **Conclusions:** Over half of treated mRCC patients in this study were found to be noncompliant with therapy. There were differences found between individual drugs. Compliance was significantly better with IV administered temsirolimus relative to the reference oral therapy, sunitinib. Real-world analysis of adherence behaviors provides information for clinicians in monitoring and optimizing targeted therapy.

MPR in 1L and all lines.

Compliance	Sunitinib*	Sorafenib	Pazopanib	Everolimus	Temsirolimus
1L MPR, mean (SD)	0.76 (0.19)	0.84 (0.19)	0.86 (0.19)	0.89 (0.14)	0.83 (0.19)
All lines, MPR, mean (SD)	0.74 (0.20)	0.78 (0.23)	0.84 (0.20)	0.76 (0.24)	0.81 (0.19)

* Reference group. In 1L, all differences were significant at $P < 0.05$.

4547 Poster Session (Board #220), Mon, 1:15 PM-4:45 PM

Randomized phase II study of sunitinib + CXCR4 inhibitor LY2510924 versus sunitinib alone in first-line treatment of patients with metastatic renal cell carcinoma. *First Author: John D. Hainsworth, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: Sunitinib is a standard first-line treatment for patients (pts) with metastatic renal cell carcinoma (RCC). CXCR4 and its only known ligand, SDF-1, are both overexpressed in tumor and vascular cells of clear cell RCC. LY2510924 is a selective peptide antagonist of CXCR4. We compared the results of open-label treatment with LY2510924 + sunitinib vs sunitinib alone. **Methods:** Previously untreated metastatic clear cell RCC pts were randomized (2:1) to receive standard-dose sunitinib (50 mg qd for 4 weeks [wk], then 2 wk off) + LY2510924 (20 mg sc, qd) (Arm A) or sunitinib alone (Arm B). Pts were evaluated (per RECIST v.1.1) every 8 wk. The primary analysis was done when all pts completed 72 wk of treatment, discontinued, progressed, or died and compared progression-free survival (PFS) between arms using a Bayesian time to event analysis incorporating prior information about sunitinib along with the trial data. PFS was also analyzed using the hazard ratio (HR) with only trial data. The Bayesian design was simulated to size the trial. The objective response rates (ORR) in each arm were compared using the chi-squared test. **Results:** 72 and 36 pts were treated in Arms A and B, respectively. Key pt characteristics (ECOG PS, Motzer risk score, prior nephrectomy) were similar in Arms A and B. Median number of cycles administered in each arm was 5. Median PFS was 8.1 and 12.3 months in Arms A and B, respectively (HR [95% CI]: 1.19 [0.73, 1.94]). The ORR (95% CI) was 30.6% (19.9%, 41.2%) in Arm A and 38.9% (23.0%, 54.8%) in Arm B. The most frequent (> 5% Arm A) grade 3/4 AEs (Arm A, Arm B) were hypertension (13.9%, 19.4%), fatigue (9.7%, 13.9%), diarrhea (6.9%, 16.7%), thrombocytopenia (8.3%, 5.6%), and anemia (8.3%, 2.8%). Of interest, there were more bleeding-related events (mostly grade 1 or 2) in Arm A than B (39%, 14%). More pts in Arm A discontinued treatment due to AE (18.1%, 8.3%). Two deaths in Arm A were due to adverse events (pulmonary edema/respiratory arrest/cardiac arrest and intracranial tumour hemorrhage). **Conclusions:** Adding the CXCR4 inhibitor LY2510924 to sunitinib as first-line treatment for metastatic RCC was tolerated but did not improve efficacy. Clinical trial information: NCT01391130.

4548 Poster Session (Board #221), Mon, 1:15 PM-4:45 PM

***CYP3A5* and *ABCB1* polymorphisms as predictors for sunitinib outcome in metastatic renal cell carcinoma.** *First Author: Meta Diekstra, Leiden University Medical Center, Department of Clinical Pharmacy and Toxicology, Leiden, Netherlands*

Background: In our exploratory studies we have associated single nucleotide polymorphisms (SNPs) in candidate genes with efficacy and toxicities of sunitinib in metastatic renal cell carcinoma (mRCC). The aim of the present study is to test these SNPs for association with sunitinib treatment outcome in the largest patient cohort to date. **Methods:** mRCC patients treated with sunitinib and a DNA sample available were pooled from 3 exploratory studies conducted in the US, Spain and the Netherlands. A total of 22 SNPs and 6 haplotypes in 10 candidate genes related to pharmacokinetics and pharmacodynamics of sunitinib were tested for associations with toxicity, dose reductions, progression-free survival (PFS), overall survival (OS) and best objective response. **Results:** Three-hundred and thirty-three patients were included. The presence of *CYP3A5*1* was associated with dose reductions (OR = 2.0, CI = 1.0-4.0, *P*= 0.039). Presence of CGT in the *ABCB1* haplotype was associated with an increased PFS (HR = 1.9, CI = 1.3-2.6, *P*= 0.000275) and remained significant after Bonferroni correction. These associations are consistent with prior observations. Similar size and direction of effect were observed for the association of *VEGFA* rs1570360 with hypertension (OR = 1.9, CI = 0.8-4.5, *P*= 0.173) and *FLT3* rs1933437 with leukopenia (OR = 3.6, CI = 0.8-16.7, *P*= 0.088). **Conclusions:** The confirmation of previously reported associations between polymorphisms in *CYP3A5* and *ABCB1* with sunitinib toxicity and efficacy respectively indicates that genotyping of these genetic variants may be useful for guiding sunitinib treatment.

4549 Poster Session (Board #222), Mon, 1:15 PM-4:45 PM

Randomized phase II study of two different doses of AVE0005 (VEGF Trap, aflibercept) in patients (pts) with metastatic renal cell carcinoma (RCC): An ECOG-ACRIN study [E4805]. *First Author: Roberto Pili, Roswell Park Cancer Institute, Buffalo, NY*

Background: AVE0005 (VEGF Trap), or aflibercept, is a recombinantly-produced fusion protein consisting of human VEGF receptor extracellular domains fused to the F_c portion of human IgG_1 that has potent anti-VEGF activity. We tested whether aflibercept has clinical activity in clear cell RCC. The recommended Phase 2 dose was 4 mg/kg but several pts treated at 1 mg/kg demonstrated prolonged progression-free survival (PFS). We therefore tested both doses in a parallel group randomized trial. **Methods:** Eligible pts had metastatic clear cell RCC and previous treatments including prior exposure to a VEGF TKI. Pts were stratified on prior immunotherapy (IL2/IFN) and MSKCC Risk Category. Patients received aflibercept (either 1 mg/kg or 4 mg/kg) day 1 of a 14-day cycle until progression. Patients randomized to 1 mg/kg could crossover to 4 mg/kg at progression. The primary endpoint was proportion alive and progression-free at 8 weeks. A 2-stage design was used for each arm with 33 and 24 eligible pts/arm enrolled in stages 1 and 2. If 17 pts were alive and PF at 8 wks or an objective response was observed, an arm would continue to stage 2, and if 34 of 57 eligible pts were PF at 8 wks, the arm would be considered for further study. This design had 91% power and 10% Type I error. **Results:** 94 pts were enrolled, 59 and 35 to 4 mg and 1 mg doses respectively. Median age was 61 with 72% male, 96% white, and 72% with 1 prior tx (most commonly sunitinib). 16 eligible pts crossed over at progression to the 4 mg dose. The most common adverse events were hypertension, proteinuria, and fatigue. Only 4 pts reported Grade 4 or higher toxicity. With 36/59 (61%) pts PF at 8 wks, the 4-mg/kg dose met protocol specified efficacy criteria. **Conclusions:** At a dose level of 4mg/kg, 61% of patients were progression free at 8 weeks, meeting pre-specified criteria. Aflibercept at a dose of 4 mg/kg is active in previously treated ccRCC and may be worthy of further study. Clinical trial information: NCT00357760.

	Arm A (4 mg/kg)	Arm B (1 mg/kg)	Crossover
Enrolled	59	35	17
Eligible	59	32	16
PF at 8 Wks	36 (61.0%)	15 (42.9%)	
90% CI	49.5 – 71.7%	28.6 – 58.1%	
Median PFS (wks)	10.9	8.3	18.1
90% CI (wks)	8.7 – 15.4	7.9 – 9.6	8.0 – 24.1
ORR	1.7%	3.1%	
90% CI	0.1 – 7.8%	0.2 – 14.0%	

4550 Poster Session (Board #223), Mon, 1:15 PM-4:45 PM

Pancreatic metastases from renal cell carcinoma: Prognostic relevance and outcome in patients treated with targeted agents. *First Author: Paolo Grassi, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: Pancreatic metastases from renal cell carcinoma (PmRCC) are uncommon and their prognostic role in the era of targeted terapies (TTs) is not well defined. We evaluated the outcome of a cohort of PmRCC patients (pts) who were treated with either surgery and TTs **Methods:** PmRCC pts treated between 1993 and 2014 were identified from the databases of 11 European centers. Clinical records were retrospectively reviewed and clinical outcome was analyzed. Kaplan-Meier methods and log-rank test were used to evaluate progression-free survival (PFS) and overall survival (OS). Cox proportional hazard models were used to analyse covariates associated to OS **Results:** A total of 276 pts were evaluated. PmRCC were synchronous to the primary in 80 pts (29%). Pts treated with pancreatic local treatment (PLoT), including surgery, were 77 (28%) while pts receiving systemic treatment were 256 (93%). Pts with only PmRCC were 42 (15%) whereas lung (47%), lymph nodes (28%) and liver (23%) were the most common metastatic sites in the remaining pts. Most of pts (95%) received nephrectomy (Nx). Median time from Nx to PmRCC occurrence was 91 months (mo) (IQR 54-142). First-line TTs included: sunitinib (44%), sorafenib (12%), pazopanib (9%), interferon + bevacizumab (6%) and temsirolimus (1%); 37% of pts received cytokines and 53% received subsequent lines of TTs. Best response to first-line TTs were complete response (5%) partial response (40%) and stable disease (39%) with a disease control rate of 84% and a median PFS of 12 mo (IQR 10-14). Median OS (calculated from the time of PmRCC diagnosis to death) was 73 mo (IQR 61-86) with a 5-yr OS of 58%. Median OS for pts treated with PLoT was 106 mo (IQR 78-204) with a 5-yr OS of 75%. At univariate analysis MSKCC/Heng prognostic score (*p*= .0004), Nx (*p*= .0002) and PLoT (*p*= < .0001) were significantly associated with OS.At multivariate analysis these variables confirmed their prognostic role **Conclusions:** PmRCC are associated with long-term survival, usually occur many years after Nx and lead to an indolent growth thus initial observation might be an option for this pts subgroup. Surgery should be considered in oligometastatic pts while TTs are active in widespread disease

4551 Poster Session (Board #224), Mon, 1:15 PM-4:45 PM

Early tumor shrinkage (eTS) as a predictive and prognostic factor in metastatic renal cell carcinoma (mRCC). *First Author: Viktor Gruenwald, Medical School of Hannover, Hannover, Germany*

Background: Tumor shrinkage (TS) has predictive value in mRCC, and early TS has been reported to be associated with prognosis in small series with mRCC, but the optimal cut-off has not been defined. We therefore quantitated the degree of tumor shrinkage at first scan that has predictive or prognostic value in mRCC. **Methods:** Data from Pfizer-sponsored clinical trials with sunitinib, axitinib, sorafenib, IFN or temsirolimus in mRCC were included for this posthoc analysis (A6181006, A6181034, A6181061, A6181065, A6181110, RTKC-0511-014, A4061032, A4060146, A4061051, 3066K1-304, 3066K1-3311, 3066K1-404). Objective tumor response was captured by protocol-defined tumor imaging according to RECIST. Target lesions were followed for TS. eTS was assessed at first post-baseline scan and analyzed for sensitivity and specifity by receiver-operating characteristic (ROC) analyses to predict response measured by median progression free survival (PFS) or overall survival (OS). Patients were classified as responders if PFS (7 mo.) or OS (20 mo.) were above the median. **Results:** 4736 pts (71% male) with median age 59 years were identified within the database. Most patients were treatment naïve (67%), had clear cell histology (89%), and favorable performance status (ECOG 0/1: 53/47%). Overall, an eTS of 7% or 8% was identified as the optimal cut-off for prediction of PFS or OS, respectively. Subgroups were analyzed and are depicted in table. **Conclusions:** Using a large clinical trials database in mRCC, we explored the predictive value of eTS in mRCC. Our analyses showed that the conventional 30% tumor shrinkage threshold is too high and that a cut-off at approximately 10% early TS predicts PFS and OS in mRCC. This finding is confirmed by a recent report on observer variability of eTS in mRCC. eTS should be further explored as a novel endpoint for clinical studies in mRCC.

eTS as predictor in mRCC.

	PFS	sensitivity/specifity	OS	sensitivity/specifity
all	7%	0.611/0.674	8%	0.603/0.632
1st line	11%	0.632/0.684	8%	0.596/0.621
2nd line	4%	0.530/0.724	5%	0.673/0.704
axitinib, sorafenib, sunitinib	10%	0.647/0.598	10%	0.653/0.659
temsirolimus	11%	0.652/0.631	12%	0.616/0.621
IFN	1%	0.728/0.621	1%	0.712/0.508

4552 Poster Session (Board #225), Mon, 1:15 PM-4:45 PM

Novel chromosome copy number changes to predict clinical response to sunitinib in patients with advanced renal cell carcinoma. *First Author: Chung-Han Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Sunitinib is a 1st-line therapy for clear cell Renal Cell Carcinoma (ccRCC); however, 20-30% of tumors show primary resistant disease (PRD) with progression as the best response. This study identifies the chromosomal copy number changes that are associated with sunitinib clinical response. **Methods:** Whole genome comparative genomic hybridization (aCGH) was performed on pretreatment tumor derived DNA from 76 sunitinib treated patients. Differential copy number alterations (CNAs) were identified using Fisher's exact test with p-values < 0.05 and a 15% minimum threshold difference. Identified CNAs were univariately tested for association with PFS, and compared to two publically available ccRCC SNP datasets, TCGA-436 (N = 436, TCGA, Nature, 2013, 499: 43) and University of Tokyo-240 (N = 240, Nature Genetics, 2013, 45: 860). **Results:** In patients with PRD gains of 22q and 6p were more common, and univariate PFS analysis for these CNAs showed a worse PFS (table). In patients with objective radiographic response (CR/PR), losses of 4q, 8p, and 10q were more common, and univariate PFS analysis identified loss of 4q and 8p trended toward improved PFS (table). Using databases comprising of largely sunitinib naïve patients (TCGA-436 and University of Tokyo-240), these CNAs were not correlated with overall survival, suggesting that these CNAs reflect sunitinib response, and not sunitinib-independent tumor biology. **Conclusions:** aCGH analysis of sunitinib treated ccRCC patients reveal multiple novel CNAs associated with clinical response. These CNAs warrant further investigation and may provide insight into mechanisms of sunitinib resistance.

Chromosome copy number changes.

Worse Prognosis		Improved Prognosis	
PD as best response	Worse PFS	CR/PR as best response	Improved PFS
Gain 22q (P = 0.03)	Gain 22q (p = 0.06)	Loss 4q25 (P = 0.03)	Loss 4q13.1-q13.3
Gain 6p21.1	Gain 6p21.2	Loss 4q28.1-q28.2	(P = 0.07)
(P = 0.03)	(p < 0.001)	(P = 0.03)	Loss 8p21.1
		8p21.1 (P = 0.03)	(P = 0.06)
		10q21.3-q22.1	
		(P = 0.03)	
		10q23.32-23.33	
		(P = 0.03)	

4553 Poster Session (Board #227), Mon, 1:15 PM-4:45 PM

Updated survival results from a randomized, dose-ranging phase II study of nivolumab (NIVO) in metastatic renal cell carcinoma (mRCC). *First Author: Elizabeth R. Plimack, Fox Chase Cancer Center, Philadelphia, PA*

Background: NIVO, a programmed death-1 immune checkpoint inhibitor, demonstrated encouraging clinical activity in a randomized phase II study in pts with mRCC pretreated with targeted VEGF pathway agents. Here we present updated survival results. **Methods:** NIVO was administered at 0.3, 2, or 10 mg/kg IV Q3W until progression or toxicity to pts with clear-cell mRCC ($\leq$ 3 prior systemic therapies, $\geq$ 1 agent targeting VEGF pathway). Treatment beyond progression was allowed in pts who tolerated NIVO and experienced clinical benefit. Primary endpoint (progression-free survival) was reported previously. Other endpoints included overall survival (OS), adverse event rate, and association of tumor PD-L1 expression with clinical outcomes. OS was calculated by Kaplan-Meier method. PD-L1 expression was measured in archival tumor tissue by immunohistochemistry (28-8 antibody; Dako). PD-L1 positivity was defined as $\geq$ 5% tumor membrane staining. Data cutoff, January 6, 2015. NCT01354431. **Results:** 168 pts were randomized.Of the treated pts (n = 59, 54, and 54 at 0.3, 2, and 10 mg/kg, respectively), 55 (33%) continue on study; 14 (8%) remain on treatment. Median doses given (range) was 6 (1–54), 7.5 (1–56), and 8 (1–59) for 0.3, 2, and 10 mg/kg, respectively. Median OS and OS rate are presented in the table. 64% of pts were evaluable for PD-L1 expression, 27% of whom had PD-L1 expression $\geq$ 5%. Median OS (80% CI) was 29.9 mo (13.4–not available [NA]) in the PD-L1+ subgroup and 18.2 mo (12.7–27.2) in the PD-L1– subgroup across doses. OS by MSKCC risk group and number of prior therapies, as well as long-term safety, will be presented. **Conclusions:** NIVO continues to demonstrate OS benefit across dose levels and in PD-L1+ and PD-L1– pts in this phase II mRCC study with 3 years minimum follow-up. Survival rates at 2 and 3 years compare favorably with other therapies in this setting of heavily pretreated pts with clear-cell mRCC and suggest potential for pts to achieve long-term survival with NIVO treatment. A phase III confirmatory study is underway. Clinical trial information: NCT01354431.

	NIVO, Q3W		
	0.3 mg/kg n = 59	**2 mg/kg n = 54**	**10 mg/kg n = 54**
Median OS, mo (80% CI)	18.5 (16.7–NA)	25.5 (19.8–31.2)	24.8 (15.3–26.0)
OS rate, %			
12 mo	63	72	70
24 mo	42	53	52
36 mo	33	40	32

4554 Poster Session (Board #228), Mon, 1:15 PM-4:45 PM

Final overall survival analysis for the RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC (mRCC). *First Author: Jennifer J. Knox, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: RECORD-3 (ClinicalTrials.gov ID, NCT00903175) was a multicenter, randomized phase 2 trial that compared first-line everolimus followed by sunitinib (EVE→SUN) with first-line sunitinib followed by everolimus (SUN→EVE) at progression of disease (PD) in patients with mRCC. In the final primary analysis comparing PFS of EVE and SUN as first line therapy, the noninferiority margin was not achieved; therefore, the primary endpoint was not met (*J Clin Oncol* 2014;32:2765). The objective of this analysis was to evaluate mature data for secondary endpoints. **Methods:** Patients with mRCC (clear or non-clear cell) and without prior systemic therapy were randomly assigned 1:1 to either first-line EVE 10 mg/day or SUN 50 mg/day (4 weeks on, 2 weeks off) until first occurrence of PD (RECIST v1.0). Patients then crossed over and continued on the alternate drug until second occurrence of PD. For this final analysis, mature data for combined first- and second-line progression-free survival (cPFS) and overall survival (OS) were assessed. Data lock for final analysis was November 25, 2014. **Results:** From October 2009 to June 2011, 471 patients were enrolled (EVE→SUN, n = 238; SUN→EVE, n = 233) and most patients in both arms had clear cell RCC (~85%). Among patients who discontinued first line, 128 (55%) crossed over from EVE to SUN and 116 (51%) crossed over from SUN to EVE. The primary protocol-related reason for not crossing over was ineligibility related to poor performance status or PD-related decline in condition (~40%). Median duration of follow-up was ~3.7 years. At final OS analysis, median cPFS was 21.7 months for EVE→SUN and 22.2 months for SUN→EVE (hazard ratio [HR], 1.2; 95% confidence interval [CI], 0.91-1.59). Median OS was 22.4 months for EVE→SUN and 29.5 months for SUN→EVE (HR, 1.09; 95% CI, 0.87-1.37). The rate of grade 3 or 4 adverse events suspected to be drug related was 62% in the EVE→SUN arm and 71% in the SUN→EVE arm. **Conclusions:** Results of this final analysis are consistent with initial results and further support the standard sequence of SUN followed by EVE at PD. Safety profiles of EVE and SUN were consistent with those previously reported. Clinical trial information: NCT00903175.

4555 Poster Session (Board #229), Mon, 1:15 PM-4:45 PM

Phase II study of individualized sunitinib as first-line therapy for metastatic renal cell cancer (mRCC). *First Author: Georg A. Bjarnason, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada*

Background: Higher sunitinib drug exposure is associated with better response (RR), progression free (PFS) and overall survival (OS). Retrospective data show poorer PFS and OS in patients (pts) with minimum toxicity on the 28 day (d)/14 d schedule vs pts needing dose/schedule changes. We hypothesized that toxicity-driven dose/schedule changes would optimize drug exposure. **Methods:** In a prospective phase II study (eligibility identical to EFFECT trial, JCO 30(12):1371) with the primary endpoint of improving PFS from 8.5 (EFFECT 4/2) to 14 months (mo), pts start on 50 mg/d for 28 d with treatment (Rx) breaks reduced to 7 d. Pts with grade-2 toxicity before d 28 stay on 50 mg with the d on Rx individually reduced aiming for $\leq$ grade-2 toxicity. Dose is reduced to 37.5 mg in pts that do not tolerate 50 mg for at least 7 d and to 25 mg in pts that do not tolerate 37.5 mg for 7 d with individualized duration of Rx. Pts with minimum toxicity on d 28 are dose escalated to 62.5 mg and then 75 mg on a 14/7 d schedule. Pts that develop grade-2 toxicity by d 28, stay on a 28/7d schedule. **Results:** With accrual completed and 116 pts entered at 12 centers, 83 pts are evaluable for RR (at least two CTs 2 mo apart) with median followup of 11.6 mo (Heng favorable 25%, intermediate 63%, poor 12%). Nine pts came off study early due to toxicity (5), non-compliance (2) or global deterioration (2). Of 61 pts still on therapy, 24 are too early for RR. Of 83 evaluable pts (37 still on Rx), 18 (21.7%) were dose escalated to 62.5 mg (11) and 75 mg (7). For 39 pts (47%), who would have been dose reduced by standard criteria, a 50 mg dose was continued for 7 - 24 d, while 7 pts (8.4%) stayed on a 28d schedule. Dose was reduced to 37.5 mg in 13 pts (15.7% vs 36 - 63% in 4 trials) and to 25 mg in 6 pts (7.2 % vs 15 - 19% in 4 trials). Rx was stopped due to toxicity in 7/116 pts (6% vs 15-19% in 4 trials). Best response was complete (CR) in 4 pts, partial (PR) in 38 pts, stable (SD, median 6.4 mo on Rx) in 32 pts and progression in 9 pts (10.8% vs 24.6% in EFFECT) for a CR+PR (median 14.3 mo on Rx) rate of 50.6% (vs 32% in EFFECT) and CR+PR+SD rate of 89.2% (vs 75% in EFFECT). **Conclusions:** Individualized dosing is safe and feasible in a multicenter setting and associated with improved dose intensity and one of the highest RR reported for mRCC. Clinical trial information: NCT01499121.

4556 Poster Session (Board #230), Mon, 1:15 PM-4:45 PM

Molecular analysis of sarcomatoid renal cell carcinoma (sRCC). *First Author: Thai Huu Ho, Mayo Clinic, Scottsdale, AZ, Scottsdale, AZ*

Background: Patients with sRCC have a have a poor prognosis and decreased likelihood of response to targeted therapy or IL-2. Predictive biomarkers of response are lacking in sRCC. We evaluated a cohort of RCC patients to identify potentially actionable recurrent molecular aberrations. **Methods:** 112 renal cases referred to Caris Life Sciences over 2 years were evaluated for sarcomatoid components with central pathology review. 91 cases were clear cell (ccRCC) and 21 were sRCC. Testing included sequencing (next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]), and gene amplification (CISH or FISH). For sequencing, DNA was isolated by microdissection of the sarcomatoid component. 20 RCC cases with sarcomatoid differentiation from Mayo Clinic Arizona were analyzed for external validation. **Results:** The sRCC cohort showed 54% aberrant expression of PD-L1 and all but 1 case was infiltrated with PD-1+ tumor infiltrating lymphocytes (TILs). 100% of ccRCC with sarcomatoid features (n = 4) showed aberrant expression of PD-L1 and were infiltrated with PD-1+ TILs; of ccRCC without sarcomatoid features, only 17% had PD-L1 and 62% had PD-1 involvement. ccRCC had a 54% loss of PTEN, while sRCC had a 33% loss (p value = 0.2). Loss of PBRM1 expression was observed in 30% of sRCC. Loss of histone 3 lysine 36 trimethylation (H3K36me3), associated with *SETD2* mutations, was observed in 19% of sRCC and 30% of ccRCC. Key differences are shown in the table below. **Conclusions**: Multiplatform molecular profiling of sRCC identifies numerous predictive biomarkers to cytotoxic agents and immunotherapies. In other solid tumors, overexpression of TOPO2A and loss of RRM1 are associated with sensitivity to anthracyclines and gemcitabine, respectively. sRCC have increased infiltration of PD-1+ TILs and may respond to PD1/PD-L1 targeted immunotherapies. Further evaluation of TOPO2A, RRM1 and PD-1/PD-L1 as predictive biomarkers in sRCC is warranted.

	% Overexpression			TILs	% Loss	
	TOPO2A	AR	PD-L1	PD-1	RRM1	PBRM1
ccRCC	25	26	17	62	100	58
sRCC	67	5	54	96	74	30
p value	0.0001	0.04	0.005	0.003	0.0001	0.02

4557 Poster Session (Board #231), Mon, 1:15 PM-4:45 PM

Tivozanib vs sorafenib targeted therapy for advanced renal cell carcinoma: Final results of a phase III trial (901) and efficacy results of a 2nd line tivozanib extension study (902). *First Author: Thomas Hutson, Texas Oncology–Baylor Charles A. Sammons Cancer Center, Dallas, TX*

Background: An extension and open access study allowed follow up of patients (pts) from TIVO-1 (301), an open label, phase III multinational trial in which pts with metastatic renal cell carcinoma (mRCC) were randomized to either tivozanib or sorafenib (both VEGF TKIs). TIVO-1 met its primary endpoint of improved median progression free survival (PFS) over sorafenib, but overall survival (OS) was shorter (*J Clin Oncol*. 2013; 31:3791). Follow up analysis of all pts from that trial is presented. **Methods:** Pts were treated until documented progression or unacceptable tolerability on both treatments. These pts were followed for OS, investigator assessed PFS, and long term safety. The majority of pts who received first line tivozanib had no subsequent therapy; the majority of pts initially treated with sorafenib were crossed over to tivozanib per protocol. **Results:** Few second line therapy options were available to pts who discontinued initial tivozanib. Of the 259 tivozanib pts, 69.3% received no subsequent therapy, 11.7% VEGF therapy (not tivozanib), 9.7% mTOR inhibitor therapy, and 10.0% non-targeted therapy. All 257 pts discontinued initial sorafenib therapy and 168 (65.4%) went on to subsequent VEGF therapy (163 treated with tivozanib), 1.2% to mTOR, 2.0% to non targeted therapy, and 31.5% to no additional therapy. Follow up PFS and OS from initial randomization for the 260 pts originally receiving tivozanib was 14.6 and 29.0 mos, and for the 257 pts originally receiving sorafenib was 9.7 and 34.1 mos, respectively (PFS HR = 0.77, OS HR = 1.18). Long term safety assessment of pts who continued tivozanib indicated that incidence of the most common on target AEs (hypertension and dysphonia) decreased over time. For the 163 pts who crossed over from sorafenib to second line tivozanib, median PFS was 11 mos and median OS was 21.6 mos from the start of second line tivozanib. **Conclusions:** This long term analysis of PFS and OS underscores the positive impact of tivozanib treatment after sorafenib failure in mRCC. Lack of access to second line therapies in pts in the tivozanib arm due to geographical reasons most likely affected trial results. Clinical trial information: NCT01030783, NCT01076010, NCT01369433.

4558 Poster Session (Board #232), Mon, 1:15 PM-4:45 PM

Characteristics of metastatic renal cell carcinoma (mRCC) patients treated with delayed targeted therapy: Results from the International mRCC Consortium (IMDC). *First Author: Haoran Li, Tom Baker Cancer Center, Calgary, AB, Canada*

Background: A small proportion of patients with mRCC may not require immediate targeted therapy (TT). Their clinicopathological features and prognoses are not well characterized. **Methods:** A retrospective analysis was conducted in mRCC patients who did not start TT until at least 1 year after diagnosis of metastatic disease (delayed TT). Patients treated with traditional immunotherapy were excluded. For comparison, patients that received immediate TT within 1 month of metastatic diagnosis were used (immediate TT). **Results:** 467/3202 (14.6%) mRCC patients had delayed TT. The majority of patients (96.6%) in delayed group had prior nephrectomy. Compared to patients who received immediate TT (n = 800), patients with delayed TT were more likely to have clear cell histology (87.8% vs. 82.7%, $p = 0.02$), lower grade primary lesions (low/int grade: 38.3% vs. 31.2%, $p = 0.03$), less likely to have sarcomatoid features (7.1% vs. 13.1%, $p = 0.002$), greater percentage of normal LDH (74.8% vs. 67.1%, $p = 0.02$) and less hyponatremia (11.9% vs. 19.3%, $p < 0.01$). However, slightly more brain and bone metastases at baseline were seen in the delayed TT vs immediate TT groups (8.7% vs. 5.7%, $p = 0.046$ and 38.3% vs. 31.4%, $p = 0.02$, respectively) and it is unknown if these patients were delayed due to metastatectomy or radiotherapy. IMDC risk factors were more favorable in delayed TT group, with less anemia (43.2% vs. 65.0%, $p < 0.001$), hypercalcemia (6.9% vs. 11.7%, $p < 0.01$), neutrophilia (11.3% vs. 22.0%, $p < 0.001$), thrombophilia (8.6% vs. 18.4%, $p < 0.001$), KPS < 80 (20.9% vs. 26.6%, $p = 0.03$). The response rate of TT was similar between two groups (27.0% vs. 27.0%, $p = 1.0$). The median PFS was 9.3 months in delayed TT patients vs 5.6 months in immediate group ($p < 0.001$), and the median OS was 26.6 months in delayed group vs 17.2 months in immediate group ($p < 0.001$). The differences in survival are due to patient selection. **Conclusions:** Patients with fewer adverse IMDC criteria were more likely to receive delayed systemic treatment. 14.6% of patients who start targeted therapy do so over a year from diagnosis of mRCC. Further studies are warranted to determine who can benefit most from delayed TT.

4559 Poster Session (Board #233), Mon, 1:15 PM-4:45 PM

A phase I study of buparlisib (BKM120) with bevacizumab (BEV) in patients (pts) with metastatic renal cell carcinoma (mRCC) progressing on prior vascular endothelial growth factor (VEGF) therapies. *First Author: Rana R. McKay, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: BKM120 is a pan-PI3K inhibitor with demonstrated activity in advanced solid tumors. The primary aim of this study was to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of BKM120 + BEV. Secondary objectives included safety, efficacy, and biomarker discovery. **Methods:** This was a 3+3 dose escalation study of BKM120 (60-100 mg/day (d)) + BEV (10 mg/kg every 2 weeks). After the MTD was defined, 14 pts were accrued to the expansion cohort. **Results:** A total of 32 pts were accrued (5 treated at 60 mg/d, 19 at 80 mg/d (2 remain on therapy), 6 at 100 mg/d, and 2 never received therapy). The majority had clear cell histology (88%) and 50% had ≥2 prior lines of systemic therapy. The MTD of BKM120 was 80 mg/d. With the exception of 1 case of cognitive disturbance deemed related to both agents, all DLTs (Table 1) were attributed to BKM120. 28 pts discontinued therapy: 16 due to progression, 7 dueto toxicity, 1 due to death, and 4 due to other reasons. Toxicity leading to therapy discontinuation included rash/pruritis, transaminitis, elevated lipase/amylase, suicidal ideation, and cognitive disturbances. Of the 30 pts who received at least 1 dose, 13% had a partial response (PR) (95% CI 4%, 31%), 50% had stable disease (SD), and 20% had progressive disease (PD). Of the 19 pts treated at the MTD, 11% had a PR (95% CI 1%, 33%), 53% had SD, and 16% had PD. The median time-to-treatment failure (TTF), progression-free survival (heavy censoring) and overall survival were 4 (95% CI 2, 9), 9 (95% CI 2, 9), and 18 (95% CI 4, not reached) months (mos) for the total cohort and 4 (95% CI 2, 9), 6 (95% CI 2, 9), and 13 (95% CI 5, not reached) mos for pts treated at the MTD, respectively. Of the 9 pts evaluated, 2 had activating PI3K mutations. One achieved a PR (TTF 13 mos) and the other achieved SD with 16% tumor shrinkage (TTF 9 mos). **Conclusions:** BKM120 at 80 mg/d + BEV was a tolerable regimen with preliminary activity in VEGF-refractory mRCC. Clinical trial information: NCT01283048.

Summary of DLTs.

Case	DLT	Grade	BKM Dose
11	Anxiety	3	100 mg
	Depression	3	
	Suicidal ideation	3	
12	Anorexia	3	100 mg
	Weight loss	3	
15	Cognitive disturbance	2*	80 mg

*≥1 CTCAE grade level increase defined as DLT.

4560 Poster Session (Board #234), Mon, 1:15 PM-4:45 PM

Prognostic value of genomic signatures in metastatic Clear Cell Renal Cell Carcinoma (mRCC) using The Cancer Genome Atlas (TCGA) data. *First Author: Guillermo de Velasco, Dana- Farber Cancer Institute, Boston, MA*

Background: Gene-expression signatures for prognosis have been reported in localized RCC. The aim of this study was to validate two different signatures; ClearCode34, a 34-gene signature model (Brooks et al. *Eur Urol.*, 2014) and an 8-gene signature model (Choudhury et al. *Eur Urol.*, 2015) in a population of mRCC. **Methods:** mRCC patients from five institutions who were part of TCGA KIRC were identified and clinical data were retrieved. Normalized RNAseq gene expression data were downloaded from the public TCGA portal. mRCC patients were dichotomized to good and poor prognostic risk groups using the 2 models. Cox proportional hazard regression was used to investigate an association between molecular subtype and overall survival (OS) from first-line therapy. **Results:** Overall, 56 patients were included in the analysis**.** Median age was 62 years. The proportions of patients in IMDC prognostic risk groups were 14%, 66%, and 20% for good, intermediate, and poor risk respectively. Fifty two (92.8%) patients received VEGF-targeted therapy. Median follow-up from initiation of first-line therapy was 25.2 months. Applying the ClearCode34, median survival for the ccA (n = 18) and ccB (n = 38) subtypes were 27.6 and 22.3 months (HR: 2.33; 95% CI, 1.02 to 5.31; P = 0.03), respectively. On multivariable analyses and adjusting for IMDC groups, ccB remained independly associated with a worse OS (p = 0.044). On the other hand, the 8-gene signature molecular subtypes did not predict survival in this cohort (HR 1.76; 95% CI, 0.8 to 3.85, P = 0.15). **Conclusions:** ClearCode34, but not the 8-gene molecular signature model, is prognostic in patients with mRCC. These data need to be externally and prospectively validated.

4561 Poster Session (Board #235), Mon, 1:15 PM-4:45 PM

Metastatic chromophobe renal cell carcinoma treated with target therapies: A Renal Cross Chanel Group (RCCG) study. *First Author: Emeline Colomba, Institut Gustave Roussy, Villejuif, France*

Background: Metastatic Chromophobe renal cell carcinoma (mChRCC) is a rare entity with no specific targeted therapy recommended. We aim to assess the outcome of targeted therapy (TT) in a large cohort of mChRCC patients (pts). **Methods:** RCCG collected data from 27 centers in France, UK and Italy. Patients' characteristics, treatments, best response and outcomes were collected. Time to treatment failure (TTF) for first-line treatment was calculated from the initiation of first-line treatment (t0) until failure (progression disease, toxicity, death). Overall survival (OS [95%CI]) was calculated from t0 until death. Survival outcomes were described using Kaplan-Meier method with 95% confidence interval. **Results:** Overall, 91 mChRCC pts were collected. Among these, 63 were treated with TT with a median follow-up of 3 years (range: 0.1-14). Median age at diagnosis was 58 years with a majority of men (62%, n = 39). Most pts had nephrectomy (92%, n = 58). International Metastatic RCC Database Consortium (IMDC) prognosis groups were good: 4% (n = 2), intermediate: 74% (n = 35), poor: 21% (n = 10), or unknown (ukn) = 16. Patients were treated either with anti-angiogenic (AA) (79%, n = 50), mTORi (17%, n = 11) or other (3%, n = 2) as first line. Most pts (84%) received sunitinib as AA. Best overall response with AA was CR+PR: 36% (n = 16), SD: 33% (n = 15), PD: 31% (n = 14), ukn = 5. Median TTF in first line in the entire population was 7 months [4-9]. Median TTF with AA was 8 months [5-10]. Median TTF was 7.9 [3.8-13.6], and 2.4 [0.7-8.0] months for intermediate and poor IMDC prognosis groups respectively. Second line treatment was administered in 30 pts (48%) and third line in 9 (14%) pts. Median OS was 23 [12-36], 30 [12-46] and 9 [2-NR] months for overall, AA and mTORi, respectively. Median OS was NR [11.6-NR], 22 [9.8-35.9] and 9 [1.1-35.1] months for good, intermediate and poor IMDC prognosis group respectively. **Conclusions:** We report the largest cohort of patients with mChRCC treated with targeted therapy. TTF and OS with VEGF/VEGFR inhibitors are similar to outcomes in patients with clear cell RCC. Integration of newly characterized biological insights in ChRCC will be the next step to improve outcomes of patients with mChRCC.

4562 Poster Session (Board #236), Mon, 1:15 PM-4:45 PM

Clinical effect of TKI dose-escalation after disease progression in patients with metastatic renal cell carcinoma. *First Author: Moshe Chaim Ornstein, Cleveland Clinic Fdntn, Cleveland, OH*

Background: Given the variability in drug levels with tyrosine kinase inhibitors (TKI) in patients (pts) with metastatic renal cell carcinoma (mRCC), escalation of dose at the time of progressive disease (PD) may have anti-tumor effect. **Methods:** Pts with mRCC who were treated at Cleveland Clinic with TKIs and were dose-escalated following PD per RECIST 1.1 were retrospectively reviewed. Patient and disease-related data were collected and summarized as frequency counts and percentages, or medians and ranges. The Kaplan-Meier method was used to summarize treatment duration on escalated doses. **Results:** Nineteen patients were identified. The majority of patients (84%) were male; median age was 58 (range, 40-71). The most common histology was clear cell (79%), 78% of pts were intermediate risk by IMDC criteria, and all but one patient had prior nephrectomy. Axitinib was the most frequently escalated agent following disease progression (89%); starting at 5mg BID and generally escalating by 1-2mg BID as tolerated. Sunitinib was the dose-escalated TKI in the remaining 2 patients; starting at 50 mg on a 4/2 schedule and escalating to 62.5mg on a 2/1 schedule. Prior to PD/dose-escalation, best response was partial response (PR) in 7 (37%) pts, stable disease (SD) in 10 (53%), and PD in 2 (11%) pts with a median treatment duration of 6.7 months (range, 1.6-49.8). Of pts with evaluable tumor measurements during the escalation period (n = 15), 11 pts (73%) had a decrease in tumor burden. Median decrease in tumor burden after dose-escalation was 11% (range, 0-58%); 6 (40%) pts had decreases > 10%: 3 (20%) > 20%, and 1 (7%) > 30%. Most pts continue to be treated at escalated doses; median duration of escalated therapy is estimated to be 9.8 months (range 0.6+ to 21.1+ months). **Conclusions:** Dose-escalation of TKIs after PD in select mRCC can lead to reduction in tumor burden and extend the duration of therapy.

4563 Poster Session (Board #237), Mon, 1:15 PM-4:45 PM

Clinical impact of loss of H3K36me3 expression in patients with clear cell renal cell carcinoma. *First Author: Abhisek Swaika, Mayo Clinic, Jacksonville, FL*

Background: Mutations in chromatin modifying enzymes play a role in the pathogenesis of clear cell renal cell carcinoma (ccRCC). However the clinical impact of histone methylation regulated by chromatin modifying enzymes remains unknown. Herein we analyze the clinical impact of loss of histone H3 lysine 36 trimethylation (H3K36me3) in a large cohort of ccRCC tumors and associate its expression with renal cell cancer-specific survival (RCC-SS) and pathologic features. **Methods:** We utilized the Mayo Clinic Renal Registry and identified 1454 patients who underwent nephrectomy to treat clinically localized ccRCC between 1/3/1990 and 4/14/2009 and who also had available tissue samples. We used immunohistochemistry (IHC) to detect H3K36me3 expression, and a central pathologist blinded to the outcomes scored tumors as either positive or negative. Tumors with heterogeneous or equivocal staining were not included in this analysis. For associations with pathologic features we employed Mann-Whitney U tests, and for associations with relapse free survival (RFS) and ccRCC-SS we generated Cox proportional hazard regression models. **Results:** Of the total 1454 samples, 1205 (83%) were scored as either positive or negative for H3K36me3 with 978 (81%) positive and 227 (19%) negative samples. H3K36me3 negative tumors strongly associated with male gender, older age, larger tumor size, higher grade (3-4), and positive tumor necrosis ($p < 0.001$ for all). After adjusting for age, H3K36me3 negative patients had decreased RFS (HR 2.87, $p < 0.001$) and decreased RCC-SS (HR 3.10, $p < 0.001$). After adjusting for age and the Mayo Clinic-Stage, Size, Grade, and Necrosis (SSIGN) score, H3K36me3 negative tumors continued to have decreased RFS (HR 1.30, p = 0.041) and trended towards decreased RCC-SS (HR 1.31, p = 0.064). **Conclusions:** This is the largest study evaluating the clinical significance of H3K36me3 expression in patients with ccRCC. Loss of H3K36me3 is a marker of poor prognosis and an independent predictor of decreased RFS. Efforts to elucidate the mechanisms of how loss of H3K36me3 contributes to worse tumor biology are underway.

4564 Poster Session (Board #238), Mon, 1:15 PM-4:45 PM

Precision medicine approach in kidney cancer: A pan renal cell carcinoma (RCC) study across three cancer genome atlas (TCGA) datasets for clinically relevant target identification. *First Author: Bradley Murray, Broad Institute, Boston, MA*

Background: Comprehensive molecular evaluation of clear cell (ccRCC),papillary (pRCC) and chromophobe (ChRCC) tumors through TCGA has provided significant insights into the biology of RCC. Yet, the translation of these efforts in terms of clinical impact remains under developed. We aim to report clinically relevant molecular alterations events that can be identified by precision medicine screening approach across 3 RCC datasets. **Methods:** TCGA datasets for ccRCC, pRCC and ChRCC were analysed for focal mutations using a previously reported 121-gene panel relevant for genomics-driven therapy (TARGET) that may have therapeutic, prognostic and diagnostic implications for patients with cancer (Van Allen, *Nature Medicine* 2014), and for relevant copy number alterations (CNA) defined as focal amplification (Amp) or homozygote deletion. **Results:** Overall, 760 RCC including 420 ccRCC, 275 pRCC and 65 ChRCC were analysed. A total of 1,089 clinically relevant somatic mutations and 110 clinically relevant somatic CNA were identified. Tumor specific incidence of mutation and CNA are reported (Table). **Conclusions:** Overall, at least 78.7% of RCC tumors (598/760) present a genomic alteration considered potentially clinically relevant. Both ccRCC and pRCC exhibit a large number of small incidence events. This report provides a strong rational for including RCC in ongoing clinical trials of target identification and to assess the clinical relevance of these events.

	ccRCC		pRCC		ChRCC	
Number of cases	420		275		65	
Mutation						
% of cases with at least one TARGET gene with somatic mutation	89%		64%		75%	
High (>10%)	VHL PBRM1 SETD2 BAP1	53% 32% 11% 10%	MET	19% 12% somatic, *7% germline*	P53 PTEN	48% 14%
Intermediate (2-10%)	MTOR PTEN ATM NOTCH2 SMARCA4 PI3K	7% 4.7% 3.5% 3% 2.8% 2.4%	SETD2 BAP1, SMARCA4 PBRM1 NF2 NOTCH2 TET2, TSC2 FGFR3, mTOR, PI3K, PTEN, SMARCB1 BRAF, ERBB2, ERBB3, KRAS,PIK3R1, NF1	6.5% 4.7% 4% 3.6% 3% 2.5% 2.2% 2%	RB1 ATM, NOTCH1, TSC2, GNAQ ERG, ATR, EPHA3, ERBB3, FBXW7, MTOR, SETD2, NTRK3	6% 4.5% 3.1%
CNA						
Amp – High Level	MYC	2.4%	MET	2.5%		
Homozygous Deletion	CDKN2A PTEN	7.2 % 4.8%	CDKN2A NF2	4.9% 2.7%	PTEN	3.1%

4565 Poster Session (Board #239), Mon, 1:15 PM-4:45 PM

Extension of overall survival (OS) beyond objective responses (OR) in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with high dose interleukin-2 (HD IL-2). *First Author: David D. Stenehjem, Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, UT*

Background: The aim of this study is to determine if achievement of stable disease as a best response to HD IL-2 may improve survival outcomes. Recent data suggest that immunotherapy may improve survival even in those pts who do not experience objective responses (CR+PR). **Methods:** All sequential mRCC pts treated with HD IL-2 at the University of Utah (1988-2013) and University of Michigan (1997-2013) were included. Best responses to HD IL-2 were correlated with survival outcomes using landmark analysis at 2 months—the median time to first disease assessment. **Results:** A total of 391 pts (75% male; median age 55 yrs, range 13-77) were included and belonged to the following risk categories: 80 (20%) good, 251 (64%) intermediate, and 60 (15%) poor. A CR was identified in 35 (9%), PR in 39 (10%), SD in 125 (32%), progressive disease (PD) in 164 (42%), and not evaluable for response (NE) in 28 (7%) pts. Median OS for the favorable, intermediate and poor risk groups were 53.8 ($p=0.0015$ vs intermediate), 26.4 ($p<0.0001$ vs poor), and 12.2 ($p<0.0001$ vs favorable) months, respectively. Table shows correlation of response to survival. **Conclusions:** Stable disease as best response to HD IL-2 was achieved in 32% of pts and survival outcomes were not statistically different in these pts from those achieving PR, however significantly greater than those with PD. Stable disease is an important response criterion for treatment with HD IL-2, and may be discussed with the pts.

Correlation of best responses with survival outcomes in mRCC pts treated with HD IL-2: Landmark analysis at 2 months.

	Median PFS, months	Median OS, months
Overall	6.9	49.2
CR vs PR	113.8 vs 11.8 (HR 0.18, CI 0.09-0.37)	156.7 vs 37.8 (HR 0.21, CI 0.09-0.47)
CR vs SD	113.8 vs 9.0 (HR 0.13, CI 0.06-0.23)	156.7 vs 38.4 (HR 0.13, CI 0.05-0.26)
SD vs PD	9.0 vs 3.9 (HR 0.19, CI 0.12-0.31)	38.4 vs 19.9 (HR 0.41, CI 0.24-0.72)
OR vs (SD and PD)	26.4 vs 4.9 (HR 0.26, CI 0.18-0.36)	101.2 vs 24.1 (HR 0.24, CI 0.15-0.37)
(CR, PR, SD) vs PD	10.4 vs 2.6 (HR 0.10, CI 0.07-0.14)	53.9 vs 12.2 (HR 0.23, CI 0.16-0.33)
PR vs SD	11.8 vs 9.0 (HR 0.69, CI 0.44-1.04)	37.8 vs 38.4 (HR 0.60, CI 0.34-1.01)

4566 Poster Session (Board #240), Mon, 1:15 PM-4:45 PM

Efficacy and safety of endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors (TKI) after programmed cell death 1 (PD-1) inhibitor treatment in patients with metastatic clear cell renal cell carcinoma (mccRCC). *First Author: Rosa Nadal, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Emerging agents blocking the PD-1 pathway show activity and may transform the current treatment landscape of mccRCC. The aim of this study was to evaluate the efficacy and safety of VEGFR -TKI therapy after PD-1 treatment. **Methods:** Patients (pts) with mccRCC treated with PD-1 monotherapy or in combination - with either cytotoxic T-lymphocyte antigen 4(CTLA4) inhibitor (PD1/CTLA4) or TKI (PD-1/VEGFR-TKI) - who subsequently received VEGFR-TKI, were retrospectively reviewed. The efficacy end points were objective response rate (ORR) and progression-free survival (PFS) stratified by type of prior PD-1 regimen. Safety by type and PD-1 exposure was also evaluated. **Results:** 63 patients were included, 84% of pts had at least one VEGFR-targeted therapy prior to PD-1-based therapy. The ORR for VEGFR -TKI therapy (68%, 17%, 14% and 1% pts received axitinib, pazopanib, sunitinib and sorafenib, respectively) after any PD-1 combination was 27% (17/63 PR). An additional 26 (41%) pts achieved SD. The median PFS (mPFS) was 6.9 months (mo) (95%, CI: 3.7 to 10.1). In the analysis by type of prior PD-1 therapy, there was a trend toward a higher ORR in pts who had prior therapy with PD1 monotherapy or PD1/CTLA4 therapy 33% versus 14% for pts previously treated with PD-1/VEGFR-TKI therapy ($p = 0.094$). The mPFS was longer in those pre-treated with PD-1 monotherapy or PD-1/CTLA4 therapy: 8.3 mo (95%, CI: 4.0-12.7) compared to those who previously received PD-1/VEGFR-TKI combinations: 6.4 mo (95%, CI: 3.9-8.8); $p = 0.049$. The most common adverse events (AEs) (all grades/g3-4) were asthenia (69%/11%), hypertension (41%/2%) and diarrhea (30%/0%). One patient experienced grade-2 immune-related colitis during VEGFR-TKI therapy. **Conclusions:** The efficacy and safety of VEGFR-TKIs after PD-1 treatment was demonstrated in this retrospective study. The response rate was lower and the mPFS shorter in those pts who received prior PD-1 in combination with VEGFR-TKI. PD-1 exposure does not seem to influence the safety of subsequent VEGFR-TKI treatment compared to historical control and immune-related AEs were rare.

4567 Poster Session (Board #241), Mon, 1:15 PM-4:45 PM

The DART Study: Part 1 results from the dalantercept plus axitinib dose escalation and expansion cohorts in patients with advanced renal cell carcinoma (RCC). *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Activin receptor-like kinase 1 (ALK1) is a novel target in angiogenesis involved in blood vessel maturation and stabilization. Concurrent targeting of ALK1 and vascular endothelial growth factor (VEGF) signaling results in dual angiogenic blockade and augmented inhibition of tumor growth in RCC xenograft models. Dalantercept (Dal) is an ALK1 receptor-fusion protein that acts as a ligand trap and has demonstrated monotherapy activity with an acceptable safety profile in a completed Phase 1 study. **Methods:** Part 1 of this study evaluated the safety, tolerability, and preliminary activity of escalating dose levels of Dal plus standard dose axitinib in pts with advanced RCC. 3-6 pts each received 0.6, 0.9, or 1.2 mg/kg Dal SC Q3W and axitinib 5 mg PO BID. Key eligibility: predominantly clear cell RCC, 1 prior VEGFR TKI, ≤ 3 prior tx. **Results:** As of January 16, 2015, a total of 29 pts were enrolled. During dose escalation, 15 pts were enrolled in 3 cohorts ($n = 6, 4, 5$) at dose levels of 0.6, 0.9 and 1.2 mg/kg, respectively. There were no DLTs. The 1.2 mg/kg dose level was expanded to include 9 more pts and edema events including peripheral edema ($n = 8$), fluid overload ($n = 1$), and ascites ($n = 1$) were reported. The 0.9 mg/kg dose level was then expanded to include 5 more pts. This dose level was well tolerated (4 pts with grade 1 edema, 1 pt with pleural effusion and no ascites), and selected for Part 2. AEs ($> 30\%$) regardless of attribution included: fatigue, diarrhea, dysphonia, peripheral edema, nausea, decreased appetite, epistaxis, hypertension, arthralgia, creatinine rise, cough, and hand-foot rash. There were no grade 4/5 related adverse events. 28 pts were evaluable by RECIST v1.1. The ORR was 25% ($n = 7$). Disease control (PR+SD) at 6 months was 57% ($n = 16$). The preliminary median PFS is 8.3 months for all dose levels combined. The mPFS at the 0.9 mg/kg dose level has not been reached. **Conclusions:** The combination of dalantercept and axitinib is well tolerated and has shown encouraging activity in pts who have received prior VEGF, mTOR, and immune therapies. Part 2 of this study will randomize 130 pts to dalantercept + axitinib vs. placebo + axitinib and is actively accruing patients. Clinical trial information: NCT01727336.

4568 Poster Session (Board #242), Mon, 1:15 PM-4:45 PM

Impact of salvage surgery and radiotherapy on overall survival in patients with recurrent primary urethral cancer. *First Author: Georgios Gakis, Eberhard-Karls University Tuebingen, Tuebingen, Germany*

Background: To evaluate the impact of salvage therapy (ST) on overall survival (OS) in recurrent primary urethral cancer (PUC). **Methods:** A series of 154 patients (109 men, 45 women; median age: 66, IQR: 58-76) were diagnosed with PUC at ten referral centers between 1993 and 2012. Kaplan-Meier analysis with log-rank was used to estimate the impact of ST on OS. The median follow-up was 21 months (mean: 32 months; IQR: 4-48). **Results:** The modality of primary treatment was cystectomy+urethrectomy in 43 (27.9%), total/partial urethrectomy in 39/6 (25.3/3.9%), transurethral resection in 39 (25.3%), chemoradiotherapy (CRT), radiotherapy (RT), chemotherapy (CT) and other in 9 (5.8%), 4 (2.6%), 3 (1.9%) and 9 (5.8%) patients, respectively. Neoadjuvant CT/CRT and adjuvant CT were administered to 16/9 (10.4/5.8%) and 23 (14.9%) patients, respectively. The locations of recurrences were: urethral in 28 (18.2%), lymph nodes (LN) in 18 (11.7%), LN+distant in 12 (7.8%), LN+distant+urethral in 9 (5.8%), LN+urethral in 6 (3.9%), distant in 5 (3.3%), distant+urethral in 4 (2.6%) and no recurrence in 72 (46.8%). In the 82 patients with recurrences, the modality of ST was surgery in 32 (39.0%), RT in 8 (9.8%), surgery+RT in 5 (6.1%) and none in 37 (45.1%). The 3-year OS for patients free of any recurrence (I), with solitary and/or concomitant urethral recurrence (II) and non-urethral recurrence (III) were 86.7%, 74.5/% and 41.7% respectively ($p < 0.001$ for I vs. III, $p = 0.001$ for II vs. III, $p = 0.53$ for I vs. II). In patients with recurrences, those who underwent ST had similar 3-year OS (surgery: 84.9%, RT: 80%, surgery+RT: 80%) compared to patients with no recurrence (86.7%, $p = 0.79$), and exhibited superior 3-year OS compared to patients who did not undergo ST (27.6%; $p < 0.001$ compared to surgery; $p = 0.016$ to RT-based ST; $p = 0.53$ for surgery vs. RT-based ST). Receipt of perioperative CT/CRT ($N = 16$) did not impact on 3-year OS after ST (79.3%) compared to no CT/CRT ($N = 29$, 85.5%, $p = 0.95$). **Conclusions:** In this study, patients who underwent surgery or RT-based ST for recurrent PUC demonstrated improved OS compared to those who did not receive ST and exhibited similar survival to those who never developed recurrence after primary treatment.

4569 Poster Session (Board #243), Mon, 1:15 PM-4:45 PM

Multi-institutional validation of the predictive value of Ki-67 in patients with high-grade urothelial carcinoma of the upper urinary tract. *First Author: Laura-Maria Krabbe, University Hospital of Münster, Münster, Germany*

Background: To validate the independent predictive value of Ki-67 in patients with high-grade upper tract urothelial carcinoma (UTUC). **Methods:** 475 patients from the international UTUC collaboration who underwent extirpative surgery for high-grade UTUC were included in this study. Immunohistochemical staining for Ki-67 was performed on tissue microarray (TMA) formed from this patient cohort. Ki-67 expression was assessed in a semi-quantitative fashion and considered overexpressed at a cut-off of 20%. Multivariate analyses (MVA) were performed to assess independent predictors of oncological outcomes and Harrell's C indices (HCI) were calculated for predictive models. **Results:** Median age of the cohort was 69.7 years and 55.2% of patients were male. Ki-67 was overexpressed in 25.9% of patients. Ki-67 overexpression was significantly associated with ureteral tumor location, higher pT-stage, lymphovascular invasion, sessile tumor architecture, tumor necrosis, concomitant carcinoma in situ (CIS), and regional lymph node metastases. In Kaplan-Meier analyses, overexpressed Ki-67 was associated with worse recurrence-free (RFS) (HR 12.6, $p < 0.001$) and cancer-specific survival (CSS) (HR 15.8, $p < 0.001$). In MVA, Ki-67 was an independent predictor of RFS (HR 1.6, 95% CI 1.07-2.30, $p = 0.021$) and CSS (HR 1.9, 95% CI 1.29-2.90, $p = 0.001$). Ki-67 improved HCI from 0.66 to 0.70 ($p < 0.0001$) for both RFS and CSS in our preoperative model, and from 0.81 to 0.82 ($p = 0.0018$) for RFS and 0.81 to 0.83 ($p = 0.005$) for CSS in our post-operative model. **Conclusions:** Ki-67 was validated as an independent prognostic predictor of RFS and CSS in patients treated with extirpative surgery for high-grade UTUC in a large, multi-institutional cohort.

TPS4570 Poster Session (Board #244a), Mon, 1:15 PM-4:45 PM

Design of an open label, randomized, phase II study of paclitaxel and panitumumab compared to paclitaxel alone in patients with relapsed or refractory urothelial cancer. *First Author: Andrea Necchi, Istituto Nazionale Tumori of Milan, Milano, MI, Italy*

Background: The paradigm shift in the treatment of urothelial cancer (UC) is perceived by the oncology community as a long-standing medical need under multiple aspects. For patients (pts) with advanced disease and who have failed chemotherapy attempts, no FDA-approved agent is still available. One plausible target in UC is the Epidermal Growth Factor Receptor (EGFR). Strong expression of EGFR is found in 50% of advanced UC and it is associated with a more aggressive phenotype. Signals of activity of anti-EGFR agents combined with chemotherapy have been observed. **Methods:** Pts will receive paclitaxel (TXL) and will be randomly assigned 2:1 to also receive Panitumumab or not until disease progression, unacceptable toxicity, or withdrawal of consent. The doses of the study drugs will be as follows: panitumumab 6 mg/Kg IV every 14 days and TXL 80 mg/m2 IV on days 1, 8 and 15 of a 28 day cycle. Pts will undergo computed tomography (CT) and positron emission tomography (PET)/CT scan at baseline and q2 months. The primary endpoint will be progression-free survival (PFS). It is foreseen an accrual of 120 patients, 80 + 40 in the two arms, corresponding to 114 disease progressions or deaths. This is the number of events necessary to yield 90% power of a one-sided logrank test at the 5% significance level in case of an improvement in PFS from a median of 2.5 months (H_0) to a median of 4.5 months (H_1), corresponding to a 44% hazard rate reduction in the experimental arm compared to control. Computations were done taking into account an annual 10% drop out rate and the use of O'Brien-Fleming type efficacy and futility stopping rules at the interim analysis, to be performed when 51 (50%) of the expected number of events will be recorded. Eligibility will include diagnosis of metastatic UC and failure of 1 or 2 chemotherapy regimens. A relapse within 6 months of a perioperative chemotherapy will be counted as one line. Pharmacodynamic analyses are planned on pre- and post- tissue samples and will include molecular alterations of EGFR/RAS pathways. The trial is currently open to accrual (registered with EudraCT, number 2014-000857-35). Clinical trial information: 2014-000857-35.

TPS4571 Poster Session (Board #244b), Mon, 1:15 PM-4:45 PM

KEYNOTE-045: Randomized phase 3 trial of pembrolizumab (MK-3475) versus paclitaxel, docetaxel, or vinflunine for previously treated metastatic urothelial cancer. *First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Boston, MA*

Background: Paclitaxel, docetaxel, and vinflunine are commonly used as second-line therapy for advanced urothelial cancer, but median OS is only 7-9 months. The PD-1 pathway plays a key role in evading the tumor immune response. Pembrolizumab is a highly selective anti–PD-1 monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. In KEYNOTE-012, pembrolizumab 10 mg/kg every 2 weeks (Q2W) provided a 24% ORR (RECIST v1.1, central review) and an acceptable safety profile in 33 pts with PD-L1–positive advanced urothelial cancer, 76% of whom received $\geq$ 1 prior therapy. **Methods:** In the international, open-label, phase 3 KEYNOTE-045 trial (ClinicalTrials.gov, NCT02256436), pts with confirmed metastatic or locally advanced/unresectable urothelial cancer (transitional cell or predominantly transitional cell histology) of the bladder, renal pelvis, ureter, or urethra that has recurred or progressed following platinum-based chemotherapy are randomized 1:1 to pembrolizumab 200 mg Q3W or investigator's choice of paclitaxel 175 mg/m^2 Q3W, docetaxel 75 mg/m^2 Q3W, or vinflunine 320 mg/m^2 Q3W. Key eligibility criteria include $\leq$ 2 prior chemotherapy regimens and measurable disease per RECIST v1.1. Randomization is stratified by ECOG PS (0/1 vs 2), liver metastases (presence vs absence), hemoglobin level ($<$ 10 vs $\geq$ 10 g/dL), and time from last chemotherapy dose ($<$ 3 vs $\geq$ 3 mo). All pts must provide a recently obtained biopsy sample for PD-L1 evaluation at a central laboratory. Pembrolizumab will be given for up to 24 mo or until disease progression, unacceptable toxicity, or investigator decision. Treatment may be continued beyond initial radiographic progression in select pts. Pts who achieve complete response may discontinue pembrolizumab. Response will be evaluated at wk 9 and every 12 wk thereafter. After discontinuation, pts will be followed for survival every 12 wk. Primary end points are OS and PFS assessed per RECIST v1.1 by independent central review. Secondary end points include ORR and duration of response. Enrollment began in Oct 2014 and will continue until approximately 470 pts are enrolled. Clinical trial information: NCT02256436.

TPS4572 Poster Session (Board #245a), Mon, 1:15 PM-4:45 PM

KEYNOTE-052: Phase 2 study of pembrolizumab (MK-3475) as first-line therapy for patients (pts) with unresectable or metastatic urothelial cancer ineligible for cisplatin-based therapy. *First Author: Dean F. Bajorin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Standard first-line therapy for advanced urothelial cancer is cisplatin-based chemotherapy. Pts who are ineligible for cisplatin therapy, mainly due to renal dysfunction and/or poor performance status, have limited treatment options. The programmed death receptor 1 (PD-1) pathway is used by tumors to suppress immune control. Pembrolizumab is a highly selective, IgG4 anti-PD-1 humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. In the phase 1 KEYNOTE-012 trial, pembrolizumab 10 mg/kg once every 2 weeks (Q2W) demonstrated an ORR of 24% (RECIST v1.1, central review) in 33 pts with PD-L1–positive advanced urothelial cancer, 76% of whom received $\geq$ 1 prior therapy. **Methods:** KEYNOTE-052 (ClinicalTrials.gov, NCT02335424) is an international, open-label, phase 2 trial of pembrolizumab 200 mg Q3W as first-line therapy for adults with unresectable or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra who are ineligible to receive cisplatin. Pts are considered cisplatin ineligible if they have $\geq$ 1 of the following: ECOG PS 2, creatinine clearance (calculated or measured) $<$ 60 but $\geq$ 30 mL/min, grade $\geq$ 2 (CTCAE v4) audiometric hearing loss or peripheral neuropathy, or NYHA class III heart failure. All pts must provide a recently obtained biopsy sample for PD-L1 evaluation at a central laboratory. Pembrolizumab will be given for up to 24 mo or until disease progression, unacceptable toxicity, or investigator decision; treatment may be discontinued following complete response. Select pts may continue pembrolizumab beyond initial evidence of radiographic progression. Response will be evaluated per RECIST v1.1 by independent central review at 9 wk and every 6 wk thereafter. Survival follow-up will occur every 3 mo. Primary end point is ORR in pts with PD-L1–dependent tumors. Secondary end points include ORR in all pts, PFS, OS, duration of response, and the association between PD-L1 positivity and ORR. Up to 350 pts will be enrolled. KEYNOTE-052 is currently enrolling pts. Clinical trial information: NCT02335424.

TPS4573 Poster Session (Board #245b), Mon, 1:15 PM-4:45 PM

A multicenter randomized phase II trial comparing nab-paclitaxel to paclitaxel in patients with advanced urothelial cancer progressing on or after a platinum containing regimen: NCIC Clinical Trials Group BL 12 (NCT02033993). *First Author: Srikala S. Sridhar, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Metastatic urothelial cancer remains an incurable disease, for which there is no standard second line treatment. A previous phase II study of nab-paclitaxel in this setting demonstrated activity and good tolerability. The current study is designed to characterize the activity of nab-paclitaxel compared to paclitaxel in the second line treatment setting for advanced urothelial cancer. **Methods:** This is an NCIC Clinical Trials Group (NCIC CTG) led intergroup trial with the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP). The primary objective is to compare the progression free survival (PFS) between the two arms. Secondary objectives include: objective response rate, clinical benefit rate, time to response, response duration, toxicity, quality of life, and cost effectiveness. Correlative biological studies relating to tissue predictive and prognostic biomarkers and pharmacogenomics will be conducted. Clinicodemographic factors will be prospectively collected using a health and demographic questionnaire to further understand the relationships between biomarkers and clinical outcome measures. **Statistical Design**: Planned accrual is 199 patients over 3 years with followup of 4 months. Assuming median PFS of 4 months with paclitaxel, the target hazard ratio is 0.67 (PFS of 4 mo vs. 6 months, 1-sided, 5% significance with 80% power). Estimated sample size accounts for loss to followup or withdrawal of consent. **Conduct to Date:** Study activation: Mar 2014 (NCIC), Feb 2015 (ANZUP). As of February 2 2015, current accrual is 38. In November 2014 an independent DSMC recommended trial continuation. Supported by Celgene Corporation Clinical trial information: NCT02033993.

TPS4574 Poster Session (Board #246a), Mon, 1:15 PM-4:45 PM

Phase II randomised placebo controlled neoadjuvant chemotherapy study of nintedanib with gemcitabine and cisplatin in locally advanced muscle invasive bladder cancer. *First Author: Syed A. Hussain, University of Liverpool, Clatterbridge Cancer Centre, Liverpool, United Kingdom*

Background: The triple angiokinase inhibitor nintedanib (nin) has shown reduced proliferation and elevated apoptosis to a greater extent than chemotherapy alone in animal models. We aim to compare the effectiveness of nin vs placebo in combination with gemcitabine (gem) and cisplatin (cis) in muscle invasive bladder cancer (MIBC) patients prior to radical treatment. A safety sub-study will run in parallel with the main study to establish the maximum tolerated dose (MTD) of nin for patients with impaired glomerular filtration rate (GFR). **Methods:** The study opened in September 2014 and has recruited 4 patients to date (3 to main study, 1 to sub-study). 14 UK sites are planned. All patients must have localised muscle invasive carcinoma with no evidence of metastatic disease, ECOG performance status grade 0 – 1 and adequate haematological and hepatic function. Linked-in tissue collection and translational samples are built into the protocol. **Main Study** Patients will be stratified by centre and baseline GFR and randomised to receive 4 x 21 day cycles of gem 1000 mg/m2 and cis 70mg/m2 with 200mg BD nin or placebo. The primary outcome measure is cystoscopic and pathological complete response rate, with secondary outcome measures of progression free survival and toxicity. Overall survival is not assessed in order to facilitate seamless expansion into a phase III study. 120 patients (60 per arm) will provide 80% power to detect a 20% response difference, $p < 0.01$. Initially patients' GFR must be $>$ 60ml/min. After sub-study data analysis and determination of MTD in patients with GFR 40 – 60 ml/min, these patients may be included in the main study with split dose cis. **Sub-study** A 3+3 design is followed with an initial cohort of 3 patients with GFR 40 – 60 ml/min receiving 4 x 21 day cycles of gem 1000mg/m2 and split dose cis 35mg/m2 on day 1 and day 8 with 150mg BD nin. Nin dose-escalation/de-escalation for future cohorts of 3 – 6 patients will occur based on the no. of dose limiting toxicities, with a max. 12 patients recruited. The primary outcome measure is the MTD and safety of nin in combination with gem and split dose cis in patients with impaired renal function. Clinical trial information: 56349930.

TPS4575 Poster Session (Board #246b), Mon, 1:15 PM-4:45 PM

A phase 2 study of the histone deacetylase (HDAC) inhibitor mocetinostat in patients with urothelial carcinoma (UC) and inactivating alterations of acetyltransferase genes. *First Author: Noah M. Hahn, Johns Hopkins Kimmel Cancer Center, Baltimore, MD*

Background: Platinum-based chemotherapy is standard treatment for advanced UC, but no standard exists after first-line therapy. Mocetinostat (MGCD0103) is a spectrum selective inhibitor of HDAC 1, 2, 3 and 11. Site specific histone acetylation is regulated by the interaction of CREBBP and EP300 acetyltransferases with HDACs 1 and 2. Inactivating alterations of the genes *CREBBP* and/or *EP300* are associated with responsiveness to mocetinostat in preclinical cancer models and are reported in the tumors of ~28% of patients (pts) with UC (TCGA, *Nature*2014; 507:315), providing a clinical proof of principle opportunity for mocetinostat. **Methods:** This single-arm Phase 2 trial evaluates the efficacy of mocetinostat in pts with unresectable or metastatic UC and inactivating alterations of *CREBBP* and/or *EP300* as determined by next generation gene sequencing performed by qualified local labs or the FoundationOne platform. Eligible pts have received at least one prior platinum-based chemotherapy regimen and have measurable disease. The primary endpoint is Objective Response Rate (ORR) by RECIST 1.1. Secondary objectives evaluate safety, progression-free and overall survival, and pharmacokinetics. Exploratory objectives assess predictive biomarkers of response and mechanisms of acquired resistance through analysis of gene alterations in tumor and circulating tumor DNA. The study will enroll in 3 stages; among 15 pts, if at least 3 experience objective response or 6 are progression-free at 4-months, 18 pts will be added; if at least 9 objective responses are observed among these 33 pts, 67 pts will be added, for a total of 100 pts. Mocetinostat capsules are administered orally three times weekly, beginning with 70 mg per dose during the first cycle in pts in the first stage and then increasing to 90 mg per dose for the remainder of the study, as tolerability permits. The final sample size of 100 pts will provide 99% power to reject the null hypothesis that ORR rate is $\leq$ 15% (assuming a true ORR of 35%), using an exact test for single proportion (two-sided $\alpha = 5\%$). Status: Enrollment into the study opened in December 2014. Clinical trial information: NCT02236195.

TPS4576 Poster Session (Board #247a), Mon, 1:15 PM-4:45 PM

A phase I/II multi-center study of intravesical nanoparticle albumin-bound rapamycin (ABI-009) in the treatment of BCG refractory non-muscle invasive bladder cancer. *First Author: James M. McKiernan, Department of Urology, Columbia University Medical Center, New York, NY*

Background: Inactivation of p53 and PTEN mutations promotes progression in bladder cancer via deregulation of the mammalian target of rapamycin signaling pathway (mTOR). mTOR expression increases as a function of the disease stage as it progresses from superficial to invasive bladder cancer. Our group has proven the efficacy of intravesical rapamycin to treat bladder cancer in a mouse model. With the advent of the nanoparticle albumin bound (nab) version of rapamycin (ABI-009), this hydrophobic entity can now be tested intravesically. We sought to investigate the safety and efficacy in the management of Bacillus Calmette-Guerin (BCG) refractory non-muscle invasive urothelial carcinoma of the bladder (NMIBC). **Methods:** Funded via the NIH small business innovation research program (grants 1R42CA171552 and 3R42CA171552), this combined phase I/II study is currently enrolling patients with BCG refractory NMIBC at Columbia University and Vanderbilt University. BCG refractory is defined as disease recurrence after BCG therapy ($>$ 9 doses). This population was chosen given the dearth of effective, non-surgical second line options. Inclusion criteria include: histologically confirmed NMIBC including CIS and/or papillary lesions of high-grade Ta/T1, refractory to BCG; be eligible and refuse radical cystectomy; have all grossly visible disease fully resected. A maximum of 15 patients will be recruited in phase I with a dose-escalation scheme starting at 100 mg and escalating in the 3 remaining cohorts by 100 mg following a 3+3 rule. After the dose is determined, the phase 2 segment will enroll 29 patients. Success will be defined by a complete response in 20% of patients with negative biopsy 6 weeks post-treatment. This trial is enrolling with Cohorts 1 and 2 complete with no DLTs. Cohort 3 has 2 patients who received treatment and 1 receiving treatment with no DLTs thus far. In conclusion, ABI-009 will be the first-in-human molecularly guided mTOR pathway intravesical therapy to be studied for patients with BCG refractory NMIBC. Clinical trial information: NCT02009332.

TPS4577 Poster Session (Board #247b), Mon, 1:15 PM-4:45 PM

The Borealis-2 clinical trial: A randomized phase 2 study of OGX-427 (Apatorsen) plus docetaxel versus docetaxel alone in relapsed/refractory metastatic urothelial cancer. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

Background: Heat shock protein 27 (Hsp27) is over-expressed in many cancers including bladder, lung, prostate, and breast. Increased Hsp27 has been associated with inhibition of chemotherapy-induced apoptosis, increased tumor cytoprotection, and development of treatment resistance. OGX-427 (apatorsen) is an antisense oligonucleotide designed to bind Hsp27 mRNA, inhibiting production of the Hsp27 protein. Inhibition of Hsp27 has been shown to increase apoptosis, inhibit tumor growth and metastasis, and sensitize tumor cells to chemotherapy in a variety of malignancies, including urothelial cancer. Results of preclinical and phase 1 studies suggest that addition of apatorsen to chemotherapy is well tolerated and may improve treatment efficacy. Borealis-2 is a randomized, multicenter, phase 2 study of apatorsen in combination with docetaxel (DOC) vs. DOC alone in locally advanced/metastatic bladder cancer patients who received at least one line of prior platinum-based therapy. The primary objective is to evaluate overall survival. Secondary objectives include comparisons of safety and tolerability, disease response, and serum levels of Hsp27 and other pathway-related proteins. Associations between clinical outcomes, levels of Hsp27 and other proteins, and circulating tumor cells will be evaluated. **Methods:** Patients (N = 200) are randomized in a 1:1 ratio following stratification (time from prior systemic chemotherapy; Bellmunt criteria). Up to 2 prior systemic therapies are allowed. Treatment-arm patients receive three loading doses of apatorsen (600 mg) followed by up to ten 21-day treatment cycles (apatorsen 600 mg on Days 1, 8, and 15 and DOC 75 mg/M^2 IV on Day 1). Control-arm patients receive DOC 75 mg/M^2 IV on Day 1 of each cycle. Treatment may continue until disease progression, unacceptable toxicity, completion of ten cycles, or patient withdrawal. Patients who discontinue DOC due to toxicity after $\geq$ 2 cycles and do not have disease progression may receive maintenance therapy with apatorsen. One interim futility analysis will be performed. The trial will not be stopped early based on efficacy. Clinical trial information: NCT01780545.

TPS4578 Poster Session (Board #248a), Mon, 1:15 PM-4:45 PM

CheckMate 214: A phase III, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma. *First Author: Hans J. Hammers, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Therapeutic options have improved outcomes for patients (pts) with metastatic renal cell carcinoma (mRCC). Nivolumab, a fully human IgG4 programmed cell death-1 immune checkpoint inhibitor antibody, has shown clinical activity in RCC and in other tumor types. In CheckMate 016, a phase I study, nivolumab + ipilimumab demonstrated acceptable safety and encouraging antitumor activity in patients with mRCC (Hammers HJ, et al. *J Clin Oncol*. 2014;3215 suppl]:4504). This phase III study evaluates nivolumab + ipilimumab compared with sunitinib monotherapy for previously untreated mRCC (NCT02231749). **Methods:** Adults with advanced or metastatic clear-cell RCC with no prior systemic therapy are eligible. Pts with one prior adjuvant/neoadjuvant therapy (excluding VEGF targeted therapies) following RCC resection are eligible if recurrence occurred $\geq$ 6 months after the last dose. Other key inclusion criteria include: Karnofsky Performance Status $\geq$ 70%, measurable disease per RECIST v1.1, and available tumor tissue. Pts with a history of, or current, central nervous system metastases are ineligible. Prior treatment with systemic corticosteroids/immunosuppressants within 14 days before first dose of study drug, or with any agent targeting T cell co-stimulation or checkpoint pathways is not permitted. The study is expected to randomize ~1,070 pts stratified by International mRCC Database Consortium prognostic score (0 vs 1–2 vs 3–6) and region (US vs Canada/Europe vs rest of world). Pts will be randomized to either: i) nivolumab 3 mg/kg intravenously (IV) + ipilimumab 1 mg/kg IV every 3 weeks for four doses, followed by nivolumab monotherapy 3 mg/kg IV every 2 weeks or ii) sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off. Treatment will be discontinued for unacceptable toxicity or withdrawal of consent. Pts may continue treatment beyond progression (RECIST v1.1) if investigator-assessed clinical benefit is achieved and treatment is well tolerated. The co-primary endpoints are progression-free survival and overall survival. Secondary endpoints include objective response rate and safety. Clinical trial information: NCT02231749.

TPS4579 Poster Session (Board #248b), Mon, 1:15 PM-4:45 PM

Randomized phase 2 study to assess the safety and efficacy of CRLX101 in combination with bevacizumab in patients (pts.) with metastatic renal cell carcinoma (RCC) versus standard of care (SOC). *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Up to 30% of pts. with RCC present with metastatic disease and 5-year survival among these pts. is less than 10%. VEGF-targeted and mTOR inhibiting drugs constitute SOC in this setting but anti-tumor effects are generally short-lived and there exists a pressing need for new therapeutic strategies. Among pts. with tumors progressing through multiple prior lines of therapy, the GOLD trial (Motzer et al., Lancet Oncology 2014) reported that sorafenib and the comparator agent dovitinib achieved PFS of approx. 4 mos. CRLX101 is a novel camptothecin (CPT)-containing nanoparticle drug conjugate that delivers sustained levels of active CPT into cancer cells while reducing systemic exposure and toxicity. In addition to its topo-1 effect, CRLX101 durably inhibits HIF-1α, a hypoxia-induced transcription factor implicated in tumor angiogenesis, metastasis, and resistance to VEGF inhibitors. Clear cell RCC (ccRCC) accounts for approx. 80% of RCC and is characterized by high levels of HIF-1α, providing an ideal clinical setting in which to evaluate potential synergy between CRLX101 and the VEGF inhibitor bevacizumab (BEV). Phase 2 data presented separately at this conference highlight notable signals of RCC activity for this combination with objective response rate (ORR) and median progression free survival (mPFS) exceeding 20% and 9 mos., respectively. **Methods:** This randomized clinical trial is being conducted at approx. 40 U.S. cancer centers and will enroll 110 pts. with advanced, unresectable metastatic RCC who have completed 2 or 3 prior regimens of therapy. The primary endpoint will compare PFS among 90 ccRCC pts. treated with concurrently administered CRLX101 + BEV vs. SOC (any approved agent per investigator choice not previously used in the same patient). Statistical power is set at 80% to detect an increase in mPFS from 3.5 mos. to 5.8 mos. (HR~0.6). Secondary/exploratory endpoints incl. OS, ORR, safety, PK, and plasma biomarkers of efficacy. Additionally, 20 pts. with non-ccRCC histology will be evaluated independently. Enrollment is ongoing and is expected to be complete by the end of 2015. Clinical trial information: NCT02187302.

TPS4580 **Poster Session (Board #249a), Mon, 1:15 PM-4:45 PM**

A multicenter, open-label, proof of concept phase 1b/2 study to evaluate the safety and efficacy of RX-0201 in combination with everolimus to treat subjects with advanced renal cell carcinoma. *First Author: Christine Peterson, Rexahn Pharmaceuticals, Rockville, MD*

Background: RX-0201 is a 20-mer oligonucleotide that is complementary to AKT-1 messenger ribonucleic acid (mRNA). The specificity of RX-0201-mediated effect on AKT-1 mRNA levels was examined in human renal cell carcinoma (von Hippel-Lindau protein-deficient renal cell carcinoma cell line) UMRC2 cells and resulted in a reduction of AKT-1 mRNA levels **Methods:** The current study is a proof of concept phase 1b/2, multicenter, open label study conducted in 2 stages. Stage 1 is an open-label, dose-escalation phase 1b study of RX-0201 administered in combination with everolimus. RX-0201 will be administered by a 24 hour continuous intravenous infusion for 14 days followed by 7 days of rest. It is expected that 250 mg/m2/day or a lower dose of RX-0201 will be identified as safe and well-tolerated when administered in combination with 10 mg of everolimus. The dose of RX-0201 identified in Stage 1 will be studied further in Stage 2 which is the randomized, open-label, 2-arm study of RX-0201 in combination with 10 mg of everolimus versus 10 mg of everolimus alone. Up to 8 cycles of study treatment will be permitted. Approximately 9 subjects are targeted to receive escalating doses of RX-0201 in combination with everolimus in Stage 1. The initial dose of RX-0201 is 125 mg/m2/day. In Stage 2 approximately 30 subjects are planned to be randomized in a 1:2 ratio (i.e., up to 10 subjects in the everolimus arm and up to 20 subjects in the everolimus/RX-0201 arm). Eligible subjects must have confirmed histologic or cytologic evidence of renal cancer with a clear cell component, measurable or evaluable disease as defined by RECIST, received at least 1 course of therapy with a VEGFR inhibitor and progressed within 6 months of planned first dose of on study treatment and received no more than 3 prior treatments of systemic renal cancer therapy. Radiological imaging for disease assessments will be according to RECIST ver. 1.1 Clinical trial information: NCT02089334.

TPS4581 **Poster Session (Board #249b), Mon, 1:15 PM-4:45 PM**

A randomized, open label, multicenter phase 2 study to evaluate the efficacy of sorafenib in patients (pts) with advanced Renal Cell Carcinoma (RCC) after a radical resection of the metastases. *First Author: Elena Verzoni, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: Complete response with targeted agents approved for metastatic renal cell carcinoma (mRCC) is rarely achieved. Retrospective findings seem to indicate that metastasectomy (Mtx) may improve survival in selected pts. The RESORT study was designed to evaluate whether Mtx followed by sorafenib may provide an additional clinical benefit. VEGF expression may represent a prognostic factor for survival **Methods:** Overall 132 mRCC pts undergoing complete Mtx will be randomized 1:1 (66 pts per arm) to receive either sorafenib or best supportive care (BSC) for 52 weeks or until disease recurrence. Prognostic factors including time from nephrectomy, site of disease and number of lesions will be used to stratify pts Key inclusion criteria: · Maximum 3 metastatic lesions. · Complete removal of all metastatic lesions. · Microscopic examination of margins showing no tumor cells (R0 resection) · No more than three months from Mtx Pts will be recruited from 16 Italian centers. The primary endpoint is recurrence-free survival (RFS), defined as the time from randomization to diagnosis of disease relapse or death. Secondary endpoints are Overall survival (OS) and safety. Circulating levels of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) will be evaluate from consenting pts (optional) at baseline, every 3 months, and at the end of treatment. Sorafenib will be administered at the dose of 400 mg orally once daily for 21 days and then increased to 400 mg twice daily if the patient has not experienced grade 2 skin toxicity or any other grade 3 toxicities. Imaging assessments will be performed every 12 weeks *Statistical plan* Kaplan-Meier methods will be used for survival analyses and the log-rank test to compare sorafenib arm and BSC arm according to the stratification factors. The hazard ratio (HR) will be determined at the 95% confidence interval (CI). The hypothesis is to increase the RFS time from 12 months (BSC arm) to 18 months (sorafenib arm), corresponding to a 50% improvement. With a study power of 80% and a 1-sided error of 0.15, the estimated number of events required is 86. Twenty-six out of 132 pts have been enrolled Clinical trial information: NCT01444807.

TPS4582 **Poster Session (Board #250a), Mon, 1:15 PM-4:45 PM**

Patient identification and eligibility insights in the synchronous metastatic RCC population: An update from the ongoing ADAPT* phase 3 study experience. *First Author: Robert A. Figlin, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: AGS-003 is an autologous immunotherapy designed to induce a T-cell response specific to a patient's tumor antigens. Sunitinib is a TKI and first-line therapy for mRCC that also reverses the immune suppression observed in these patients. In a single arm phase 2 study, AGS-003 plus sunitinib was safe and yielded a median overall survival (OS) of over 30 months in newly diagnosed mRCC patients. **Methods:** The ADAPT study is a randomized (2:1) international phase 3 study comparing standard targeted therapy plus AGS-003 to standard therapy alone. The primary objective is to compare the median OS between treatment arms. The study is enrolling adults with synchronous, metastatic, clear cell RCC who are good candidates for surgery and standard targeted therapy (initiating with, but not limited to, sunitinib), KPS $\geq$ 70%, life expectancy of at least 6 months, between 1-4 Heng risk factors, and adequate end organ function. Initial enrollment patterns were investigated in order to gain insight on the features of mRCC patients that are candidates for cytoreductive nephrectomy. More than 130 sites in North America and other select countries have been activated and $>$ 840 patients have been consented and tumor samples collected. Enrollment is expected to conclude in the 1st half of 2015. To date, approximately 50% of patients screened for tumor collection were ineligible to participate in the treatment phase of the ADAPT study after surgery, with about half of these being excluded because of non-clear cell histology. Other major reasons include ineligibility for sunitinib and lack of evaluable metastatic disease after nephrectomy. The DMC last reviewed the trial in December 2014 and suggested that the trial continue as planned. Clinical Trials registry number: NCT 1582672 * ADAPT: An International Phase 3 Randomized Trial of Autologous Dendritic Cell Immunotherapy (AGS 003) Plus Standard Treatment in Advanced Renal Cell Carcinoma (RCC) Clinical trial information: NCT1582672.

TPS4583 **Poster Session (Board #250b), Mon, 1:15 PM-4:45 PM**

The DART Study: A phase 2 randomized double-blind study of dalantercept plus axitinib versus placebo plus axitinib in advanced clear cell renal cell carcinoma (RCC). *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Activin receptor-like kinase 1 (ALK1) is a novel target in angiogenesis involved in blood vessel maturation and stabilization. Concurrent targeting of ALK1 and vascular endothelial growth factor (VEGF) signaling results in dual angiogenic blockade and augmented inhibition of tumor growth in RCC xenograft models. Dalantercept is an ALK1 receptor-fusion protein that acts as a ligand trap by binding to ligands, bone morphogenetic proteins (BMP) 9 and 10. Part 1 of this study evaluated the safety, tolerability, and preliminary activity of escalating dose levels of dalantercept (0.6, 0.9, and 1.2 mg/kg) plus standard doses of axitinib (5 mg PO BID) every 3 weeks in patients with advanced RCC who received at least one prior VEGFR TKI and no more than 3 prior tx. 29 pts were enrolled in Part 1 and the combination was associated with an acceptable safety profile and preliminary activity (25% RR, preliminary median PFS of 8.3 months for all dose levels combined). The mPFS for the 0.9mg/kg dose level has not been reached. AEs ($>$ 30%) regardless of attribution: fatigue, diarrhea, dysphonia, peripheral edema, nausea, decreased appetite, epistaxis, hypertension, arthralgia, creatinine rise, cough, and hand-foot rash. There were no grade 4/5 related adverse events. The 0.9 mg/kg dose level was selected for Part 2. **Methods:** Part 2 is a multi-center Phase 2 study and is actively accruing patients across approximately 50 sites in the US. In Part 2, 130 patients will be randomized 1:1 to dalantercept plus axitinib or placebo plus axitinib in a double-blinded fashion. Key eligibility: predominantly clear cell RCC; ECOG 0-1; 1 prior VEGFR TKI. 1 prior mTOR inhibitor and any number of prior immune therapies are also permitted. An independent DMC will evaluate safety data during the study. The primary endpoint is PFS. Secondary endpoints include: ORR by RECIST v1.1, OS, pharmacokinetic assessments, and pharmacodynamic evaluations of ALK1 pathway and other angiogenesis markers in serum and archived tumor specimens. Clinical trial information: NCT01727336.

TPS4584 Poster Session (Board #251a), Mon, 1:15 PM-4:45 PM

Phase II study of pazopanib and weekly paclitaxel in metastatic or locally advanced squamous penile carcinoma patients previously treated with cisplatin-based chemotherapy: PAZOPEN study. *First Author: Miguel Angel Climent, Fundación Instituto Valenciano de Oncología, Valencia, Spain*

Background: Metastatic or locally advanced squamous penile carcinoma (MLASPC) is an infrequent disease, with extremely bad prognosis. Platinum based chemotherapy is the most active treatment with a response rate (RR) of 30% and only 12 months of overall survival. New active agents are urgently needed. The combination of the antiangiogenic agent Pazopanib and paclitaxel have been tested in transitional carcinoma and melanoma with high number of responses and good tolerance profile. The aim of this study is to test the activity and safety of the combination in patients (pts) with MLASPC progressing to platinum based regimens. **Methods:** Phase II open label, single arm, multicentre study. Main inclusion criteria are: diagnosis of squamous penile carcinoma, ECOG 0-1, measurable disease by RECIST criteria, progressive disease after previous platinum based treatment, either in neoadyuvant, adyuvant or metastatic setting, adequate hepatic, renal and haematological function. Patients will receive treatment with pazopanib 800 mg p.o daily and paclitaxel 65 mg/m2/weekly D1, 8 and 15 every four weeks cycle. Main objective is RR (complete (CR) and partial response (PR) measured by RECIST criteria). Secondary objectives: Clinical benefit rate, (CR+ PR + SD), progression-free survival, response duration, overall survival, toxicity and tolerance profile. Whole exome sequencing will be performed to describe most frequent alterations in penile cancer. This is a two stage Simon optimal design for phase II trials. Considering an estimated 30% RR with P0 = 10%, (alpha error 5%, beta 20%), 10 patients will be included in first stage and if 2 or more responses are observed, then 19 additional patients will be included in second stage. If more than 5 responses are observed efficacy of treatment will be considered. The sample size, taking into account a 10% drop out rate will be 32 pts. Trial will be performed in 8 hospital centres of the SOGUG group. Study has been approved by ethic committees and health authorities. Funded by a grant from GlaxoSmithKline. NCT02279576. Clinical trial information: NCT02279576.

TPS4585 Poster Session (Board #251b), Mon, 1:15 PM-4:45 PM

ATR-101 phase 1 clinical study for adrenocortical carcinoma. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ATR-101 (Atterocor, Inc., Ann Arbor, MI, USA) is a selective inhibitor of ACAT1 (acyl coenzyme A:cholesterol acyltransferase) in clinical development for the treatment of adrenocortical carcinoma (ACC). ACAT1 catalyzes cholesterol ester formation from cholesterol and long-chain fatty acyl-CoA and, in the adrenals, is particularly important in creating a reservoir of substrate for steroid biosynthesis. ATR-101 selectively distributes to the adrenals, inhibits steroidogenesis and causes apoptosis of cells of the adrenal cortex, as well as in H295R ACC cells. ACC is an ultra-rare malignancy, occurring in about 2 per million population annually. ACC is frequently discovered in Stage 4 and the overall disease survival is approximately 17 months. Tumors often overproduce steroids normally produced in the adrenal cortex and cause therapy-resistant Cushing's syndrome. Current therapies are toxic, difficult to administer, and poorly effective. **Methods:** ATR-101-001 is a phase 1 study being conducted at four centers in the United States and one in Germany. It is a "3+3" design: 3 subjects with advanced ACC who have failed or declined existing therapies are enrolled at each dose level for 28 days. If no Dose Limiting Toxicity is observed, three additional subjects are enrolled at a higher dose. An expansion cohort of 20 subjects will be enrolled after the MTD has been determined. Subjects who appear to be deriving benefit may stay on ATR-101 indefinitely. ATR-101 is taken by mouth. The primary objective is to determine the safety and tolerability of ATR-101 in subjects with advanced ACC. Secondary objectives include efficacy by RECIST, measurement of production of steroid hormones and intermediates, determination of pharmacokinetics, the Maximum Tolerated Dose and the recommended phase 2 dose. The study is open to patients age 18 and over with advanced ACC. Patient's mitotane level must be 5 μg/ml or less; the QTcF 470 ms or less; and if present, CNS metastases must be treated and inactive. Full study information is available on ClinicalTrials.gov, Identifier NCT01898715. Clinical trial information: NCT01898715.

4586 Poster Discussion Session; Displayed in Poster Session (Board #187), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Impact of gemcitabine + cisplatin + ipilimumab on circulating immune cells in patients (pts) with metastatic urothelial cancer (mUC). *First Author: Matt D. Galsky, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Immune checkpoint blockade may play a role in the treatment of mUC. However, the role of CTLA4 blockade, the impact of chemotherapy on immune cell populations, and the optimal approach to combination regimens in pts with mUC remains poorly defined. An increase in tumor infiltrating and circulating CD4+ICOS+ cells after ipilimumab has been shown in pts with localized UC and correlated with improved outcomes in ipilimumab-treated melanoma pts (Carthon, Clin Can Res, 2010). **Methods:** Pts with mUC were enrolled on a phase 2 trial of chemotherapy + CTLA4 blockade. Patients received 2 cycles of gemcitabine + cisplatin (GC) followed by 4 cycles of GC + ipilimumab (GCI). Flow cytometry was performed on peripheral blood mononuclear cells at baseline, after GC, and after GCI to determine the impact of treatment on the frequency and phenotype of CD4+ and CD8+ T cells, regulatory T cells (CD4+CD25+CD127-CD45RA- Tregs), and myeloid-derived suppressor cells (CD13+CD14+CD11b+HLA-DR- MDSCs). Comparisons between time-points were made using Wilcoxon's rank test. **Results:** The trial has completed enrollment (n = 36) and flow cytometry data are available for the complete treatment sequence on 17 pts as of 2/2015 (Table). **Conclusions:** GC alone generally had no significant impact on the median % of circulating immune cell subsets though the increase in CD4+ICOS+ cells warrants confirmation. GCI resulted in an increase in CD4+ and CD8+ T cells, including the subset of CD4+ICOS+ cells, with a lesser increase in Tregs. The impact of individual changes in immune cell subsets on pt outcomes, and the role of GCI in mUC, will be further defined as efficacy data matures. Clinical trial information: NCT01524991.

Impact of treatment on immune cell subsets (median % (IQR)).

	Baseline (BL)	Post-GC	Post-GCI	p (GC v. BL)	p (GCI v. GC)
CD3+CD8+	4.9% (8.3%)	4.0% (5.0%)	6.8% (10.1%)	0.2	0.04
CD8+ICOS+	0.01% (0.4%)	0.05% (2.4%)	0.4% (3.7%)	0.2	0.9
CD8+PD1+	0.02% (0.3%)	0.02% (0.2%)	0.02% (0.2%)	0.7	0.7
CD3+CD4+	9.0% (7.4%)	5.0% (6.8%)	15.9% (11.2%)	0.7	0.001
CD4+ICOS+	0.2% (0.7%)	0.5% (5.4%)	3.1% (8.9%)	0.03	0.04
CD4+PD1+	0.1% (0.2%)	0.1% (0.3%)	0.4% (0.4%)	0.08	0.03
TReg	0.4% (0.6%)	0.4% (1.0%)	1.0% (0.9%)	0.5	0.04
MDSC	0.7% (3.8%)	0.4% (2.1%)	0.6% (6.7%)	0.6	0.6

5000 **Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

The Prostate Cancer Working Group 3 (PCWG3) consensus for trials in castration-resistant prostate cancer (CRPC). *First Author: Howard I. Scher, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The availability of new agents for men with CRPC, recognition of new disease phenotypes, and an evolving regulatory environment have created the need for new CRPC clinical trial guidelines to succeed PCWG2, published in 2008. **Methods:** Eight face-to-face meetings were convened over 3 years to create the PCWG3 guidelines, with subcommittees meeting more frequently. PCWG2 criteria were updated or revised based on new evidence from clinical trial data and validation studies of PCWG2 recommendations **Results:** PCWG3 distinguishes between prostate adeno- and non-adenocarcinomas; considers the sequence and number of prior systemic therapies in lieu of the pre- and post-taxane distinctions in PCWG2; encourages detailed reporting of disease subtypes based on distribution patterns; and defines endpoints for patients transitioning between non-metastatic and metastatic disease. For non-cytotoxic therapies, outcomes are focused on establishing proof-of-mechanism and determining the optimal biologic dose. The strength of association between patient-reported outcomes, radiographic progression-free survival, circulating tumor cell enumeration, and time to clinical events is emphasized rather than alterations in individual biomarkers. Similarly, PCWG3 underscores the distinction between first evidence of progression based on one disease manifestation in contrast to terminating treatment because the patient is no longer benefitting. We emphasize the importance of documenting progression in existing lesions as distinct from the development of new lesions. The revised guidelines highlight the importance of serial biologic profiling of the disease from biopsies and/or blood to understand treatment resistance and identify predictive biomarkers of sensitivity for use in prospective trials. **Conclusions:** PCWG3 updates the PCWG2 consensus criteria based on available new treatments and disease manifestations, and data validating biomarkers that were proposed in PCWG2. The revised criteria define the endpoints for the M0 to M1 transition. These recommendations will guide clinical trial design and conduct for therapeutics being tested in both M0 and M1 CRPC patient populations.

5001 **Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First overall survival results from STAMPEDE (NCT00268476). *First Author: Nicholas David James, University of Warwick, Coventry, United Kingdom*

Background: STAMPEDE is a randomised controlled trial using a novel multi-arm multi-stage design. It recruits men (pts) with high-risk locally advanced or metastatic prostate cancer (PCa) starting long-term hormone therapy (HT) for the first time. The trial initially assessed adding 1 or 2 of 3 treatment approaches to standard of care (SOC). We report primary survival results for 3 research comparisons that recruited through all their intermediate analyses: docetaxel (D), zoledronic acid (ZA) & the combination (D+ZA). **Methods:** SOC was hormone therapy for > = 3yrs; RT was encouraged for N0M0 pts up to Nov-2011, then mandated; RT was optional for N+M0 pts. Stratified randomisation allocated pts 2:1:1:1 to SOC (control), SOC+D, SOC+ZA or SOC+D+ZA. 4mg ZA was given for six 3-weekly cycles then 4-weekly until 2yrs. D was given as 75mg/m^2 for six 3-weekly cycles with prednisolone 10mg daily. The primary outcome measure was survival (time from randomisation to death from any cause). Pairwise comparisons to control on survival for each research arm had 90% power at 2.5% 1-sided alpha for a hazard ratio of 0.75 requiring ~400 control arm deaths, accounting for 3 intermediate lack-of-benefit analyses on failure-free survival. Analyses used the Cox model of the logrank test, adjusted for stratification factors. **Results:** From Oct-2005 to Mar-2013, 2,962 pts were randomised to the 4 arms. The groups were balanced with median age 65yrs; 61% metastatic, 14% N+/XM0, 22% N0M0; 93% diagnosed within 6m of randomisation; median PSA 65ng/ml. Median follow-up was 42m. Grade 3-5 toxicity was reported for 31% SOC, 50% SOC+D, 32% SOC+ZA and 52% SOC+D+ZA.There were 405 deaths on the control arm (84% from PCa). The hazard ratio was 0.76 (95% CI 0.63, 0.91; p = 0.003) for SOC+D vs SOC; 0.93 (95% CI 0.79, 1.11; p = 0.437) for SOC+ZA vs SOC; and 0.81 (95% CI 0.68, 0.97; p = 0.020) for SOC+D+ZA vs SOC. Median survival was increased by 10m from 67m on SOC to 77m on SOC+D. Results in M0 and M1 disease will be shown. **Conclusions:** Survival data from STAMPEDE show a clinically and statistically significant improvement in survival from adding docetaxel but not from adding zoledronic acid in men starting long-term hormone therapy for the first time. Clinical trial information: NCT00268476.

LBA5002 **Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). *First Author: Howard M. Sandler, Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

5003 **Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

Characterization of neuroendocrine prostate cancer (NEPC) in patients with metastatic castration resistant prostate cancer (mCRPC) resistant to abiraterone (Abi) or enzalutamide (Enz): Preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDT). *First Author: Eric Jay Small, UC San Francisco, San Francisco, CA*

Background: Mechanisms of resistance to androgen signaling inhibitors such as Abi or Enz are poorly understood. An increasing % of these pts develop NEPC. Pathologic (path), clinical, and genomic characterization of pts with NEPC was undertaken in the context of the WCDT project, which seeks to identify genetic pathways underlying primary and acquired resistance to Abi and Enz. **Methods:** Eligible mCRPC pts underwent a metastasis (met) biopsy (bx) at one of 5 WCDT centers, using a standardized bx protocol, and were uniformly followed for clinical outcomes. Tissue was both frozen, and formalin fixed/paraffin embedded. Independent path review was undertaken by 3 pathologists. Frozen specimens underwent laser capture micro-dissection, RNA isolation, library preparation and RNA sequencing (seq). Machine learning was used to derive a NEPC expression signature. **Results:** 150 of 300 planned mCRPC pts have undergone bx. Path review has been undertaken in 101. Classic small cell cancer (SmCC) was identified in 12%, adenocarcinoma (adenoca) in 33%. An intermediate histology distinct from SmCC or adenoca was seen in 27%. The remaining 28% were mixed histologies or were not classifiable. Anatomic site of bx (node, bone, liver) did not appear to enrich for a particular histology. Median overall survival was: not reached at 22 mos of follow-up in pts with adenoca, 8.9 mos in pts with intermediate histology, and 6.6 mos in pts with SmCC (log rank p = 0.027). RNAseq data are available on 45 biopsies. A 50 gene signature with 97% accuracy for NEPC (defined as SmCC or intermediate histology) was developed. **Conclusions:** RNAseq and expression analysis can be accomplished in small bone and soft tissue mCRPC biopsies. A distinct histology, intermediate to SmCC and adeno, was observed in 27% of pts. The development of NEPC in mCRPC resistant to Abi or Enz is far more common than previously appreciated and appears to result in poor survival. A 50 gene NEPC expression signature was derived which provides insight into the biology and potential treatment of NEPC.

5004 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Defining a molecular subclass of treatment resistant prostate cancer. *First Author: Himisha Beltran, Weill Cornell Medical College, New York, NY*

Background: A subset of advanced prostate cancers can progress from an androgen receptor (AR)-driven state to AR independence, often associated with low or absent AR expression and extensive neuroendocrine differentiation. Once neuroendocrine prostate cancer (NEPC) develops, patients often demonstrate an aggressive clinical course and poor overall survival. Diagnosis is important but remains challenging as the clinical and pathologic features associated with AR independence and NEPC are poorly defined. **Methods:** We performed whole-exome sequencing of 124 metastatic tumors from 81 patients (35 with morphologic features of NEPC). Serial or synchronous samples were included to characterize heterogeneity and the transition from adenocarcinoma to NEPC. Computational analysis of clonality and allele-specific quantification were performed using CLONET. Quantitative mRNA assessments, including AR signaling genes and DNA methylation, were evaluated in the context of genomic changes. **Results:** The mutational landscape of NEPC and castration-resistant prostate cancer (CRPC) did not differ significantly by rate of non-synonymous mutations or copy number burden (average $>$ 40% of genome was aberrant), and polyploidy was frequently detected together with common allelic imbalances. Comparative analysis at the DNA and mRNA level identified decreased AR signaling in NEPC and a range of AR signaling in CRPC, enrichment of copy number losses (including RB1 and multiple genes on 16q) in NEPC, and focal high level AR amplification in CRPC in contrast to NEPC ($p = 0.0007$). DNA allele-specific analysis of multi-sample cases suggested diverse genomic state of key lesions including aberrations in MYCN and CDKN1B. **Conclusions:** This is largest study to date focused on the molecular landscape of the NEPC resistance phenotype. NEPC is characterized by a molecular profile defined by distinct genomic alterations and decreased AR signaling. A subgroup of CRPC demonstrates lower AR signaling and molecular overlap with NEPC. This study supports clonal evolution of prostate adenocarcinoma to NEPC, provides new insight into NEPC biology and disease heterogeneity, and may aid in the detection of AR independence and emergence of the NEPC subclass of treatment resistance.

5005 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Biological heterogeneity in localized high-risk prostate cancer (LHRPC) from a study of neoadjuvant abiraterone acetate plus leuprolide acetate (LHRHa) versus LHRHa. *First Author: Eleni Efstathiou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Biological heterogeneity may have important implications for development of novel therapeutic approaches for LHRPC. This study examined clinical and biological heterogeneity of response and resistance to abiraterone acetate with prednisone (AA)+LHRHa vs LHRHa. **Methods:** A preoperative study of 12 wks of AA+LHRHa vs LHRHa alone (randomized 2:1) in pts with LHRPC (clinical stage T1c/T2 with biopsy Gleason $\geq$ 8, or $\geq$ T2b with Gleason $\geq$ 7 and prostate-specific antigen [PSA] $>$ 10 ng/mL). The effect of treatment on pathologic stage, androgen metabolites, and tumor epithelial cellular density (TECD, % of epithelial component [cellularity] in total tumor volume) in the residual tumor, and the link between TECD and PSA response, were evaluated, as was the association of key immunohistochemical (IHC) markers (eg, androgen receptor splice variant [ARv7], glucocorticoid receptor [GR], chromogranin A [CHROM], phospho-Src [p-Src]) with clinical, pathologic, and cellular responses. The difference in TECD between arms was assessed using the Wilcoxon rank sum test, with tumor volume determined using the Chen method. Correlations were evaluated using the Spearman method. **Results:** Sixty-five pts were accrued. Pathologic downstaging ($\leq$ pT2) occurred in 24/44 (54.5%) pts given AA+LHRHa vs 8/21 (38.1%) given LHRHa, $p = 0.21$. Post-treatment PSA nadir was $\leq$ 0.2 ng/mL in 41/44 (93.2%) for AA+LHRHa vs 3/21 (14.3%) for LHRHa, $p < 0.0001$. Despite these high rates of undetectable PSA, high TECD heterogeneity was observed in the AA+LHRHa arm (ie, 34% had $>$ 50% cellularity). Still, TECD was lower for AA+LHRHa vs LHRHa (median, 35% [range 1-75%] vs 70% [range 50-85%], $p <$ 0.0001). Specific to AA+LHRHa, higher ARv7, GR, and CHROM expression by IHC was associated with worse pathologic response, and higher ARv7, GR, and p-Src expression and lower CYP17 expression were correlated with higher TECD. **Conclusions:** We observed significantly lower TECD for the AA+LHRHa arm vs LHRHa.Our findings conclusively demonstrate greater cytoreduction with AA+LHRHa in hormone-naïve LHRPC and early emergence of resistance within 3 months of treatment initiation despite PSA declines. Clinical trial information: NCT01088529.

5006 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for biological relapse (BR) after radical prostatectomy (RP): Results of the GETUG-AFU 16 phase III randomized trial—NCT00423475. *First Author: Christian Carrie, Department of Radiation Oncology, Centre Léon Bérard, Lyon, France*

Background: RT is the standard as salvage treatment after RP. The role of HT is not demonstrated to date. This trial assessed the efficacy of RT alone *vs* RT+HT on progression-free survival (PFS) (biological or/and clinical relapse) for patients with BR after RP. Secondary objectives were overall survival (OS), toxicity and quality of life. **Methods:** Patients (pts) were randomized (1:1; stratification on risk factors at RP and type of planned RT) to RT alone (66Gy on prostate bed +/- pelvic irradiation according to pN status and risk of initial node involvement) or RT+HT (goserelin, for 6 months). Assuming 5-year PFS of 45% for RT arm, the trial required 369 pts per arm to detect an improvement of 12% on PFS in RT+HT arm (90% power and 5% alpha risk). BR was evaluated according to Astro-consensus. **Results:** From Oct. 2006 to Mar. 2010, 743 pts (RT: 374; RT+HT: 369) were randomized. Baseline characteristics were well balanced between the arms, median age: 67 y, pT2ac: 54%, pT3ac: 46%, gleason $>$ 6: 76%, positive margins: 51%, seminal vesicles' involvement 13%. PSA doubling time at relapse was $>$ 6 months in 74%. With a median follow-up of 63.1 months, 216 events were notified (138 in RT *vs* 78 in RT+HT). The intent to treat analysis showed an improved 5-y PFS of 62.1% (CI95%: 57-67) vs 79.6% (IC95%: 75-84) for RT and RT+HT, respectively (log-rank: $p <$ 0.0001). The 5-y OS was 94.8% for RT *vs* 96.2% for RT+HT ($p = 0.18$). Cause of death was progressive disease in 2.1% pts on RT arm *vs* 0.8%. Acute toxicities occured more frequently in RT+HT arm (89% *vs* 79%). No difference was found in grade ^{3}3 acute toxicities (1.9% *vs* 2.2%) and late toxicities (18.8% *vs* 21.9%). No toxic death was observed. **Conclusions:** GETUG-AFU 16 is the first randomized trial comparing RT *vs* RT+ short HT as salvage treatment for BR after RP with undetectable post-op PSA. RT+HT significantly improve the 5-y PFS without increasing acute or late grade 3 toxicities. A longer follow up is required to quantify the impact on OS but RT+HT could be considered as the standard in this situation. Clinical trial information: NCT00423475.

5007 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

TROG 03.06 and VCOG PR 01-03: The "timing of androgen deprivation therapy in prostate cancer patients with a rising PSA (TOAD)" collaborative randomised phase III trial. *First Author: Gillian M. Duchesne, Peter MacCallum Cancer Centre, East Melbourne, Australia*

Background: This randomized, prospective phase III trial investigated if immediate intervention with androgen deprivation therapy (ADT) (Arm B) improved overall survival compared to delayed ADT introduction (Arm A) in prostate cancer patients with PSA relapse after definitive therapy, or in asymptomatic men not suitable for curative therapy at diagnosis. **Methods:** Eligible patients were randomised 1:1, and stratified by planned intermittent or continuous (I or C) ADT; treatment centre; prior therapy (prostatectomy or radiation therapy); relapse-free interval $<$ or $\geq$ 2 years; and PSA doubling time of $<$ or $\geq$ 10 months. The primary endpoint was unadjusted overall survival by intention-to-treat. Secondary endpoints were cancer specific survival, time-to-clinical progression, time-to-castration resistance, cancer- and treatment-related complications, and quality of life. Sample size calculations for 80% power, α level of 5%, and a 2-sided statistical test required 750 patients to show a 10% improvement in survival. **Results:** From September 2004 to July 2012, 293 patients were randomised (A: 151, B:142) with a median follow-up of 5.0 years. There were 46 deaths, 30 for Arm A (delayed) and 16 for Arm B (immediate). Overall survival (OS) (log rank unadjusted) was significantly higher in Arm B than Arm A ($p = 0.047$), with 6-year survival rates of 86% and 79% respectively. The hazard ratio (HR) for death from all causes for Arm B relative to Arm A (Cox adjusted regression analysis) was 0.54, 95% confidence interval (CI) 0.27,1.06, $p = 0.07$. Death from prostate cancer was reduced in Arm B (HR 0.50 CI 0.17,1.51, $p = 0.22$), as was death from other causes (HR 0.57 CI 0.31,1.05, $p = 0.07$), both non-significantly. Overt local and distant disease progression were significantly reduced in Arm B (HR 0.51 CI 0.34,0.76, $p = 0.001$; HR 0.54 CI 0.32,0.90, $p = 0.018$). There was no difference in the time to castrate resistance. In Arm A 34% of patients started ADT within 2 years, while 49% started later than 4 years on trial or had not yet commenced therapy. **Conclusions:** Overall survival and time to clinical progression were significantly improved for immediate versus delayed ADT. Clinical trial information: 12606000301561.

5008 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Long-term consequences of intermittent and continuous androgen deprivation in older patients with metastatic prostate cancer. *First Author: Dawn L. Hershman, Columbia University Medical Center, New York, NY*

Background: Although intermittent androgen deprivation therapy (ADT) has not been associated with better overall survival in prostate cancer (PC), it has the potential for lower side effects and potential for better quality of life (QOL). The incidence of long-term side effects has not been reported. **Methods:** We analyzed a subset of patients from S9346, a randomized SWOG trial of intermittent vs. continuous ADT in patients with metastatic PC. To identify late-effects by treatment arm , we established an innovative linkage between patient trial data and corresponding Medicare claims. To incorporate time from beginning of observation through evidence of a late effect, and to account for potential competing risks of death, we analyzed claims to determine the cumulative incidence of late effects. Cox regression was used to examine time-to-late effects, adjusting for covariates. **Results:** In total, n = 1134 eligible U.S.-based patients with metastatic prostate cancer were randomized to continuous vs. intermittent ADT on S9346. A total of 636 (56%) of trial participants had ≥ 1 year of continuous Medicare parts A & B coverage and no HMO participation. The mean age was 71.5 years. The most common late effects recorded in claims in the cohort were hypercholesterolemia (31%) and osteoporosis (21%). the 10-year cumulative incidence of ischemic and thrombotic events were differed by arm; 23% for continuous therapy and 32% for intermittent therapy patients (Hazard Ratio = 0.68, p = .02). On the IAD arm, there was no difference in the mean percentage of time receiving therapy between those with and without ischemic or thrombotic events (47% vs 47%, p = 0.86). There were no statistically significant differences by arm in any other late effects. **Conclusions:** Despite beliefs that intermittent ADT could reduce long-term health-related effects compared to continuous ADT, we found that older men assigned to intermittent therapy had a slightly increased incidence of ischemic and thrombotic events and no apparent reduction in bone related, endocrine, or cognitive events

5009 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase III SYNERGY trial: Docetaxel +/- custirsen and overall survival in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and poor prognosis. *First Author: Kim N. Chi, BC Cancer Agency, Vancouver, BC, Canada*

Background: Clusterin is a chaperone protein associated with treatment resistance and upregulated by apoptotic stressors such as chemotherapy. Custirsen is a 2nd-generation antisense that inhibits clusterin production. The SYNERGY trial evaluated docetaxel +/- custirsen as 1st-line therapy in men with mCRPC (N = 1022). Following 509 deaths, median overall survival (OS) was 23.4 months (m) vs. 22.2 m for custirsen and control arms, respectively (hazard ratio [HR] 0.93; P = 0.42). To explore the hypothesis that clusterin inhibition may be more relevant in poor prognosis disease, we evaluated outcomes by prognostic sub-groups retrospectively. **Methods:** A prognostic scoring system was developed in the control arm using multiple variable modeling. The modeling included evaluation of interactions and used hierarchical step down. Results of the final model included the following main effects: liver mets, opioid use, Karnofsky < 90, PSA, LDH, alk phos, and hemoglobin. The median score dichotomized pts into good and poor prognosis. Outcomes included survival and PSA progression as defined by PCWG1 and PCWG2. **Results:** The analysis included 984 pts with complete data. Median survival for the poor and good prognosis groups in the control arm was 14.0 m and 30.4 m, respectively (HR = 3.66). The custirsen HR effect differed between poor and good prognosis groups (interaction P = 0.069). The HR estimate for custirsen survival benefit was 0.73 (95% CI: 0.0589 to 0.902) for poor prognosis and 1.02 (95% CI: 0.760 to 1.37) for good prognosis. The poor prognosis group was analyzed separately for treatment effect (n = 492). The median OS was 17.0 m in the custirsen arm vs. 14.0 m in the control arm (stratified HR = 0.72, 95%CI: 0.579 to 0.892, P = 0.0026). PSA progression in the poor prognosis group also favored custirsen with a HR of 0.73 (95% CI: 0.589 to 0.907) for PCWG1 and 0.808 (95% CI: 0.633 to 1.031) for PCWG2. **Conclusions:** CRPC pts with a poor prognosis appeared to benefit from custirsen when added to docetaxel as 1st-line therapy. This finding underscores the importance of enriching for a study population based on the mechanism of action for targeted agents. Clinical trial information: NCT01188187.

5010 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A multi-institutional randomized phase II study (NCT01505868) of cabazitaxel (CAB) plus or minus carboplatin (CARB) in men with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Paul Gettys Corn, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Standard chemotherapy for mCRPC consists of sequential taxane monotherapy. We examined the contribution of CARB to taxane therapy (Oh, Ann Oncol 2010;21) and the hypothesis that men meeting the previously defined "anaplastic" or aggressive variant prostate cancer (AVPCa) clinical criteria (Aparicio, Clin Can Res 2013;19) derive increased benefit from a platinum-taxane combination. **Methods**: Men with mCRPC were randomized 1:1 (with stratification for AVPCa criteria) to IV CAB (25 mg/m2) or CAB/CARB (25 mg/m2; AUC4) Q21 days with growth factor support until disease progression, unacceptable toxicity or for up to 10 cycles. Imaging occurred every 2 cycles. The primary endpoint was progression free survival (PFS). Secondary objectives included evaluation of safety, PSA response rates, influence of AVPCa criteria on response, and correlation of changes in bone specific alkaline phosphatase (BAP) with response. **Results:** Since March 2013 we accrued 149 of 160 men and 135 (78 with AVPCa) have received ≥ 1 cycle of therapy. Median follow up is 11.4 months (mo). Median PFS is 4.4 mo (95%CI 2.8-5.7) with CAB vs 6.7 mo (95% CI 5.2-8.2) with CAB/CARB (p = 0.01). In men meeting AVPCa criteria, mPFS is 3.8 mo (95% CI 2.8-5.9) with CAB vs 5.7 mo (95% CI 4.4 = 8.9) with CAB/CARB (p = 0.009). Reductions in PSA > 50%, PSA > 90% and BAP > 50% occurred in 44%, 20% and 25% of men with CAB vs 60%, 28% and 63% with CAB/CARB. In men with RECIST measurable disease, a partial response occurred in 14% (5/35) vs 52% (17/33) with CAB vs CAB/CARB. The most common Grade 3-4 adverse events in the CAB vs the CAB/CARB arms were fatigue (4% vs10%), anemia (2% vs 17%), neutropenia (4% vs 15 %) and thrombocytopenia (0% vs 8%). No men with CAB and 2% with CAB/CARB had febrile neutropenia. **Conclusions:** Adding CARB to CAB is safe and improves PFS and response rates in men with mCRPC. Men meeting AVPCa clinical criteria benefit most from the CAB/CARB combination. The performance of a molecular signature for the AVPCa (Abstract #150631) will be tested in assembled tissue samples. A confirmatory phase 3 study is warranted to establish combination chemotherapy in advanced prostate cancer. Clinical trial information: NCT01505868.

5011 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Efficacy analysis of a phase III study of androgen deprivation therapy (ADT) +/- docetaxel (D) for men with biochemical relapse (BCR) after prostatectomy. *First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The optimal treatment (tx) of men with castration sensitive prostate cancer (CSPC) who biochemically recur following a radical prostatectomy (RRP) is not known. Data from E3805 suggest that men with metastatic CSPC live longer if they receive D in addition to ADT relative to ADT alone. We tested this hypothesis in non-metastatic CSPC, via a phase III study (TAX3503). **Methods:** PC pts who underwent an RRP with BCR and a doubling time ≤ 9 months (mo) were eligible. PSA ≥ 1 ng/mL and testosterone ≥100 ng/dl were required. Randomization was 1:1 to receive leuprolide 22.5 mg q3 mo x 18 mo, bicalutamide 50 mg x 30 days, with D at 75 mg/m2 q3 weeks x 10 cycles (Arm A) or without D (Arm B). The primary endpoint was PFS defined as a detectable PSA or death. Pts with T recovery >50 ng/dl were evaluable. The intent to treat population (ITT) was also examined. A sample size of 412, to yield 370 evaluable pts, was calculated to detect a HR of 1.6 with 90% power. The trial was closed by the sponsor after the pts completed treatment; remaining pts were then followed to PFS via a registry for 18 mo's. A test to detect a difference in the hazard rates between arms was generated by the log rank statistic. **Results:** 413 pts were randomized. Median f/u time in the ITT population was 31.5 mo's (0.0-60.2). Data are summarized below in the Table. **Conclusions:** The clinical benefit of ADT + D relative to ADT alone in men with high-risk BCR after RRP appears to be marginal, although there is a statistical trend towards improved PFS. Data are limited by the biases intrinsic to post-protocol registries and by short duration of follow up, although tracking of pts continues. Clinical trial information: NCT01813370.

Population	Arm	N	Events	Median PFS (95% CI)	1yr PFS prob	2yr PFS prob	3yr PFS prob	HR (A vs. B)
All randomized	A	207	138	25.6 (25.0,27.8)	0.952 (0.910,0.975)	0.593 (0.514,0.663)	0.189 (0.130,0.257)	1.270 (1.006,1.603) P=0.044
	B	206	148	23.1 (22.6,25.0)	0.960 (0.921,0.980)	0.472 (0.396,0.544)	0.104 (0.059,0.165)	
T-recovered	A	129	106	26.5 (25.3,28.1)	0.961 (0.909,0.984)	0.641 (0.552,0.718)	0.202 (0.133,0.280)	1.285 (0.980,1.683) P=0.070
	B	130	107	24.8 (22.9,25.3)	0.992 (0.947,0.999)	0.527 (0.437,0.609)	0.115 (0.060,0.188)	

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5012 Poster Discussion Session; Displayed in Poster Session (Board #4), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Effects of radium-223 dichloride (Ra-223) with docetaxel (D) vs D on prostate-specific antigen (PSA) and bone alkaline phosphatase (bALP) in patients (pts) with castration-resistant prostate cancer (CRPC) and bone metastases (mets): A phase 1/2a clinical trial. *First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Ra-223 is an approved α-emitter that prolongs survival in CRPC with symptomatic bone mets. We presented data from a phase 1/2a study of safety and antitumor effects of Ra-223 + D vs D alone showing that Ra-223 + D is safe and well tolerated (ESMO 2014). Here we report the effect of Ra-223 + D vs D on bALP and PSA dynamics. **Methods:** D-eligible pts with progressing CRPC and $\geq$ 2 bone mets received (2:1) Ra-223 (50 kBq/kg q 6 wk $\times$ 5) + D (60 mg/m^2 q 3 wk $\times$ 10) or D (75 mg/m^2 q 3 wk with a step-down option to 60 mg/m^2). bALP and PSA were recorded q 3 wk during the first 6-wk cycle, then q 6 wk and q 3 wk, respectively, and analyzed at a central laboratory. Changes in both markers are described by the % of pts whose best responses were $\geq$ 30%, $>$ 50%, and $>$ 80% declines from baseline (3 wk post last D injection); pts with elevated baseline bALP ($\geq$ 21 μg/L) were included for bALP analysis. bALP to below upper limit of normal (ULN) was also recorded, regardless of % decline. **Results:** 46 pts (33 Ra-223 + D vs 13 D alone) were enrolled. As of January 2015, 24 (Ra-223 + D) vs 5 (D) pts had all planned injections. Median (range) baseline PSA was 99 μg/L (3-1000) for Ra-223 + D pts and 43 μg/L (4-1042) for D pts. The table shows maximal changes in PSA and bALP levels from baseline. No pt had a bALP increase. Pts continue in follow-up (to 12 mo after first injection) for safety and progression. **Conclusions:** Ra-223 + D appears to favorably impact post-treatment declines in PSA and bALP and to be particularly effective at normalizing bALP levels vs D alone. Clinical benefits of such changes in serum markers require validation in larger prospective studies. Clinical trial information: NCT01106352.

	Change from baseline, n (%)			
	PSA		bALP*	
	Ra-223 + D N = 33	D N = 13	Ra-223 + D N = 23	D N = 11
Any increase	3 (9)	4 (31)	0 (0)	0 (0)
Best responses, decreases				
< 30%	4 (12)	1 (8)	0 (0)	0 (0)
≥ 30%	26 (79)	8 (62)	23 (100)	11 (100)
> 50%	21 (64)	7 (54)	22 (96)	9 (82)
> 80%	10 (30)	4 (31)	9 (39)	2 (18)

*Pts with baseline bALP > ULN (> 21 μg/L). N/A = not applicable.

5013 Poster Discussion Session; Displayed in Poster Session (Board #5), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Association of SLCO transport genes with intraprostatic abiraterone (ABI) levels and pathologic outcomes in men with high-risk localized prostate cancer (PCa). *First Author: Elahe A. Mostaghel, Fred Hutchinson Cancer Rsrch Ctr, Seattle, WA*

Background: Germline variation in solute carrier organic anion (SLCO) transport genes influences cellular uptake of steroids and has been associated with PCa outcomes. We hypothesized that due to its steroidal structure, ABI may undergo SLCO-mediated transport, and that germline variation in SLCO genes may influence intracellular ABI levels and pathologic outcomes in men with PCa. **Methods:** We measured ABI levels in prostatectomy tissue from 58 men with localized PCa treated with 6 months of castration plus ABI prior to radical prostatectomy (RP). Buffy coat DNA was genotyped for13 SNPs (minimum allele frequency $>$ 0.07) in 6 SLCO genes using TaqMan SNP assays. Transcript expression of SLCO genes was evaluated by qRT-PCR in microdissected tumor samples from a subset of patients. **Results:** SNPs in SLCO1B3 (rs4149177, p = 0.07) and SLCO2B1 (rs12422149, p = 0.0004; rs949069, p = 0.008; rs1789693, p = 0.01) were associated with significant differences in mean tissue ABI levels at RP. Contingency analysis showed higher rates of minimal residual disease (MRD, defined as tumor volume $<$ 0.5cm3) in those with good risk (higher tissue ABI) alleles of SLCO1B3 (rs4149177: 50% (14/28) vs 24% (4/17); Fisher exact p = 0.11) and in those with good risk alleles of SLCO2B1 (rs1789693: 67% (10/15) vs 27% (8/30); p = 0.02). Although not associated with tissue ABI levels, SLCO2B1 (rs1077858) and SLCO2A1 (rs34550074) were also associated with differences in MRD (p = 0.06 and p = 0.05, respectively).Transcript expression of SLCO2B1 increased 16 fold from a mean of -19 dCT (vs RPL13A) in untreated PCa to -15 dCT in ABI treated tumor samples (p = 0.01). **Conclusions:** SLCO transport genes may be pharmacogenetic determinants of intracellular ABI levels and may serve as novel predictors of response to ABI treatment. Clinical trial information: NCT00924469.

5014 Poster Discussion Session; Displayed in Poster Session (Board #6), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

EARLY CTC decline as a biomarker of response to treatment in castration-resistant prostate cancer (CRPC): Analysis of the COU-AA-301 and IMMC38 trials. *First Author: David Lorente, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Circulating tumor cell counts (CTC) are prognostic in CRPC. Baseline (BL) CTC $\geq$ 5 CTCs/7.5mL are associated with worse prognosis. A post-treatment 30% decline in CTC has been associated with improved survival (OS) (Olmos et al, 2009). We investigated the value of 30% declines in CTC after 4 and 12 weeks (wks) of treatment in the COU-AA-301 (abiraterone) and IMMC-38 (chemotherapy) trial datasets. This is the first time %CTC decline has been evaluated in phase III CRPC clinical trials. **Methods:** CTC of patients (pts) were determined (CellSearch). Pts with BL CTCs $\geq$5 and valid counts at Wk 4/Wk 12 (IMMC38) or Cycle 2/Cycle 4 Day 1 (COU-AA-301) were evaluated. CTC response was defined as a $\geq$30% decline in CTC relative to BL (30%CTCresp). Association of 30%CTCresp with OS was evaluated with Cox regression in uni- and multivariable (MV) analysis with ECOG, LDH, ALP, Alb, Hb, BL CTC and PSA as covariates (continuous). C-index was calculated to determine the performance of the MV model with and without 30%CTCresp as a covariate. **Results:** 439 pts (326 in COU-301 and 113 in IMMC38) were analyzed. Median BL CTC was 18.5 in COU-301 and 23 in IMMC38. OS in pts with 30%CTCresp at Wk 4 was significantly better in COU-AA-301 and IMMC-38 datasets (Table). BL CTC (continuous) and 30%CTCresp at Wk4 were independently associated with OS in MVA in both datasets. C-index of the MV model improved from 0.677 to 0.712 (COU-AA-301) and from 0.747 to 0.800 (IMMC-38) after including 30%CTCresp. Equivalent results were acquired when evaluating 30%CTCresp at Wk 12. **Conclusions:** BL CTC and 30% CTC falls are independently associated with OS in in CRPC pts treated with abiraterone and chemotherapy. Adding CTC response improved the performance of the MV model. A 30% decline in CTCs from BL as early as 4 wks post-treatment may be a valid biomarker of response to treatment in CRPC.

30% CTC decline at 4 weeks and survival.

	N(%)	OS (m)	HR (95%CI)	p-value
COU-AA-301	326	11.6 (10.3-13)		
30% CTC Decline	208 (64%)	14.4 (13.2-15.5)	-	
No 30% CTC Decline	118 (36%)	7.9 (6.8-9)	0.4 (0.3-0.6)	<0.001
IMMC-38	113	11.2 (9.7-12.6)		
30% CTC Decline	75 (66%)	12.3 (8.2-16.3)	-	
No 30% CTC Decline	38 (34%)	6.8 (4.4-9.2)	0.5 (0.3-0.8)	0.001

5015 Poster Discussion Session; Displayed in Poster Session (Board #7), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Genomic analysis of circulating cell-free DNA (cfDNA) to investigate mechanisms of primary and acquired resistance to enzalutamide (ENZ) in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Arun Azad, BC Cancer Agency, Vancouver, BC, Canada*

Background: ENZ is a potent androgen receptor (AR) antagonist that prolongs survival in mCRPC patients (pts). However, factors driving resistance to ENZ are incompletely understood. Genomic analysis of cfDNA is a promising, minimally invasive approach for interrogating mechanisms of therapeutic resistance in mCRPC. **Methods:** Baseline plasma samples were collected from 57 mCRPC pts commencing ENZ. In 37 pts, additional samples at 12-weeks +/- end-of-treatment were obtained. DNA was extracted and subjected to array Comparative Genomic Hybridization (aCGH) for chromosome copy number (CN) analysis and AR gene (exon 2-8) sequencing (MiSeq) for mutation analysis. Endpoints were i) PSA50 or PSA30 response rates (RR) (PSA decline $\geq$ 50% or 30% for $\geq$ 3 weeks); and ii) radiographic/clinical progression-free survival (PFS). **Results:** On aCGH, the most frequent CN changes in baseline samples (n = 57) were 8p loss (25%), 8q gain (35%), MYC gain (26%) and AR gain/amp (33%). Compared to pts with no AR gain/amp, pts with pre-treatment AR gain/amp had lower PSA50 (39% vs. 21%, P= 0.16; X^2) and PSA30 RR (44% vs. 25%, P= 0.059; X^2) and shorter median PFS (4.5 vs. 2.2 months, P= 0.002; log-rank). On multivariate analysis, pre-treatment AR gain/amp (HR 2.56 P= 0.01) was confirmed as an independent prognostic factor for PFS. In pts with 12-week +/- end-of-treatment samples, 14% (5/37) had a change in AR CN status from baseline with 3 pts converting from no AR gain to AR gain and 2 pts from AR gain to AR amp. Median PFS in these 5 pts was 2.8 months. AR gene sequencing was performed on a subset of 4 pts with 4 high-frequency mutations detected in 3 pts including H874Y (n = 2) and L702H (n = 2), the latter of which converts glucocorticoids to AR agonists. Notably, both L702H mutations were found in end-of-treatment samples from pts who progressed rapidly on ENZ (2.9 months PFS each). Neither of these pts was on glucocorticoids at progression, potentially implicating L702H in ENZ resistance. **Conclusions:** Our data indicate that AR gene aberrations may be key biomarkers of primary and acquired resistance to ENZ in mCRPC. Complete AR gene sequencing data will be presented.

5016 Poster Discussion Session; Displayed in Poster Session (Board #8), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Validation of a genomic classifier for prediction of metastasis following postoperative salvage radiation therapy. *First Author: Robert Den, The Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA*

Background: Management of patients with a postoperative rising prostate-specific antigen (PSA) level is complex. Additional local treatment such as salvage radiation therapy (SRT) may be sufficient for many patients but some may require concurrent systemic therapy in order to delay or prevent metastatic disease. As PSA recurrence on its own is a poor surrogate for metastatic disease we hypothesized that the Decipher genomic classifier (GC), a validated predictor of metastasis may be able to better distinguish those patients where additional local therapy is beneficial from those where SRT on its own is likely insufficient. **Methods:** Genomic classifier (GC) scores were calculated from 166 prostate cancer patients, who received SRT at the Veteran Affairs Medical Center Durham, Thomas Jefferson University and Mayo Clinic, between 1990 and 2010. SRT was defined as administration of RT with Pre-RT PSA levels > 0.2 ng/ml. GC and CAPRA-S scores were compared using survival c-index, competing-risks and Cox regression analysis for the prediction of metastasis. **Results:** Survival c-index for predicting metastasis 5 years post SRT was 0.87 (95% CI: 0.73-0.90) for GC and 0.62 (95% CI: 0.48-0.77) for CAPRA-S. The cumulative incidence of metastasis at 5 years post-SRT was 2.8%, 5.8%, and 33.5% for low, average, and high GC scores ($p < 0.0001$) and 17%, 2.3% and 15% for low, average and high CAPRA-S scores ($p = 0.19$). In univariable analysis only GC, extraprostatic extension and Pre-RT PSA were significant predictors of metastasis. In multivariable analyses with clinical risk factors or the CAPRA-S nomogram, GC was the only independent predictor of metastasis with a HR of 1.59 (1.17-2.16, $p = 0.0017$) for a 10% unit increase in risk score. **Conclusions:** In patients treated with postoperative SRT for PSA recurrence, GC is a powerful predictor of metastasis. Patients with low Decipher have excellent prognosis with SRT and may avoid concurrent hormone therapy. Patients with high Decipher risk are at highest risk for metastatic disease and SRT failure and may benefit from concurrent systemic therapy.

5017 Poster Discussion Session; Displayed in Poster Session (Board #9), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Progression of low- to high-grade prostate cancer: Molecular profiling of tissue obtained by serial targeted biopsy. *First Author: Ganesh S. Palapattu, The Univ of Michigan Hosp, Ann Arbor, MI*

Background: Progression of prostate cancer (PCa) from low- to high-grade is believed to be uncommon. Here, we combined serial targeted biopsy to resample specific PCa sites over time with molecular profiling to determine clonality of high grade cancer. **Methods:** Nine men in active surveillance for low-risk PCa (Gleason Score = 6; GS6) were subjects of this IRB-approved pilot employing the Artemis MR-US fusion biopsy system. Each PCa site was electronically tracked and 1 year later additional tissue obtained from the same intra-prostatic site. Five of 9 men were re-classified on follow-up biopsy to GS $\geq$ 7. ERG immunohistochemistry (IHC) and targeted multiplexed PCR based next generation sequencing (NGS) was performed at each time point. DNA was co-isolated from 6-7 x 4μm formalin fixed paraffin embedded (FFPE) sections/sample. NGS was performed using a custom Ion Torrent Ampliseq panel (containing 3,434 amplicons interrogating oncogenes and tumor suppressors) and the Ion Torrent Proton sequencer. Data was analyzed using validated in-house methods. **Results:** Across the 18 paired samples from 9 patients, 7 pairs (early/late) were evaluable for ERG IHC. In all 7 evaluable cases, PCa in paired specimens was uniformly ERG+ (4 pairs) or ERG- (3 pairs). NGS generated an average of 847x coverage/sample. Copy number analysis identified no high level gains or losses. 3 prioritized driving somatic mutations were identified across the cohort (SPOP F133L in Pt#4, BRCA2 K2524fs in Pt#7 and KMT2B Q2076X in Pt#1), each of which occurred only in the later sample in the pair. Of these 3 men on repeat biopsy, Pt#1 and #4 had GS7 and Pt#7 had GS6 disease. **Conclusions:** In this first of its kind study, our data suggest that i) GS $\geq$ 7 cancers may arise clonally from GS6 cancers through acquired genetic alterations, ii) targeted prostate biopsy allows repeat sampling of a clonal focus, and iii) comprehensive molecular profiling of minute FFPE samples is possible. Our work also supports prior observations that some GS6 cancers possess oncogenic mutations. These findings could have important implications for the management of low risk PCa.

5018 Poster Discussion Session; Displayed in Poster Session (Board #10), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Combination statin/metformin and prostate cancer specific mortality: A population-based study. *First Author: Grace L. Lu-Yao, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Obesity and metabolic syndromes (MetS) are associated with an increased risk of prostate cancer mortality. A recent pre-clinical study showed that combination statin /metformin (CSM) was more effective in inhibiting metastasis than standard chemotherapy (docetaxel) with less toxicity in an *in vivo* model. As clinical data on this topic are limited, this population-based study is to examine the association between treatment with CSM and prostate cancer specific mortality (PCSM) by obesity/MetS status. **Methods:** SEER-Medicare linked data were used to identify patients with high-risk prostate cancer (stage T3/T4 or PSA>20 or Gleason 8-10) in 2007 – 2009. Prescription drug use was identified from Medicare Part D Event files. Obesity/MetS conditions were identified by the presence of ICD-9 diagnosis codes 278.00, 278.01, or 277.7. Cox proportional hazards models were used to compare PCSM with covariates including demographic characteristics, prognostic factors, and cancer treatment(s) received. **Results:** This study cohort consisted of 22,110 high-risk prostate cancer patients, of which 1,365 died of prostate cancer by 12/31/2009. Use of CSM was associated with a 43% reduction in PCSM, more pronounced in men with obesity/MetS conditions (Table). The results were similar when we limited the analysis to patients with minimal comorbidity. **Conclusions:** To our knowledge, this is the largest clinical study to assess the potential effect of CSM on PCSM. CSM or statin use was associated with a large reduction in PCSM, particularly in patients with obesity/MetS conditions. The potential benefits of metformin use may be secondary to concomitant statin use in this population. Further studies are needed to confirm these results.

Statin/metformin rreatment and PCSM among high-risk prostate cancer patients.

Medication used	Obese or MetS HR (95% CI) +	Non-Obese & non-MetS HR (95% CI) +	Overall HR (95% CI) +
Statin + Metformin (N=1,356)	0.30 (0.07 – 1.27)	0.60 (0.39 – 0.93)	0.57 (0.38 – 0.88)
Statin alone (N=4,481)	0.09 (0.01 – 0.64)	0.64 (0.50 – 0.82)	0.60 (0.47 – 0.76)
Metformin alone (M=471)	---	0.98 (0.57 – 1.68)	0.92 (0.54 – 1.57)

+HR=Hazard Ratios compared to non-users (N= 15,802) and 95% confidence intervals (CI).

5019 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase III trial of short-term androgen deprivation therapy in intermediate-risk prostate cancer treated with radiotherapy. *First Author: Abdenour Nabid, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada*

Background: The place of short term androgen deprivation therapy (STADT) in combination with radiotherapy (RT) for patients with intermediate risk prostate cancer (IRPC) remains controversial. The purpose of this prospective, randomized trial was to compare outcomes between patients with IRPC treated with different doses of RT with or without STADT, (PCS III trial, Clinical Trials.gov, #NCT00223145). **Methods:** From December 2000 to September 2010, 600 patients with IRPC were randomized to 6 months of STADT and two levels of prostate RT doses of 70 (arm 1) or 76 Gy (arm 2) versus prostate dose-escalated RT alone at 76 Gy (arm 3). STADT consisted of bicalutamide and gosereline for six months. RT (2 Gy per fraction) started four months after the beginning of STADT. Biochemical failure and disease-free survival (DFS) were primary end-points, with overall survival (OS) as secondary endpoint. DFS and OS rates were estimated with Kaplan-Meier and compared with log rank test and Cox regression. **Results:** Patient's characteristics were well balanced among the 3 arms (median age 71 years, median PSA 10 ng/ml, median Gleason score 7 and clinical stage). At a median follow-up of 6.5 years, biochemical failure occurred in 96 (16%) patients (arms 1 to 3: 13.5%, 11%, 23.5%) with statistical difference between arm 1 and 3 ($p = 0.01$) and arm 2 and 3 ($p < 0.001$) but not between arm 1 and 2. A total of 130 (21.7%) patients died with only 7 deaths (1.2%) attributed to prostate cancer. The 5-/10-year DFS rates were 92.8%, 97.1% and 85.5%, and 78.4%, 78.3% and 65.9%, respectively. Significant differences in DFS between the treatment arms were observed at 5 and 10 years between arm 1 and 3 ($p = 0.015$, $p = 0.012$) and arm 2 and 3 ($p < 0.001$ at 5-/10-year) but not between arm 1 and 2 ($p = 0.052$, $p = 0.385$). The 5-/10-year OS rates were 90.9%, 93.6% and 90.8%, and 63.8%, 70.8% and 75%, respectively. There was no statistical difference in OS between arms at 5 and 10 years. **Conclusions:** In patients with IRPC, the use of STADT in association with RT, even at lower doses, leads to a superior biochemical control and DFS as compared to dose-escalated RT alone. These outcomes did not translate into an improved OS. Source of Funding: AstraZeneca Pharmaceuticals Grant. Clinical trial information: #NCT00223145.

5020 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

***HSD3B1* and resistance to androgen deprivation therapy in prostate cancer.** *First Author: Jason W.D. Hearn, Cleveland Clinic, Cleveland, OH*

Background: The somatic mutation *HSD3B1*(1245A > C) has been mechanistically linked to castration-resistant prostate cancer by encoding a mutant enzyme that augments intratumoral dihydrotestosterone (DHT) synthesis. Given the *HSD3B1*(1245C) allele is also frequently found in the germline, we hypothesized men inheriting this variant allele would exhibit resistance to androgen deprivation therapy (ADT), as manifested by worse clinical outcomes. **Methods:** We used a large, prospectively maintained prostate cancer registry to identify men treated with ADT for biochemical failure in the post-prostatectomy setting who were without evidence of metastatic disease. We analyzed progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) according to *HSD3B1* genotype using Kaplan-Meier methods. Cox proportional hazards regression was performed to evaluate potential gene-dosage effects, with homozygous wild-type men serving as the reference group. Demographic and treatment characteristics were compared to assess for possible confounders using Fisher's exact test and Kruskal-Wallis analysis of variance. Multivariable analysis (MVA) was performed to assess whether *HSD3B1* genotype independently predicted clinical outcomes. **Results:** Of 118 men genotyped, 37% were homozygous wild-type, 53% were heterozygous, and 10% were homozygous variant. Demographic and treatment characteristics did not differ across groups. Median PFS diminished as a function of the number of variant alleles inherited (6.6 years in homozygous wild-type men, 4.1 years in heterozygotes, and 2.5 years in homozygous variant men; P = 0.01). Median DMFS likewise decreased according to the number of variant alleles inherited (9.1 years vs. 6.8 years vs. 3.6 years, respectively; P = 0.01). Finally, OS similarly diminished (5-year and 10-year OS: 82% and 55% vs. 74% and 35% vs. 58% and 0%, respectively; P = 0.006). On MVA, the associations between *HSD3B1* genotype and metastasis (hazard ratio (HR) 2.76; P = 0.023) and death (HR 3.33; P = 0.016) were maintained. **Conclusions:** Inheritance of the variant *HSD3B1*(1245C) allele that enhances DHT synthesis may be a powerful predictor of resistance to ADT for prostate cancer.

5021 Poster Session (Board #13), Sat, 1:15 PM-4:45 PM

Association of the prostate cancer risk mutation G84E in HOXB13 with the subtype of ETS fusion negative adenocarcinoma with early age of diagnosis. *First Author: Thomas J. Schnoeller, University of Ulm, Medical School, Department of Urology, Ulm, Germany*

Background: *HOXB13* was discovered as the first prostate cancer (PrCa) specific high-risk susceptibility gene. The most prevalent *HOXB13* germline mutation in PrCa patients of European descent is *HOXB13*G84E, which likely originated in Northern Europe. Previous molecular examination of a set of G84E driven tumors suggested a distinct somatic phenotype, where oncogenic ETS gene fusions appear at unusually low frequencies as compared to the general prevalence of ETS fusions in PrCa (22 % vs approx. 50 %). **Methods:** We have analyzed 942 cases from three European ancestry populations for the coincidence of *HOXB13* G84E and the most common ETS fusion, *TMPRSS2-ERG*(T2E), in corresponding tumor samples. **Results:** While the prevalence of T2E fusions was similar among study sites (range: 56.5% - 60.7%), the frequency of G84E genotypes differed markedly between US (1.5%), German (3.6%) and Finnish samples (8.3%). Despite the expected frequency gradient among study populations, all subsamples showed a strong enrichment of G84E mutation carriers among T2E fusion negative cases as compared to fusion positive cases (center adjusted OR = 4.90; 95%CI = 2.19 - 11.0; p = 0.0001). Consistent with the previous study, the crude frequency of the T2E fusion in *HOXB13*G84E carriers was 23.5 % (range 16.7 % - 28.5 %). Examination of disease characteristics highlighted age at diagnosis, with fusion positive cases being diagnosed 1.75 (0.87 - 2.63) years earlier than negative cases (p < 0.0001). Age at diagnosis in G84E carriers did not differ significantly from non-carriers (p = 0.26). However, within the subtype of fusion negative carcinoma, which is usually associated with later ages at diagnosis, carriers of G84E were diagnosed on average 2.93 (0.49 - 5.37) years earlier (p = 0.02). No associations were seen for tumor stage, tumor grade or diagnostic PSA levels. **Conclusions:** This study demonstrated a tumor type specific association for *HOXB13* G84E mutation carriers having a higher frequency of T2E fusion negative PrCa. Although the T2E fusion negative subtype is known to be associated with later ages of diagnosis, *HOXB13* driven tumors within this subtype may represent an early onset subgroup.

5022 Poster Session (Board #14), Sat, 1:15 PM-4:45 PM

Project Data Sphere: A first look at prostate cancer including concomitant medication use, prognosis, and toxicity. *First Author: Anthony M. Joshua, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: PDS (www.projectdatasphere.org) enables patient-level analyses of control arms of cancer trials. We aimed to include the use of concomitant medications (CM) to (i) validate and improve established prognostic metastatic prostate cancer (mCRPC) models (ii) establish novel predictive factors of toxicity. **Methods:** Data was obtained for 2,747 control subjects with mCRPC from 7 Phase III clinical trials (1962 subjects were available for OS analyses from 5 studies). OS was estimated using the Kaplan-Meier method. Cox-proportional hazards models, stratified by trial, were used to estimate hazard ratios. **Results:** Of 23 medication classes examined patients taking proton pump inhibitors (HR: 1.17, p = 0.017) and Erythropoietin (HR: 1.45, p < .001) had worse OS. Patients taking fish oil (HR: 0.67, p = 0.025) and non-lipophilic statins (HR: 0.67, p = .0.017) had improved OS. Initially, metastatic site was significant for OS (predicted median: Node 24.61m, Bone 22.77 m, Lung 21.39 m, Liver 15.18 m; p < 0.001). After adjusting for metastatic site, these medication classes remained significant (HR 1.15, p = 0.017; HR 1.493, p < 0.01; HR 0.68, p = 0.03; HR 0.68, p = 0.0278 respectively). We then validated and combined 2 multi-variate prognostic models for OS (Templeton et al, Sonpavde et al) after inclusion of CM. Patients taking metformin (HR = 0.729, p = .008) and Cox2 inhibitors (HR = 0.708, p = .015) had improved OS whilst those taking low molecular weight heparin (HR = 1.352, p = .004) had worse OS. Thereafter, a simplified prognostic model based on albumin and LDH alone, equivalent in prognostication was established. For docetaxel trials from baseline, baseline neutrophil to lymphocyte ratio was the best predictor of any toxicity (OR 4.23, p = .004) after accounting for number of cycles, whilst the lymphocyte count had an inverse relationship with the occurence of any severe AE (OR 0.31, p = 0.03). The incidence of toxicity after cycle 1 was the best predictor of subsequent adverse events (OR 5.82, p < 0.01) **Conclusions**: Initial analyses of PDS data in mCRPC allowed for insights into prognostic models and predictors of docetaxel toxicity. Expansion of trials and quality of data will facilitate future analyses.

5023 Poster Session (Board #15), Sat, 1:15 PM-4:45 PM

PET imaging with ^{68}Gallium-labelled ligand of prostate-specific membrane antigen (^{68}Ga-HBED-PSMA) for staging of biochemical recurrent prostate cancer after radical prostatectomy. *First Author: Tobias Maurer, Department of Urology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany*

Background: Staging of recurrent prostate cancer (PCa) after radical prostatectomy (RP) remains challenging especially at low PSA values. Prostate-specific membrane antigen (PSMA) shows increased expression on most PCa and might therefore be useful for detection of PCa lesions. Aim of this retrospective analysis of consecutive pts was to evaluate the detection rate of PET hybrid imaging using the PSMA inhibitor Glu-NH-CO-NH-Lys-(Ahx)-[(68)Ga(HBED-CC)] (^{68}Ga-HBED-PSMA) in pts with biochemical recurrence (BCR) of PCa after RP. **Methods:** 332 consecutive pts with BCR of PCa after RP and a median PSA value of 1.7 ng/ml (range 0.2-63 ng/ml) were included in this analysis. After injection of 122±17 MBq ^{68}Ga-HBED-PSMA-PET/CT or PET/MR was performed in 256 pts and 76 pts, respectively. One nuclear medicine physician and one radiologist reviewed imaging in consensus. Detection rates according to PSA value were determined. **Results:** In total, detection rates for ^{68}Ga-HBED-PSMA-PET hybrid imaging were 96.0% (143/149) for PSA values ≥ 2ng/ml, 92.0% (80/87) for PSA values 1-2ng/ml, 72.3% (34/47) for PSA values 0.5-1ng/ml and 53.0% (26/49) for PSA values 0.2–0.5ng/ml, respectively. In 28.9% (96/332) of pts solely PSMA-PET detected suspicious lesions whereas 2.7% (9/332) of pts only showed positive findings in morphological imaging. Additional lesions were seen in 21.4% (71/332) of pts in PSMA-PET and in 6.3% (21/332) in CT or MRI. **Conclusions:** ^{68}Ga-HBED-PSMA-PET hybrid imaging shows higher detection rates in pts with recurrent PCa at low PSA values than reported for other PET-tracers like ^{18}F-FDG or choline derivatives. Thus, ^{68}Ga-HBED-PSMA-PET hybrid imaging has the potential to replace PET imaging with these tracers for staging of BCR of PCa after RP in the future.

5024 Poster Session (Board #16), Sat, 1:15 PM-4:45 PM

Statin use at the time of initiation of androgen deprivation therapy and time to progression in patients with hormone-sensitive prostate cancer. *First Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA*

Background: Statin use has been associated with improved prostate cancer outcomes such as decreased risk of recurrence after local therapy and a lower risk of prostate cancer mortality. DHEAS is a precursor of testosterone and a substrate for SLCO2B1, an organic anionic transporter. We previously demonstrated that genetic variants of *SLCO2B1* correlated with time to progression (TTP) on androgen deprivation therapy (ADT). Statins utilize SLCO2B1 to enter cells, thus, we hypothesized that statin use at ADT initiation might prolong TTP by competing with DHEAS uptake. **Methods:** To determine if statins interfere with DHEAS uptake, we performed in vitro studies using prostate cancer cell lines. Next, we queried our institutional clinical database for patients treated with ADT for biochemical or metastatic recurrence or *de novo* metastatic prostate cancer (ADT cohort). The association between statin use and TTP on ADT was estimated using multivariable Cox regression and adjusted for known prognostic factors. **Results:** In vitro, we demonstrated that statins block DHEAS uptake by competitively binding to SLCO2B1. In our ADT cohort of 926 patients treated between January 1996 and November 2013, 283 (31%) were taking a statin at ADT initiation. After a median follow-up of 5.8 years, 644 patients (70%) had progressed on ADT. Median TTP on ADT was 20.3 months (95% CI: 18,24). Men on statins had a longer median TTP on ADT compared to non-users (27.5 vs. 17.4 months, p = 0.0005). The association remained statistically significant after adjusting for pre-defined prognostic factors [adjusted HR = 0.83 (p = 0.039)]. The positive statin effect was observed for both patients with and without metastases. **Conclusions:** Statin use at ADT initiation was associated with a significantly longer TTP on ADT even after adjusting for known prognostic factors. Our in vitro findings that statins competitively reduce DHEAS uptake and thus, effectively decrease the available intratumoral androgen pool, afford a plausible mechanism to support the clinical observation of prolonged TTP in statin users.

5025 Poster Session (Board #17), Sat, 1:15 PM-4:45 PM

Phase II trial of the PI3 kinase inhibitor BKM120 with or without enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC). *First Author: Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC*

Background: PI3K pathway activation is common in mCRPC. BKM120 (buparlisib) is an oral, pan-class I PI3 kinase inhibitor. Preclinical data demonstrated a reciprocal feedback loop between PI3K and androgen receptor (AR) signaling; thus, we evaluated the efficacy of BKM120 in men with heavily pre-treated mCRPC including those progressing on enzalutamide (E). **Methods:** This was a 3 site phase 2 Dept of Defense Prostate Cancer Clinical Trials Consortium open-label trial of BKM120 100 mg once daily with ongoing ADT in men with mCRPC who had failed or were not candidates for docetaxel. Continuation of E was permitted in men progressing on E with subsequent addition of BKM120. The primary endpoint was the rate of composite of radiographic and clinical PFS at 6 months with a goal of 40% vs. a historic rate 25% using a two-stage design with interim futility analysis. **Results:** Thirty men were accrued: 63% post-docetaxel; median PSA was 70 ng/dl, 83% had > 4 prior therapies for CRPC; 43% men received concurrent E. The trial met criteria for futility, with a 6 month PFS rate of 10% (95% CI 2.5-23.6%). Median composite PFS was 1.9 months (95% CI: 1.8, 3.4) and 3.5 months (95% CI 1.2, 5.5) with concurrent E. Median OS was 11 months (95% CI 4.8, 14.4). E did not appear to increase the BKM120 side effect profile. The PSA decline proportion was 23%, but no patients achieved a > 50% decline, with median PSA change of +39%. No objective responses were observed. Related SAEs occurred in 3 men including respiratory infection and organ failure (1), urinary tract obstruction due to local progression (1), and severe confusion (1). One seizure was observed in a man who was found to have a new CNS metastasis during concurrent BKM120/E therapy. Grade 3 related AEs were seen in 47% of patients, with 10% stopping BKM120 due to toxicity. The most common related AEs included grade 1-2 weight loss, diarrhea, nausea, fatigue, anorexia, rash, hyperglycemia, and anxiety and mood disorders. **Conclusions:** BKM120 did not improve PFS over historic control data in men with mCRPC, either alone or when added to AR inhibition in men progressing on enzalutamide. These data suggest that PI3K inhibition is not sufficient to block mCRPC progression. Clinical trial information: NCT01385293.

5026 Poster Session (Board #18), Sat, 1:15 PM-4:45 PM

National prostate cancer screening rates following the 2012 United States Preventive Services Task Force recommendation discouraging prostate-specific antigen (PSA)-based screening. *First Author: Michael William Drazer, University of Chicago, Chicago, IL*

Background: The prostate cancer screening debate intensified following the 2012 United States Preventive Task Force (USPSTF) recommendation discouraging prostate specific antigen (PSA) testing-based screening. Previously published USPSTF recommendations did not appreciably reduce screening among groups at high risk for over-diagnosis and over-treatment. The effects of the 2012 guidelines on screening are unknown. **Methods:** We used the National Health Interview Survey (NHIS), a nationally representative survey, to estimate the proportion of men age 40 and older screened for prostate cancer in 2010 and 2013. We utilized an externally validated nine-year mortality index to analyze screening rates based on remaining life expectancy. We used logistic regression to compare screening rates from 2010 to 2013 and explored which subgroups had significant changes in PSA screening. **Results:** Screening significantly declined from 2010 to 2013 among all men over 50. Men ages 60-74 were most heavily tested, with 51.2% screened in 2010 and 43.6% in 2013 ($P < 0.01$). Screening significantly declined for men ages 50-59 ($P < 0.01$) and over 75 ($P = 0.03$) but not among 40-49 year olds ($P = 0.4$). A large percentage of men with a high predicted likelihood (> 52%) of 9 year mortality were screened for prostate cancer, including approximately 32.2% of men over 75. Interestingly, college-educated men had higher screening rates than less college educated men but also had a larger screening decline from 2010 (62.7%) to 2013 (50.2%). **Conclusions:** Prostate cancer screening significantly declined among men over 50 following the 2012 USPSTF guideline discouraging PSA-based screening. A large proportion of men continue to be screened despite a high risk (> 52%) of nine-year mortality, including 32.2% of men age 75 and older.

5027 Poster Session (Board #19), Sat, 1:15 PM-4:45 PM

The combination of DNA ploidy status and PTEN/6q15 deletions to provide strong and independent prognostic information in prostate cancer. *First Author: Maximilian Lennartz, Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: Aberrant DNA ploidy has been long discussed as a potential prognostic feature in prostate cancer. **Methods:** In this project, we analyzed the clinical significance of DNA ploidy in combination with the most frequent chromosomal deletions (PTEN, 6q15) with known prognostic impact in a contemporary series of 3,845 prostate cancers. Ploidy status was assessed in 3,845 cancers by using flow cytometry for which the 6q15 and PTEN deletion status was available from earlier projects. **Results:** The DNA status was diploid in 67.8%, tetraploid in 25.6% and aneuploid in 6.8% of tumors. Abnormal DNA content was significantly linked to high Gleason grade, advanced tumor stage, and positive nodal status ($p < 0.0001$ each). Deletions were seen for PTEN in 17.8% and for 6q15 in 20.3% of cases. Both deletions were significantly linked to high Gleason grade and advanced stage ($p < 0.0001$ each). Comparison with outcome data revealed, that the risk of PSA recurrence increased markedly from diploid to tetraploid tumors ($p < 0.0001$) and again from tetraploid to aneuploid cases. However, many patients with unfavorable tumor phenotype (39.9% of tumors with a Gleason grade of $\geq 4+4 = 8$) or with PSA recurrence (55.2%) had a diploid DNA status. The fraction of unfavorable tumors with a normal DNA status decreased to 21.1% of Gleason $\geq 4+4 = 8$ cancers and 29.0% of cancers with PSA recurrence, if DNA abnormality was defined as non-diploid and/or at least one of the two deletions. The significance of combining both deletions and ploidy was further demonstrated in a combined recurrence analysis. Here, presence of deletions markedly increased the risk of PSA recurrence in diploid ($p < 0.0001$), tetraploid ($p < 0.0001$), and aneuploid cancers ($p = 0.0049$). Moreover, multiple models of multivariate analyses including preoperatively and postoperatively available parameters identified the "combined DNA status" as a strong independent predictor of poor patient outcome. **Conclusions:** It is concluded, that a combinatorial DNA content analysis involving general (ploidy) and specific events (deletions) have the potential for clinical utility in prostate cancer.

5028 Poster Session (Board #20), Sat, 1:15 PM-4:45 PM

Phase 1b study of ARN-509 with abiraterone acetate (AA) and prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Edwin M. Posadas, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: ARN-509 and AA target the androgenreceptor (AR) axis via different mechanisms and may have complementary activity in mCRPC. ARN-509, a potent and selective AR antagonist, inhibits AR nuclear translocation and DNA binding without significant AR agonist properties (Clegg. *Cancer Res.* 2012). AA is a prodrug of abiraterone, a CYP17 specific inhibitor that blocks androgen synthesis. No overlapping toxicities are expected for the combination. This phase 1b study evaluates potential PK drug-drug interaction, antitumor activity, and safety of ARN-509 in combination with AA + P (NCT02123758). **Methods:** Pts with progressive mCRPC and ECOG PS $\leq$ 2 received AA (1000 mg/d) + P (5 mg BID) beginning on Cycle 1 Day 1 (C1D1) with the addition of ARN-509 (240 mg/d) on C1D8 in 28-day treatment cycles. Efficacy assessment was based on RECIST and PCWG2 criteria. **Results:** 29 pts started treatment on study. Median age was 70 years (range 49 - 83) and median PSA was 56.8 μg/L (range 4.1 - 2597.0 μg/L). Bone, nodal, and visceral disease were present in 25 (86%), 17 (61%), and 8 (29%) pts, respectively. 14 (48%) pts were previously treated with docetaxel, 12 (41%) with AA, 12 (41%) with enzalutamide (ENZ). 22 pts are currently on treatment and 7 discontinued for disease progression. Thus far, 41% of pts have had confirmed PSA declines $>$ 50%; 52% had any PSA decline. Confirmed PSA responses $>$ 50% included 3 pts who failed prior ENZ or AA therapy. Most common ($\geq$ 3 pts) drug-related adverse events (AEs) were grade 1-2 and included fatigue (n = 8), dysgeusia (n = 5), vomiting (n = 4), anorexia (n = 4), abdominal pain (n = 3), diarrhea (n = 3), nausea (n = 3). Grade 3 drug-related AEs (hyponatremia [n = 1], fatigue [n = 1], increased ALT [n = 1], and urinary tract infection [n = 1]) were managed by drug interruption and supportive measures. **Conclusions:** Interim data indicate that ARN-509 in combination with AA + P is well tolerated in pts with mCRPC. Further study of the efficacy and safety of ARN-509 and AA + P for mCRPC is warranted. Clinical trial information: NCT02123758.

5029 Poster Session (Board #21), Sat, 1:15 PM-4:45 PM

STEAP1 as a predictive biomarker for antibody-drug conjugate (ADC) activity in metastatic castration resistant prostate cancer (mCRPC). *First Author: Daniel Costin Danila, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: STEAP1 is overexpressed in mCRPC and is an ADC target. STEAP1 expression in tissue assayed by IHC, protein and mRNA expression levels in circulating tumor cells (CTC) and by ^{89}Zr-labeled anti-STEAP1 antibody uptake by iPET. **Methods:** Patients (pts) with progressive mCRPC received doses of the ADC ranging from 0.3 to 2.8 mg/kg once every three weeks. Antitumor activity was assessed by PSA declines, time on study and changes in CTC number (CellSearch). STEAP1 expression in tumor tissue by a validated IHC assay was used as reference biomarker on a scale of 0 (not detected) to 3+ (highest expression). Protein and mRNA expression in CTCs was explored by FACS and RT-PCR, and standardized uptake values (SUV) of ^{89}Zr-labeled anti-STEAP1 antibody by iPET. **Results:** At doses of $\geq$ 2 mg/kg, a $\geq$ 50% PSA decline was observed in 22% (10/45, 11-37%), and CTC conversions from unfavorable ($>$ 5 cells) to favorable (4 or fewer/7.5 ml of blood) in 55% (11/20, 32-77%) of cases. CTC showed a readily detectable STEAP1 +ve signal in EpCAM +ve events by FACS in 48% (14/29, 30-67%), confirmed by RT-PCR, along with AR (androgen receptor) and KLK3 expression. STEAP1 +ve events were EpCAM +ve in a range from 0-74%. ADC activity by IHC and CTC is shown in Table. For STEAP1 iPET imaged pts, PSA decline by $\geq$ 50% was noted in 4/14 (29%, 8-58%) pts. Time on treatment correlated with bone metastasis SUVmax (r = 0.63). All 8 PET-guided biopsies were confirmed STEAP1 IHC 2+/3+. **Conclusions:** The best evidence for STEAP1 ADC activity by PSA declines, time on study, and CTC conversion was seen in high expression tumors. Pts with IHC 2+/3+ tumors are being prospectively selected in an expansion study where predictive biomarkers are studied as companion diagnostics.

STEAP1 IHC score and treatment response.

IHC Score	Pts Observed/ Total (%, 95% CI)	PSA decline by $\geq$ 50%	$>$ 6 months on treatment	CTC conversion from U to F
1+	5/45 (11%, 4-24%)	1/5 (20%, 1-72%)	0/5 (0%, 0-52%)	1/3 (33%, 1-91%)
2+	27/45 (60%, 44-74%)	4/27 (15%, 4-34%)	6/27 (22%, 9-43%)	7/14 (50%, 23-77%)
3+	13/45 (29%, 16-44%)	5/13 (39%, 14-68%)	6/13 (46%, 19-75%)	3/3 (100%, 29-100%)

5030 Poster Session (Board #22), Sat, 1:15 PM-4:45 PM

Immune responses and clinical outcomes in STAND, a randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically-recurrent prostate cancer (BRPC) after local therapy failure. *First Author: Emmanuel S. Antonarakis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: STAND (NCT01431391) assessed optimal sequencing of sip-T and ADT in men with BRPC at high risk of metastases after local therapy (i.e. prostate specific antigen doubling time [PSADT] $<$ 12 mo). **Methods:** Men (n = 68) were randomized to sip-T then ADT (2 wks post infusion 3; Arm 1) or ADT (3 mo lead-in) then sip-T (Arm 2). Cellular and humoral immune responses, and clinical outcomes were analyzed. PSA recurrence was defined as $\geq$ 2 serial rises in PSA and an absolute PSA value of $\geq$ 0.2 ng/mL (prior radical prostatectomy) or $\geq$ 2.0 ng/mL (prior radiotherapy alone). PSADT post-ADT was analyzed. Time to next anticancer intervention (TTACI) was measured from first ADT to the day of the next systemic therapy. Rate of metastases at 24 mo was also investigated. **Results:** All men received 3 sip-T doses, and 96% received 12 mo ADT. Cellular and humoral responses to PA2024 increased following treatment vs baseline (BL) and were sustained at all post-sip-T timepoints through 24 mo ($p < 0.05$). PA2024-specific T cell proliferation responses were higher in Arm 1 vs Arm 2 ($p<0.001$). The number of PA2024 antibody (Ab) responders (post-BL Ab titer $\geq$ 25,600) was similar between arms. Sip-T-mediated antigen spread was observed in both arms vs BL and maintained through 24 mo ($p < 0.001$). No significant differences between arms were observed in clinical outcomes: median time to PSA recurrence (21.8 vs 22.6 mo, HR: 0.70, 95% CI: 0.39–1.28; p = 0.357), PSADT (2.54 vs 2.58 mo, p = 0.944), metastases at 24 mo (6/31 vs 3/26, p = 0.419), or TTACI (medians not reached, p = 0.199). However, across the entire cohort, PA2024 Ab responses correlated with longer time to PSA recurrence (p = 0.007). Adverse events occurring in >20% were hot flashes, fatigue, headache, and chills. **Conclusions:** In men with non-metastatic BRPC, sip-T + 12 mo ADT induced a robust immune response that persisted for 24 mo. Data suggest a greater anti-PA2024 T cell proliferative response in Arm 1 (sip-T then ADT). Induction of a PA2024 Ab response may correlate with longer time to PSA progression. Clinical trial information: NCT01431391.

5031 Poster Session (Board #23), Sat, 1:15 PM-4:45 PM

Baseline analysis of circulating tumor cell (CTC) enumeration and androgen receptor (AR) localization in men with metastatic castration-resistant prostate cancer (mCRPC) in TAXYNERGY. *First Author: Scott T. Tagawa, Weill Medical College of Cornell University, New York, NY*

Background: Microtubule-targeted therapy with taxanes is the only chemo with survival benefit in advanced PC. Emerging molecular evidence suggests sensitivity/resistance to taxanes may relate to the ability of microtubules to inhibit AR nuclear trafficking. CTCs represent a real-time biomarker for molecular testing including taxane-induced microtubule stabilization and AR nuclear localization. **Methods:** TAXYNERGY is an international, multicenter phase 2 trial in progressive, chemo-naïve mCRPC men randomized (2:1) to docetaxel or cabazitaxel. Pre-treatment CTCs were enriched from 1 ml blood via a prostate-specific microfluidic device, enumerated, and analyzed by multiplex confocal microscopy for AR cellular localization. Nuclear AR % was calculated by integrating fluorescence intensity in the total cell and nuclear area. Bivariate correlations and multiple regressions examined associations between baseline characteristics and % nuclear AR or CTC count. **Results:** 63 men were randomized (median age 70 [range 53–84], median PSA 89 [2.4–1558], 24 [38%] previously received a CYP17 inhibitor and/or enzalutamide, 17 [27%] had visceral metastases). Of 59 with evaluable samples, CTCs were detected in 52 (88%), median 10 CTCs/mL of blood [0–542]. 638 CTCs were analyzed for AR localization with a mean 61.2% [30–85] nuclear AR per subject. Higher baseline LDH, pain assessments, and ECOG performance status were associated with higher CTC counts; LDH (p = 0.013) and analgesic scores (p = 0.036) remained significant on multivariate analysis. Visceral metastases were associated with a lower fraction of nuclear AR, remaining significant on multivariate analysis (p = 0.045). **Conclusions:** Nearly 90% of men with progressive chemo-naïve mCRPC have detectable CTCs available for molecular analysis using this platform, with higher CTC counts associated with adverse prognostic variables. Lower percent of nuclear AR was associated with visceral metastases, suggesting progressive visceral CRPC may be less AR-driven. The predictive value of these biomarkers for taxane response is being evaluated. Clinical trial information: NCT01718353.

5033 Poster Session (Board #25), Sat, 1:15 PM-4:45 PM

Performance of CCP assay in an updated series of biopsy samples obtained from commercial testing. *First Author: John W. Davis, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The cell cycle progression (CCP) score is an RNA−based expression assay, which has improved the prediction of prostate cancer aggressiveness in nine separate retrospective cohorts. In this analysis, we characterized the patient population and CCP score performance in commercial testing. **Methods:** Formalin−fixed prostate biopsy samples from 4261 patients were submitted by 930 physicians to Myriad Genetic Laboratories for CCP test analysis. Patient clinicopathologic data was obtained from the test request form. The CCP score was calculated based on RNA expression of 31 cell cycle progression genes normalized to 15 housekeeping genes. Patients were sorted in to AUA risk categories and assigned a relative classification of cancer aggressiveness based on the CCP score. **Results:** Of the 4261 samples that contained sufficient carcinoma ($>$ 0.5mm linear extent), 4218 (99.0%) provided quality RNA for analysis. The CCP score distribution ranged from −2.9 to 3.4. Correlation with Gleason score was r = 0.35 and the correlation with PSA was r = 0.16. Based on the CCP score, 36.8% of men had a less aggressive cancer and 21.2% of patients had a more aggressive cancer than expected based on clinicopathologic prediction. **Conclusions:** The CCP test can improve risk stratification for men with prostate adenocarcinoma independent of other clinicopathologic variables. Fifty−eight percent of men tested in the commercial assay were assigned to a different risk category than predicted by their clinicopathologic features.

5034 Poster Session (Board #26), Sat, 1:15 PM-4:45 PM

Radium-223 in an international early access program (EAP): Effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients. *First Author: Fred Saad, University of Montreal, Montreal, QC, Canada*

Background: The pivotal ALSYMPCA study reported improved overall survival (OS) in bone symptomatic mCRPC patients (pts) treated with radium-223 (Ra-223) vs placebo (median 14.9 vs 11.6 months [mos], HR = 0.70). Data from 696 EAP pts recruited from 14 countries (Europe, Canada, Israel) are presented. **Methods:** In this prospective phase IIIb study, mCRPC pts with symptomatic or asymptomatic bone metastases (no visceral disease) received Ra-223, 50 kBq/kg (iv injection) every 4 weeks for 6 cycles. Primary endpoints were safety and OS. The effects of concomitant medications, baseline (BL) pain, alkaline phosphatase (ALP) and ECOG PS on OS were assessed. **Results:** 696 pts were treated; 58% received all 6 Ra-223 injections. At BL: median age was 72 years; 88% of pts were ECOG PS 0–1; pain was reported as: no pain, mild-moderate, and severe in 21%, 52%, and 27% respectively. 60% of pts received prior therapy with docetaxel. For pts treated with concomitant therapy: 22% were with abiraterone; 20% with denosumab; 18% with bisphosphonates and 4% with enzalutamide. Grade 3/4 AEs were reported in 38% of pts; 21% discontinued Ra-223 due to AEs. At the time of analysis median OS was 16 mos [13–not estimated (NE)]. Median time to first SSE was 18 mos [17–NE]; 24% of pts had ≥ 50% confirmed ALP decrease from BL; 8% had $>$ 50% confirmed PSA decrease from BL. In post hoc analyses OS was statistically significantly longer in pts with BL: ALP $<$220 U/L vs ≥ 220 U/L; ECOG PS 0–1 vs ≥ 2; no pain vs mild-moderate vs severe; concomitant denosumab; concomitant abiraterone (Table). **Conclusions:** In Ra-223 treated pts, OS appeared to be better in those treated concomitantly with denosumab or abiraterone. Significantly longer OS was observed in pts with a good ECOG PS, no pain and low ALP. Clinical trial information: 2012-000075-16.

Characteristic	Pts, n	Median OS, mos (95% CI)	Log-rank p-value
Concomitant denosumab			
Yes	138	NA (15–NE)	0.00940
No	558	13 (12–NE)	
Concomitant abiraterone			
Yes	156	NA (16–NE)	< 0.0001
No	540	14 (12–16)	
ALP			
< 220U/L	431	NA (NE)	< 0.0001
≥ 220U/L	263	10 (9–11)	
ECOG-PS			
0-1	609	17 (14–NE)	< 0.0001
≥ 2	87	7 (5–11)	
Pain			
No	146	NA (16–NE)	0.00018*
Mild-moderate	360	15 (13–NE)	
Severe	163	11 (8–12)	

*No vs all pain. NA, not available.

5035 Poster Session (Board #27), Sat, 1:15 PM-4:45 PM

Circulating tumor cell (CTC) enumeration in men with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide post-chemotherapy (phase 3 AFFIRM study). *First Author: Martin Fleisher, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CTC enumeration is a biomarker associated with clinical outcomes in patients (pts) with mCRPC. CTC count at baseline (BL) and post-treatment is prognostic for survival. Enzalutamide (ENZA) was approved for post-chemotherapy CRPC based on the overall survival (OS) benefit (AFFIRM trial). In this trial, CTC enumeration was embedded as a biomarker endpoint. **Methods**: AFFIRM was a phase 3 study (N = 1199; NCT00974311) randomizing men who received ≤ 2 docetaxel-based chemotherapy regimens to ENZA 160 mg/day or placebo (PBO) (2:1). CTC samples were collected at sites selected for logistics and investigator interest. Conversion rate was defined as a decline from ≥ 5 (unfavorable) to $<$ 5 (favorable) CTCs/7.5 mL of blood from BL to best post-BL result. **Results**: BL CTCs were obtained from 447 of 1199 pts at 89 of 156 study sites; BL demographics and disease history were similar to pts in whom samples were not collected. 382 pts had both BL and post-BL counts; OS, rPFS and select disease characteristics for pts with CTC data are shown in the table. Conversion from unfavorable to favorable CTC counts was observed in 61 of 127 pts (48%; 95% CI 39%-57%) treated with ENZA compared to 6 of 62 pts (9.7%; 95% CI 3.6%-20%) with PBO ($p < 0.0001$). Progression from favorable to unfavorable counts occurred in 18% of ENZA pts compared to 44% with PBO. **Conclusions:** Unfavourable baseline CTC counts were associated with higher PSA and greater disease burden. The higher rate of conversion from unfavorable to favorable and lower conversion from favorable to unfavorable for ENZA relative to placebo was consistent with observed OS benefit. Clinical trial information: NCT00974311.

Baseline	CTC < 5 ENZA n = 131	CTC < 5 PBO n = 62	CTC ≥ 5 ENZA n = 127	CTC ≥ 5 PBO n = 62
Median Age	69	70	70	70
ECOG = 0	71 (54%)	29 (47%)	36 (28%)	20 (32%)
Brief Fatigue Inventory = 0	62 (52%)	19 (34%)	38 (33%)	21 (36%)
Median PSA (ng/mL)	68	55	241	211
Median Hemoglobin (g/L)	124	126	114	115
Median Alk Phosphatase (U/L)	85	87	178	147
Median LDH (U/L)	185	190	236	242
Bone Mets >20	22 (17%)	11 (18%)	74 (58%)	36 (58%)
OS	Not reached	19.5 m	13.6 m	10.7 m
HR (95% CI)	0.52 (0.28-0.98)		0.78 (0.51-1.17)	
rPFS	11.0 m	2.8 m	5.8 m	2.8 m
HR (95% CI)	0.23 (0.16-0.35)		0.38 (0.26-0.54)	

5036 Poster Session (Board #28), Sat, 1:15 PM-4:45 PM

Enzalutamide (ENZA) in men with chemotherapy-Naïve metastatic castration-resistant prostate cancer (mCRPC): Final analysis of the phase 3 PREVAIL study. *First Author: Tomasz M. Beer, Oregon Health & Science University, OHSU Knight Cancer Institute, Portland, OR*

Background: PREVAIL (NCT01212991) was a phase 3 trial that investigated the impact of ENZA vs placebo (PBO) on overall survival (OS) and radiographic progression-free survival (rPFS) in asymptomatic or mildly symptomatic chemotherapy-naïve men with mCRPC. ENZA improved OS (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.60–0.84; $P < 0.0001$) and rPFS (HR 0.19; 95% CI 0.15–0.23; $P < 0.0001$) in a planned interim analysis after 540 deaths (Sep 16, 2013, data cutoff). On the basis of these results, ENZA was approved for chemotherapy-naïve mCRPC in the US and Europe. Final OS analysis was planned after at least 765 deaths. **Methods:** Patients (pts) were randomized 1:1 to ENZA 160 mg/day or PBO. OS and rPFS were coprimary endpoints and analyzed in the intent-to-treat population. Planned sample size was 1680 with at least 765 deaths to achieve 80% power to detect a target OS HR of 0.815, with a type I error rate of 0.049 and a single interim analysis. After the interim analysis, eligible PBO pts had the option to crossover to ENZA. All pts were followed in an open-label extension protocol. rPFS was determined by investigator review. The final OS and rPFS results reported here are from Jun 1, 2014, and Jan 15, 2014, data cutoff dates, respectively. **Results:** 1717 men were randomized (1715 treated) between Sep 2010 and Sep 2012. The final analysis at 784 deaths with a median follow-up of 31 months (mo) confirmed the OS benefits of ENZA with a 23% reduction in risk of death (HR 0.77; 95% CI 0.67–0.88; $P = 0.0002$) and a 4-mo improvement in median OS (35.3 mo [95% CI 32.2–NYR]) vs 31.3 mo [95% CI 28.8–34.2]). 42% of ENZA and 49% of PBO pts had died; 52% of ENZA and 81% of PBO pts (including 167 pts who crossed over to ENZA) received ≥ 1 subsequent life-extending prostate cancer therapy. A preliminary analysis of rPFS from the Jan 15, 2014, data cutoff showed a significant improvement with ENZA (HR 0.32; 95% CI 0.28–0.36; $P < 0.0001$). Median rPFS was 20.0 mo (95% CI 18.2–22.1) with ENZA vs 5.4 mo (95% CI 4.2–5.6) with PBO. **Conclusions:** With longer follow up time, ENZA continued to demonstrate a robust improvement in OS and rPFS in asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC. Clinical trial information: NCT01212991.

5037 Poster Session (Board #29), Sat, 1:15 PM-4:45 PM

Phase 1 study with expansion cohorts of cabozantinib (C) + abiraterone (A) in metastatic castration resistant prostate cancer (mCRPC): Investigator-sponsored study. *First Author: Christopher Sweeney, Dana-Farber Cancer Institute, Boston, MA*

Background: A and C (multi-tyrosine kinase inhibitor including MET and VEGFRs) have complementary mechanisms of action and activity in CRPC. *In vivo* work with LAPC4-CR (castration and A resistant cell line) has shown the combination has enhanced activity. **Methods:** Phase 1, 3 + 3 trial with A fixed at 1,000 mg/day and prednisone 5mg BID and escalating daily doses of C (20mg, 40mg, 60mg) in pts with mCRPC was conducted. Cycles were 28 days. **Results:** 27 patients were enrolled with a median follow-up of 9.2 months (Range: 1.6-29.4 months). 11 pts had prior docetaxel therapy. No DLTs in the first 28 day cycle of dose escalation cohorts. The 60 mg C cohort had Gr 2 adverse events (AEs) of myalgias (2), fatigue (2) and DVT (1) in cycles 2 and 3 necessitating a dose reduction to 40 mg (no change to A). Due to a preferable tolerability profile, the 20mg and 40mg C cohorts were expanded to a total of 12 pts each. See Table for activity data. Gr 3 treatment related AEs: 5 pts at 20mg C [skin infection (1); diarrhea (1); anemia (1); transaminase (1); hypophosphatemia (1)]; 7 pts at 40mg C [hypertension (1); hypophosphatemia (2); transaminase (1); colitis (1); lipase incr. (1); thromboembolic (1)]. Dose reductions: 5 pts on 40mg C; none on 20mg C. 1 pt had A dose reduction [hypokalemia with Atrial Fib (1)]. The steady-state trough concentration PK data of A and C did not indicate a drug-drug interaction. **Conclusions:** C at either 20mg or 40 mg is tolerable when combined with standard dose A/pred. The long term tolerability and preliminary efficacy data support the investigation of this combination for further clinical development in mCRPC. Clinical trial information: NCT01574937.

	20 mg N = 12	40mg N = 12
Median Age (yrs)	66	62
Median baseline PSA	41	15
Prior chemo	5 (41.7%)	4 (33.3%)
Gleason 8-10	10 (83.3%)	9 (75.0%)
Visceral mets	2	1
Opiate use baseline	5	5
PSA decline	6 (50%)	3 (25%)
> 90%	7 (58%)	5 (42%)
> 75%		
Median time on therapy Months (Q1,Q3) - 11 pts still on Rx	17 (10,28)	8 (7,17)
Pts with any Gr 3 AEs due to Rx	5 (31%)	7 (58%)

5038 Poster Session (Board #30), Sat, 1:15 PM-4:45 PM

Acute toxicity and early quality of life after dose intensified salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy: First results of the randomized trial SAKK 09/10. *First Author: Pirus Ghadjar, Department of Radiation Oncology, Charité Universitätsmedizin Berlin, Berlin, Germany*

Background: Patients (pts) with biochemical recurrence after radical prostatectomy may benefit from dose intensified salvage radiotherapy (RT) of the prostate bed. We performed a randomized phase III trial assessing dose intensification. In this first report we report acute toxicity and early quality of life (QoL). **Methods:** Pts with biochemical recurrence but without evidence of macroscopic disease were enrolled in this randomized phase III trial. Pts were randomly assigned to either 64 Gy (32 daily fractions) or 70 Gy (35 daily fractions). Three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT, or equivalent rotational techniques) were accepted techniques. The primary endpoint was freedom from biochemical recurrence. Secondary endpoints included acute toxicity according to the CTCAE v4.0 and QoL using the EORTC QLQ-C30 and PR25. **Results:** We enrolled 350 pts between 02/2011 and 04/2014. Three pts withdrew consent and three were not eligible, resulting in 344 pts in the safety population. Thirty (8.7%) and two (0.6%) pts had grade 2 and 3 genitourinary (GU) baseline symptoms. Acute grade 2 and 3 GU toxicity was observed in 22 (13.0%) and 1 (0.6%) with 64 Gy and 29 (16.6%) and 3 (1.7%) with 70 Gy, being not significantly different ($p = 0.2$). Baseline grade 2 gastrointestinal (GI) toxicity was observed in 1 (0.6%) patient. No baseline grade 3 GI toxicity was observed. Acute grade 2 and 3 GI toxicity was observed in 27 (16.0%) and 1 (0.6%) with 64 Gy and 27 (15.4%) and 4 (2.3%) with 70 Gy, again not significantly different ($p = 0.8$). Changes in QoL were marginal. However, pts receiving 70 Gy reported a more pronounced and clinically relevant worsening in urinary symptoms (mean difference between arms 3.6, $p = 0.02$). There was no significant difference between 3D-CRT and IMRT/rotational techniques. **Conclusions:** Dose-intensified salvage RT was associated with a low rate of grade 2 and 3 GU and GI toxicities. The impact of dose intensified salvage RT on QoL was marginal, with the exception of a worsening in urinary symptoms after 70 Gy. Clinical trial information: NCT01272050.

5039 Poster Session (Board #31), Sat, 1:15 PM-4:45 PM

Testosterone-guided schedule of androgen deprivation therapy (ADT) as an alternative to a fixed schedule in management of prostate cancer. *First Author: Saroj Niraula, CancerCare Manitoba and Univ of Manitoba, Winnipeg, MB, Canada*

Background: ADT with LHRH agonists that reduce testosterone production is effective initial therapy for treatment of men with advanced prostate cancer. LHRH agonists are usually administered indefinitely at a fixed interval despite their cost and serious toxicity. **Methods:** We recruited men with prostate cancer who had been on fixed-schedule injections of a LHRH agonist (most commonly given as 12 weekly injections) for at least one year and had castrate levels of serum testosterone (< 1.7 mmol/l). We measured their serum testosterone at 6-week intervals, and men resumed their injections only when their serum testosterone was ≥ 1.7mmol/l. We calculated median time to reinstitution of ADT by the Kaplan Meier method and used Cox regression analyses to identify factors predicting delay in reinstitution of treatment. Influence of this approach on quality of life (QoL) was measured by the Expanded Prostate Index Composite (EPIC). **Results:** From November 2009 to May 2014, a total of 82 men were enrolled. Median age at diagnosis was 68 years (range, 51-83 years). Median time to testosterone recovery after the last injection was 30.8 weeks (Inter-quartile range 17-65 weeks). Lower level of baseline testosterone (≤ 1 versus > 1 mmol/l) [Hazard Ratio (HR) 0.32; $p = 0.004$] and longer duration of disease (> 5 versus ≤ 5 years) [HR 0.38; $p = 0.03$] were independent predictors for prolonged time to testosterone recovery. Statistically significant improvement from baseline was noted in the hormonal domain of EPIC ($p = 0.002$) but not in overall score. Drug costs (LHRH agonist alone) dropped from a median of $4,550 to $1,900 per patient per year. **Conclusions:** Implementing a testosterone-guided approach to ADT results in a substantial reduction in exposure to, and symptoms from ADT. Drug cost is reduced by $> 60\%$ while still maintaining castrate levels of testosterone. Testosterone-guided approach to ADT can have major public health benefits. This approach should be discussed with men on ADT and be considered as the replacement of fixed schedule treatment by physicians and policy makers. Clinical trial information: NCT01007825.

5040 Poster Session (Board #32), Sat, 1:15 PM-4:45 PM

Immune response from STRIDE, a randomized, phase 2, open label study of sipuleucel-T (sip-T) with concurrent vs sequential enzalutamide (enz) administration in metastatic castration-resistant prostate cancer (mCRPC). *First Author: David I. Quinn, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: In mCRPC, data are limited regarding optimal combinatorial or sequential use of available treatments. P12-2 (STRIDE; NCT01981122) is an ongoing, randomized, open-label, phase 2 study evaluating concurrent vs sequential administration of the androgen receptor inhibitor, enz, with the autologous cellular immunotherapy, sip-T. **Methods:** Fifty-twopatients (pts) with asymptomatic or minimally symptomatic mCRPC were randomized 1:1 to receive 3 sip-T infusions with enz starting 2 wks before (n = 25, concurrent arm A) or 10 wks after (n = 27, sequential arm B) sip-T initiation. The primary endpoint is peripheral T cell proliferation response to PA2024, the sip-T immunizing antigen. Secondary endpoints include interferon (IFN)-γ ELISPOT and humoral immune responses to PA2024 and prostatic acid phosphatase (PAP), product release parameters (total nucleated cell count, $CD54^+$ cell counts, and antigen presenting cell activation [as measured by CD54 upregulation]), cytokine production, and adverse events (AEs). Results through wk 26 are described. **Results:** PA2024-specific T cell proliferative response was significantly elevated at all post-baseline time points ($p < 0.001$) and was sustained through wk 26, including a > 10-fold increase at wk 20 in both arms. This PA2024-specific response was observed in nearly all pts, 95.8% in arm A vs 92.6% in arm B. Both arms showed a significant and sustained increase in humoral responses to PA2024 and PAP as well as IFN-γ ELISPOT response to PA2024. Sip-T product parameters were similar between arms. Cytokines indicative of immune activation (such as IFN-γ, interleukin-2, and tumor necrosis factor-α) were also elevated in both arms. AEs were observed in 88% (arm A) and 100% (arm B) of pts. The incidence of grade ≥ 3 AEs was similar between arms. **Conclusions:** Most mCRPC pts receivingenz concurrently with or subsequent to sip-T demonstrated significant and sustained peripheral T cell and humoral immune responses through wk 26. These interim data suggest that both schedules were safe, and enz did not impair sip-T production or subsequent immune responses. Clinical trial information: NCT01981122.

5041 Poster Session (Board #33), Sat, 1:15 PM-4:45 PM

Relationship between abiraterone plasma concentration and PSA response in metastatic castration resistant prostate cancer patients. *First Author: Edith Carton, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France*

Background: Abiraterone (ABI) is a standard treatment in metastatic castration-resistant prostate cancer (mCRPC). However, the large interindividual variability in ABI pharmacokinetics could contribute to the lack of PSA regression observed in some patients. We aimed to explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship of ABI in progressive mCRPC patients (pts). **Methods:** We prospectively included mCRPC pts receiving ABI, pre-treated or not with docetaxel. ABI was administrated once daily at 1000 mg, in a fasted state, with 10 mg of prednisone. Trough ABI plasma concentration (C_{min}) was assayed using liquid chromatography at month 1, 2 and 3 after treatment initiation, and PSA level was measured at baseline and after 3 months (ms) of treatment. The individual average C_{min} during the first 3 ms of treatment was used for the statistical analysis. Pts who had a PSA decline of at least 50% after 3 ms were defined as responders, according to Prostate Cancer Working Group 2 (PCWG2). All pts gave their informed consent. **Results:** From December 2012 to October 2014, 57 pts were included. Forty-one pts (76%) were docetaxel-naïve. ABI C_{min} was available in 48 pts. The median average ABI C_{min} was 11.2 ng/mL (IQR 7.2 - 16.2 ng/mL). No intraindividual variability in ABI C_{min} was identified (CV = 23.5%, p = 0.79). The interindividual variability in ABI C_{min} was large (CV = 70%), but was not influenced by age, body mass index, albumin level, hepatic or renal function. Among 45 pts available for PK/PD assessment, 29 pts (64%, IC95% [50-78]) were responders at 3 ms. The average plasma ABI C_{min} was significantly higher in the responder group (median 13.1 [IC 95% 10.6 - 15.6] vs 8.5 [5.6-15.7] ng/mL, $p < 0.01$, respectively). Pts were classified into two groups based on ABI plasma C_{min}: low (quartile 1 [Q1]) and high (Q2-Q4). In 11 pts exhibiting average ABI C_{min} below 8.5ng/mL (Q1), 18% were responders. In contrast, 80% of pts in Q2-Q4 were responders (Fisher test, $p < 0.001$). **Conclusions:** In addition to molecular profiling, plasma monitoring of ABI C_{min} could help optimizing its efficacy. We propose 8.5 ng/mL as the threshold ABI C_{min} to explore the benefit of PK-guided dosing strategy in clinical practice.

5042 Poster Session (Board #34), Sat, 1:15 PM-4:45 PM

Genomic analysis of circulating tumor cells (CTCs) from men with metastatic castration resistant prostate cancer (mCRPC) in the context of enzalutamide therapy. *First Author: Jing Li, Duke University Medical Center, Chapel Hill, NC*

Background: Predictive biomarkers are essential to maximize benefit and minimize harms and costs in mCRPC. Goal of this study was to determine the feasibility of genomic analysis of DNA copy number changes and whole exome sequencing (WES) of CTCs from men with mCRPC receiving enzalutamide. **Methods:** We collected CTCs from men with mCRPC in the context of enzalutamide therapy. CTCs were isolated through red cell lysis, CD45 depletion, and flow sorting on EpCAM/CD45 expression. Whole genomic amplification, aCGH, and WES were performed. In aCGH, each sample hybridized with its own leukocytes. A copy number log ratio greater than 0.2 or less than -0.2 with at least 10 consecutive probes represents gain or loss. In WES, single nucleotide variant (SNV) or insertion/deletion (INDEL) was called if the site was covered by more than 10 reads. **Results:** We successfully profiled the genomic copy number of CTCs from 4 men with CRPC. We compiled copy gains and losses observed by aCGH in these 4 patients. Genomic copy gains in AR, EZH2, SPOP, CCND1, BRD4, MYC, FOXA1, ABL1, ABL2 and other genes were observed; while common losses of the locus including CHD1 FGFR2, PHLLP, NCOR1, NCOR2 were seen. During sequential analysis during enzalutamide resistant visceral progression, loss of AR amplification and gain of N-MYC was observed, consistent with evolution toward a neuroendocrine AR-independent clone. We successfully sequenced the whole exome from CTCs and leukocytes from a patient who progressed through enzalutamide therapy. We discovered many somatically acquired mutations in CTCs exome, including 138 SNVs and 47 INDELs in CTCs including NCOA1, MAX, NOD1,USP10, MLL, MMP8, which have been previously implicated in prostate cancer. **Conclusions:** Genomic analysis of whole genome DNA copy number changes and whole exome sequencing from CTCs of men with mCRPC are feasible and identified previously validated and novel complex genomic lesions. Our results suggest the potential of CTC genomic analysis to help identify and longitudinally track predictive biomarkers and novel targets of systemic therapy efficacy and resistance in men with mCRPC and form the basis for larger validation trials.

5043 Poster Session (Board #35), Sat, 1:15 PM-4:45 PM

Nine-year follow-up for a study of diffusion-weighted MRI in a prospective active surveillance cohort for prostate cancer. *First Author: Daniel Robert Henderson, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom*

Background: Active surveillance (AS) for untreated prostate cancer requires accurate selection of patients unlikely to need treatment in their lifetime. Most studies have selected patients on biopsy and PSA criteria alone, but show a significant number requiring treatment for disease progression. Lower tumour apparent diffusion coefficient (ADC) values, derived from diffusion-weighted MRI (dwMRI), are associated with higher risk disease. We hypothesised that ADC values could aid selection of patients for AS. Early results from this study were published in 2009; we now present findings with the benefit of long-term follow up. **Methods:** We analysed a subset of patients having pre-enrolment dwMRI in a prospective research study of AS. Inclusion criteria: untreated prostate cancer, T1/T2a/N0M0, Gleason $\leq 3+4$, PSA < 15. Protocol follow up was by biopsy at 18-24 months, then every 24 months, along with regular PSA. To avoid influencing treatment decisions, results of dwMRIs were not available to the AS study investigators. Baseline data including PSA, biopsy grade, and T stage, along with ADC value, were analysed with respect to the outcomes of: time to adverse histology (TAH; primary Gleason ≥ 4, $\geq 50\%$ positive cores) and time to deferred radical treatment (TRT). **Results:** Eighty six patients were included (90% Gleason 6; 86% cT1). Median follow up was 9.5 years. Forty six patients developed adverse histology, and 59 received deferred radical treatment (2 due to patient choice). In univariate analysis, ADC below the median was associated with shorter TAH and TRT with hazard ratios of 2.13 (CI: 1.17-3.89; $p < 0.014$) and 2.54 (CI: 1.49-4.32; $p < 0.001$), respectively. Median TRT in patients with ADC above the median was 9.3 years (CI: 7.0-11.6) but 2.4 years (CI: 1.5-6.0) for those below the median. For TRT, addition of ADC to a multivariate model of baseline variables resulted in a significant improvement in model fit (HR: 1.33, CI: 1.14-1.54, $p < 0.0001$). ROC analysis for TRT: AUC 0.80 (CI: 0.70-0.88). **Conclusions:** Long-term follow up for this study provides strong evidence that ADC is a useful marker when selecting patients for AS. Routine dwMRI is now included in our ongoing prospective AS study.

5044 Poster Session (Board #36), Sat, 1:15 PM-4:45 PM

Computer automated bone scan index (BSI) as an analytically validated imaging biomarker to quantitate change in bone scan of patients with metastatic prostate cancer. *First Author: Aseem Anand, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A consistent imaging biomarker to standardize the evaluation of change in bone scan is an unmet need for patients (pts) with bone metastasis. BSI is quantitative interpretation of bone scan in pts with metastatic prostate cancer (mPCa). Here we have performed analytical and clinical studies to evaluate the change in computer automated BSI as a consistent imaging biomarker in pts with mPCa. **Methods:** Analytical studies with bone scan simulation using XCAT phantoms and SIMIND-MC program were performed to evaluate the consistency of automated BSI. Specifically, to assess linearity and accuracy, bone scan of 50 phantoms were simulated with tumor burden ranging from low to high disease confluence – from 0.10 to 13.0 BSI. To assess precision, another set of 50 phantoms were divided into 5 subgroups, each containing simulated bone scans of 10 phantoms at 0.5, 1.0, 3.0, 5.0 and 10.0 BSI, respectively. Additionally, to evaluate the clinical utility of automated BSI, two follow-up bone scans of 145 pts with progressing mPCa, irrespective of therapy regiment, were analyzed for change in BSI. The primary objective was to evaluate the association of change in BSI against overall survival (OS). The computer automated BSI was calculated using the software EXINI bone^{BSI}. Cox regression and Kaplan Meier analysis were used to evaluate association between BSI and OS. **Results:** Pearson correlation to evaluate linearity and accuracy of BSI, in the given range from 0.10 to 13.0, was observed to be 0.995 (N = 50, 95% CI 0.99 – 0.99, $p < 0.0001$). The mean coefficient of variation indicating precision of BSI at each of the pre-defined tumor burden was observed to be less than 20%. Change in BSI of 145 pts was significantly associated with OS (HR 1.1, $p < 0.0001$). The median OS for 110 (66%) pts who had a rise in BSI (> 0.10) was 31 weeks, 35 (34%) pts who had a decline or no change in BSI reached a median 72 weeks (HR 1.9, p 0.0002). **Conclusions:** Computer automated BSI is a consistent biomarker which can standardize the quantitative analysis of change in bone metastasis of pts with mPCa. The clinical utility of automated BSI, in multivariate biomarker panel, will be validated in subsequent studies.

5045 Poster Session (Board #37), Sat, 1:15 PM-4:45 PM

Identification of germline mutations in men with early onset prostate cancer. *First Author: Patrick Pilie, University of Michigan, Ann Arbor, MI*

Background: Prostate cancer (PCa) is generally considered a disease of older men, however, approximately 10% of new diagnoses occur in young men (< 56 years) and some of these cases are clinically aggressive. Epidemiological evidence suggests that early age of cancer onset is associated with increased genetic susceptibility. **Methods:** For this pilot study, we employed a gene panel approach to identify germline mutations in cancer-associated genes among men diagnosed with early-onset (EO) PCa. Fifty-five men with PCa diagnosed before age 56 were selected from the University of Michigan (UM) Prostate Cancer Genetics Project, a large family-based study of familial and EO PCa. Each of the men also had at least one of the following characteristics: 1) family history of breast and/or ovarian cancer, 2) multiple primary cancers in addition to PCa, and/or 3) clinically aggressive PCa defined as death from disease before age 66 and/or diagnosis of metastatic disease before age 56. All patients provided written consent and this project was approved by the UM IRBMED. Germline DNA from the 55 men was sequenced using the GeneRead Human Comprehensive Cancer Panel (Qiagen) which includes 124 genes previously associated with a variety of cancers. Potentially deleterious variants were confirmed via Sanger sequencing and then tested in all family members with DNA available to assess co-segregation with PCa status. **Results:** Over 2500 germline variants were identified, including 349 missense, 4 nonsense, and 6 frameshift variants. Seven of the ten protein truncating variants were confirmed. The 7 true positives included nonsense variants in *MSH2, ATM, and KRAS*, as well as frameshift variants in *FGFR3, TET2, and BRCA2*. **Conclusions:** Overall, 7 of 55 (~13%) high selected EO PCa cases harbored protein-truncating variants in one of the genes examined. Although deleterious mutations in *BRCA2* and *MSH2* have previously been associated with PCa risk, the other genes have been less well-studied for their role in PCa susceptibility. Further studies of this unique patient population will likely uncover additional novel variants and genes linked with PCa risk which may provide new insights into the development of the disease and ultimately suggest new therapeutic targets.

5046 Poster Session (Board #38), Sat, 1:15 PM-4:45 PM

Influence of prostate cancer disease state and therapeutic selection on peripheral whole-blood RNA signature. *First Author: Bobby Chi-Hung Liaw, Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Prostate cancer is a heterogeneous disease with differences in tumor stromal interactions contributing to variability in treatment response and outcome. Gene expression of peripheral blood cells is altered by interactions with neoplastic tissue. We previously developed a peripheral whole blood six-gene signature prognostic for survival in mCRPC. Here we evaluate how different clinical disease states and treatment with different therapeutic agents impact this signature. **Methods:** Whole blood was collected in PAXgene Blood RNA tubes in two cohorts of prostate cancer patients, one at Mount Sinai (n = 135), the other in Munich (n = 59), in the context of prospective clinical studies. Whole blood RNA was extracted and the six target genes were amplified using qPCR. Scores were derived using normalized cycle threshold (ΔCT) values of the six genes, according to the model: 2 x ABL2 + SEMA4D + ITGAL – C1QA – TIMP1 – CDKN1A. Patients were categorized by disease state in the Mount Sinai cohort, and by treatment received in the Munich cohort, for data analysis. **Results:** CRPC is the only disease state with a mean six-gene score (18.06) above the high-risk cutoff (17.9), and is significantly higher than localized or hormone sensitive advanced disease (16.07, 16.52, respectively; p = 0.0002). Among patients with localized disease, there was no significant difference in the mean six-gene scores for patients with low-, intermediate-, and high-risk disease (16.07, 15.33, 16.66, respectively; p = 0.27). In CRPC patients treated with docetaxel, there are significant changes to the six-gene score over the course of treatment (p = 0.002), with a notable percentage decrease (-6.2%) at the 2-8 week timepoint that is not observed in patients treated with abiraterone or enzalutamide. **Conclusions:** Gene expression profiling of whole blood is influenced by the clinical state of prostate cancer as seen by differences to the six-gene score from localized to castrate resistant disease. Cytotoxic chemotherapy appears to modulate the six-gene score, something not seen with AR-directed therapies. Further investigation will be needed to understand the significance of these changes.

5047 Poster Session (Board #40), Sat, 1:15 PM-4:45 PM

Prognostic index model (PIM) for overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) without prior chemotherapy treated with abiraterone acetate (AA). *First Author: Charles J. Ryan, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA*

Background: Models that predict prognosis may aid in treatment planning for mCRPC. We previously presented a PIM for radiographic progression-free survival from the phase 3 COU-AA-302 trial in mCRPC pts without prior chemotherapy (ECC 2013, #P370). In the final analysis of COU-AA-302, AA + prednisone (P) significantly prolonged median OS vs P (34.7 mo vs 30.3 mo; HR: 0.81; 95% CI 0.70 - 0.93; p = 0.0033). Using the final analysis dataset from COU-AA-302, we developed a PIM for OS in mCRPC pts in the AA + P arm. **Methods:** The complete set of baseline data was available from 493/546 pts (90%), and formed the basis for the modeling. Accepted values for lower (LLN) and upper (ULN) limits of normal were used to dichotomize laboratory factors; other factors were dichotomized for ease of interpretation. Factors were assessed for association with OS through a univariate Cox model and used in a multivariate Cox model with a stepwise procedure. Internal validation of the predictive performance of the final model was assessed by a bootstrap resampling procedure. Model discriminatory power was estimated by the C-index. **Results:** Four factors associated with poor prognosis were included in the final model: Brief Pain Inventory 2 - 3 (HR: 1.71, p < 0.0001), lactate dehydrogenase > ULN (234 IU/L) (HR: 2.03, p < 0.0001), alkaline phosphatase > ULN (131 IU/L) (HR: 1.60, p = 0.0004), and ≥ 10 bone metastases (HR: 1.92, p < 0.0001). Pts were categorized into good (n = 296), intermediate (n = 117), and poor (n = 131) risk groups based on number of risk factors. Median OS was calculated for each group (Table). The C-index was 0.67 ± 0.016. **Conclusions:** We identified 4 readily available clinical and laboratory factors to generate a PIM for OS in mCRPC, and categorized pts into 3 distinct risk groups. If validated in an independent dataset, this PIM may be useful for estimating OS in mCRPC and designing risk-adapted treatment strategies. Clinical trial information: NCT00887198.

Number of risk factors	Median OS, months (95% CI)	HR (95% CI)[a]
0 or 1 (good) n = 296	53.6 (47.6 - not estimable)	—
2 (intermediate) n = 117	38.4 (33.7 - 45.8)	2.04 (1.57 - 2.66)
3-5 (poor) n = 131	26.6 (24.5 - 28.5)	3.77 (2.94 - 4.84)

5048 Poster Session (Board #41), Sat, 1:15 PM-4:45 PM

Association of single nucleotide polymorphisms (SNPs) in *ESR1* and *PRMT8* and response to treatment with abiraterone acetate (AA) in men with metastatic castration refractory prostate cancer (mCRPC). *First Author: Neeraj Agarwal, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Germline variations in genes involved in androgen biosynthesis and metabolic pathways may predict response to AA in men with mCRPC, serve as prognostic and predictive biomarkers, and guide towards more individualized therapy. **Methods:** 785 single nucleotide polymorphisms (SNPs) from the Illumina OmniExpress genotyping platform within the boundaries of 60 genes reported to be involved in the androgen metabolic pathway were investigated for association with time to treatment failure (TTF) in 49 Caucasian men with mCRPC undergoing treatment with AA. Cox proportional hazard analysis was employed using Gleason score as a covariate and assessing each SNP under an additive genetic model in which the number of minor alleles contributes increasing risk (or protection). **Results:** Five SNPs in *ESR1* (estradiol-binding domain of the estrogen receptor gene), and 5 SNPs in *PRMT8* (protein arginine methyl transferase 8 gene) were associated with TTF on AA therapy (p < .005) while controlling for Gleason Score (Table). **Conclusions:** SNPs in *ESR1* and *PRMT8* significantly associated with TTF on AA therapy, and may serve as predictive markers to treatment with AA. Further validation is being performed in a larger cohort of men with mCRPC.

					# cases (median TTF in months)		
Gene	Chromosome	SNP	bp position	p_value	0 rare	1 rare	2 rare
ESR1	6	rs2485209	152089768	0.0008	45(4.7)	4(1.33	NA
ESR1	6	rs12199102	152392561	0.0032	25(6.7)	20(3.9)	2(3.4)
ESR1	6	rs9341052	152416625	0.0028	27(6.7)	17(3.5)	5(3.1)
ESR1	6	rs2228480	152420095	0.0045	29(6.7)	19(3.5)	1(3.8)
ESR1	6	rs3798758	152421854	0.0014	22(7.2)	22(3.9)	5(3.1)
PRMT8	12	rs12371422	3360946	0.0000	38(5.9)	10(1.8)	1(1.1)
PRMT8	12	rs7956298	3361251	0.0001	18(9.7)	26(4.0)	5(1.6)
PRMT8	12	rs4766082	3373084	0.0004	15(9.4)	27(4.3)	7(2.8)
PRMT8	12	rs7296720	3374920	0.0003	15(9.4)	27(4.3)	6(2.5)
PRMT8	12	rs10848840	3399429	0.0001	42(4.8)	5(3.1)	2(.78)

5049 Poster Session (Board #42), Sat, 1:15 PM-4:45 PM

TERRAIN. *First Author: Simon Chowdhury, Medical Oncology Department, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom*

Background: Enzalutamide (ENZA), an androgen receptor inhibitor, improves survival and radiographic progression-free survival (rPFS) in patients (pts) with mCRPC. TERRAIN (NCT01288911) compared ENZA to bicalutamide (BIC), which is frequently added to androgen deprivation therapy upon progression in pts with mCRPC. **Methods:** Pts with mCRPC were randomized 1:1 to ENZA 160 mg/day or BIC 50 mg/day. Primary endpoint was progression-free survival (PFS), defined as time to centrally confirmed radiographic progression, skeletal-related event, initiation of new anti-neoplastic or death (any cause), whichever occurred first. Radiographic progression was also assessed by investigators. Circulating tumor cell (CTC) counts were evaluated at baseline and on treatment. Favorable conversion was defined as decline from ≥5 to <5 CTCs/7.5 mL of blood from baseline. **Results:** 375 pts were enrolled. The median time on ENZA treatment was 11.7 months and 5.8 months on BIC. PFS (primary endpoint) and rPFS outcomes are shown (Table). Among pts with measurable soft tissue disease, objective tumor response rates were 54% (38/70) with ENZA and 11% (8/71) with BIC. Favorable conversion rates at week 25 were 67% (29/43) with ENZA and 43% (16/37) with BIC. Serious adverse events (AEs) were reported for 31% of ENZA vs 23% of BIC pts. The most common (≥10%) AEs reported more frequently with ENZA than BIC were fatigue, back pain, hot flush, hypertension, diarrhea, weight decrease and pain in extremity. Grade 3 or higher cardiac AEs were observed in 5.5% of ENZA vs 2.1% of BIC pts. **Conclusions:** In TERRAIN, pts treated with ENZA had prolonged PFS and rPFS, a higher objective tumor response rate, and superior week 25 CTC results when compared to pts treated with BIC. ENZA demonstrated safety broadly consistent with its known safety profile in men with mCRPC. Clinical trial information: NCT01288911.

	ENZA (n=184)	BIC (n=191)
PFS	99 (54%)	141 (74%)
Central, # events	15.7	5.8
Median (mos)		
Investigator, # events		
Median (mos)		
	HR 0.44; P<0.0001	
	99 (54%)	146 (76%)
	15.3	5.7
	HR 0.42; P<0.0001	
rPFS	56 (30%)	69 (36%)
Central, # events	NYR	16.4
Median (mos)		
	HR 0.51	
Investigator, # events	**58 (32%)**	86 (45%)
Median (mos)	**27.6**	11.1
	HR 0.41	

5050 Poster Session (Board #43), Sat, 1:15 PM-4:45 PM

LBH589 (LBH) and bicalutamide (Bic) in castration-resistant prostate cancer (CRPC) patients (pts) progressing on second line anti-androgen (AA): NYU-08479/PCCTC. *First Author: Anna C. Ferrari, The Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY*

Background: Retrospective studies of CRPC pts resistant to 2nd-line AA indicate that progression develops within ~4 months (mo) of a 3rd-line AA treatment (tx). The histone-deacetylase inhibitor LBH decreases expression of androgen receptor (AR) mRNA, splice variants, protein and its targets in CRPC models. Combined with Bic, LBH induces a synergistic anti-proliferative response in Bic-resistant cells. Thus, by epigenetic modulation of AR alterations and restoration of AA sensitivity, LBH may delay AA-resistant CRPC progression. **Methods:** AA-resistant CRPC pts were randomized 1:1 to 3-week (wk) cycles of Bic 50 mg daily and LBH 40 mg (arm A) or 20 mg (arm B) tri-weekly 2 wks/cy. *Endpoints (EPs)*: *Primary* (1°), radiographic progression (rP)-free survival (rPFS) at 6 & 9 mo with activity declared if *>15%* by Fisher Exact Test; *Secondary* (2°), PSA response, safety and tolerability. Pts receiving ≥ 2 tx cycles evaluated for 1°EP; all pts evaluated for 2°EP. **Results:** 52 pts (28/24, arms A/B) treated. Median (range): age 69 (48-84) years, PSA 14 ng/mL (2-543), previous AA tx, 2 (1-4); 50 pts had mets (mCRPC), 33 each bone/LN. *Arm A*: Tx cycles before stop (cycles,pts): < 2, 7; 2-7, 12 (+1 ongoing); 8-12 (≥ 6 mo), 8, of which 5 completed 13-25 cycles (> 9 mo).13/28 (46%) pts had LBH dose reduction to 30-25 mg. rPFS was 40% (8/20 pts) at 6 mo (p = 0.006), 25% (5/20 pts) at 9 mo (p = 0.35); 5 pts (25%) had rP. PSA declines were: > 30%, 6 pts; > 50%,1 pt. Toxicities: Grade(G) G4 thrombocytopenia 8; G3 fatigue 2, diarrhea 2; G2 diarrhea 9, fatigue 5. *Arm B:* Tx cycles before stop (cycles, pts): < 2, 4; 2-7, 16; 8-12, 4; > 12, 2. Only 1/24 reduced LBH to15 mg. rPFS was 20% (4/20 pts) at 6 mo,10% (2/20pts) at 9 mo (p > 0.3); rP occurred in 7/20 pts (35%). PSA declines were: > 30%, 2 pts; > 50%,1 pt. Toxicities**:** G4 thrombocytopenia 1, Kaposi's 1, G3 fatigue 1, diarrhea 1; G2 diarrhea1, fatigue 6. **Conclusions:** The proportion of mCRPC pts resistant to 2nd-line AA that achieved rPFS at 6 mo was significant after tx with Bic combined with LBH 40 mg and frequent dose reductions to 30-25 mg for tolerance. LBH 20 mg was not effective. Studies combining LBH with new 2nd-line AA are planned to prevent/delay resistance. Clinical trial information: NCT00878436.

5051 Poster Session (Board #44), Sat, 1:15 PM-4:45 PM

Phase 1-2 study of progesterone receptor (PR) inhibition with extended-release (ER) onapristone (ONA) in patients (pts) with castration-resistant prostate cancer (CRPC): PK, safety and PR testing results from the dose escalation cohort. *First Author: Anuradha Jayaram, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: An urgent need exists for new therapies after progression (PD) onabiraterone (AA) and enzalutamide (ENZ). PR expression increases with castration resistance [Bonkhoff 2001]. ONA, a type-I PR antagonist, has clinical activity in other PR^{pos} cancers. An ER ONA tablet was developed to achieve continuous exposure, and an IHC companion diagnostic to detect activated PR. **Methods:** This open-label, phase 1-2 study with dose selection/expansion includes pts with: advanced CRPC, prior PD on AA or ENZ and ≤ 2 chemotherapies. Tumors are biopsied at baseline and on treatment to determine PR status. 1° endpoint for dose escalation is to define recommended phase 2 dose (RP2D). 2° endpoints include safety and PK. In stage 1a pts were randomized to 10/20 mg ONA BID. Stage 1b is currently open to enrollment (30/40/50 mg BID cohorts; 6 pts/cohort, 8 recruited to date). At the RP2D, 36 pts will be treated to confirm safety and activity. We present results of stage 1a (n = 10) and a separate biomarker validation cohort (n = 45). **Results:** Stage 1a is complete. There were no DLTs or significant LFT abnormalities at 10/20 mg BID. One pt had related G3/4 AEs: G3 nausea/anorexia. Most common related AEs were fatigue (n = 4) and anorexia (n = 3). 4 SAEs were reported, none considered related to ONA. There were no treatment discontinuations for AEs. Mean C_{max}/AUC/$t_{1/2}$ at 10 and 20 mg were 253 ng/mL, 5311 ng*h /mL, 5.98 hours and 384 ng/mL, 10240 ng*h /mL, 4.92 hours, respectively. 3 pts had paired biopsies: 1/3 pts had strong PR expression (> 50%) pre-treatment and no PR expression after 19 days of ONA. In the biomarker cohort, we tested pt-matched therapy-naïve (TN) and CRPC specimens and identified PR (> 1% cells) in 15 pts (33%: 5 CRPC and 10 TN). No TN but 4/45 CRPC (9%) biopsies had strong PR expression (> 50% cells). **Conclusions:** CRPC expresses PR. The IHC diagnostic method will be used for selective enrichment. The 1st stage of the study concluded with no DLTs, permitting escalation. Randomization now includes the 3 higher doses. PK appears dose proportional. Clinical trial information: NCT02049190.

5052 Poster Session (Board #45), Sat, 1:15 PM-4:45 PM

Disease burden and outcome in metastatic hormone sensitive prostate cancer (mHSPC). *First Author: Laurence Albiges, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Patients (Pts) with higher burden of mHSPC have shorter OS but there is no uniform definition of high (H) vs low (L) volume of disease (VD). **Methods:** Pts with mHSPC with known VD were analyzed [2 trials of ADT vs ADT + Docetaxel (D) and the Dana-Farber Cancer Institute Gelb center database of pts treated with ADT]. OS (95% CI) was calculated from randomisation for GETUG and E3805, and from initiation of ADT at the Gelb center, until death or censored at last follow-up. E3805 HVD defined as visceral metastases and/or 4 or more bone metastases (BM) with at least 1 beyond the pelvis/vertebrae. **Results:** 1,528 of 1,603 pts had data available to accurately categorize HVD/LVD. A gradient in outcome is noted for increasing BM burden. OS variability is seen in the 4-9 BM group and OS across the 3 cohorts. The E3805 composite definition consistently dichotomized the 5 groups (HR for HVD/LVD ≥ 2 for risk of death). **Conclusions:** A composite definition of HVD consistently dichotomized the 5 groups. Variability between cohorts may be due to different pts characteristics and CRPC therapy.

		GETUG 15		E 3805		Gelb Center
Median follow up (yrs)		6.9		2.4		5.8
		ADT N=193	**ADT+D N=192**	**ADT N=393**	**ADT+D N=397**	**ADT N=428**
Absence of localized treatment		75%	67%	73.0%	72.8%	43.9%
				Median OS (mos)		
Overall		46.5 (39.1-60.6)	60.9 (46.1-71.4)	44.0 (34.4-49.1)	57.6 (49.1-72.8)	58.4 (50.3-71.2)
Visceral mets		n=23 32.0 (23.2-66.9)	n=28 27.1 (21.9-71.4)	n=66 27.5 (19.8-42.3)	n=57 49.2 (40.3-52.7)	n=23 64.4 (21.6-NR)
# of BM (no visceral mets)	All	n=137 46.1 (37.2-54.5)	n=132 51.2 (39.8-70.5)	n=326 47.3 (36.7-52.8)	n=340 57.6 (48.8-72.8)	n=283 53.1 (46.8-62.2)
	N<4	n=60 66.1 (40.9-NR)	n=61 NR (60.9-NR)	N/A	N/A	n=108 86.4 (68.8-104.8)
	[4-9]	n=36 36.7 (30.1-62.2)	n=43 42.5 29.9-70.5	n=101 34.4 (27.2-48.1)	n=123 58.1 (38.4-72.8)	n=40 79.8 (45.4-121.6)
	N≥10	n=50 30.4 (26.3-42.2)	n=47 30.5 (21.1-46.1)	n=75 38.0 (25.8-62.6)	n=74 38.4 (25.6-57.6)	n=112 44.4 (34.4-47.7)
E3805-HVD		n=91 35.1 (29.9-44.2)	n=92 39.0 (28.0-52.6)	n=250 32.2 (28.6-39.5)	n=263 49.2 (38.4-58.1)	n=156 48.6 (42.5-60.0)
E3805-LVD		n=102 NR (61.8-NR)	n=100 83.1 (69.5-NR)	n=143 NR (49.1-NR)	n=134 NR (NR-NR)	n=197 92.4 (71.2-149.8)
Hazard Ratio (HVD/LVD)		2.5 (1.9-4.1)	2.8 (1.7-3.8)	2.96 (1.9-4.6)	2.4 (1.4-4.0)	2.1 (1.5-2.8)

5053 Poster Session (Board #46), Sat, 1:15 PM-4:45 PM

IMAAGEN trial update: Effect of abiraterone acetate and low dose prednisone on PSA and radiographic disease progression in patients with non-metastatic castration-resistant prostate cancer. *First Author: Charles J. Ryan, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA*

Background: Abiraterone acetate (AA) 1000mg, in combination with prednisone (P), 10mg daily is indicated for the treatment of patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). IMAAGEN is a phase II, multi-center study with a primary endpoint that evaluated the ability of AA plus 5 mg of prednisone (AA+5) to decrease PSA levels in pts with nmCRPC and a rising PSA; primary results have been reported earlier[1]. Herein we report updated results on secondary endpoints and safety from the IMAAGEN study (Nov 3, 2014 database cut-off date). **Methods:** All enrolled pts had high risk non-metastatic castration resistant prostate cancer (nmCRPC): PSA value $\geq$ 10ng/mL or PSA doubling time $\leq$ 10 months at screening. Pts received AA+5 daily; each treatment cycle = 28 days. Reported endpoints include time to PSA progression, time to radiographic progressive disease, and safety. **Results:** At the time of the data cutoff, 62 (47.3%) of the 131 patients enrolled in IMAAGEN remained on treatment in the study. The median duration of exposure was 17.9 months (range 0.1 – 40.7 months). Median time to PSA progression was 28.7 months (95% CI 21.2, NE). There were 21 confirmed radiographic progression events. The median time to radiographic progressive disease was not reached. 95.4% of pts had an adverse event (AE) (54.9% had a Grade 3 or higher) and 38.2% had a serious AE (SAE) with 35.9% having an SAE of Grade 3 or higher. 13.0% of pts had AEs resulting in discontinuation of study treatment. Four pts had AEs resulting in death (coronary artery disease, myocardial infarction, acute respiratory failure, and pneumonia). **Conclusions:** Treatment of high risk nmCRPC patients with AA+5 resulted in a median time to PSA progression of 28.7 months. The median time to radiographic disease progression was not reached. The safety profile of AA+5 reported in this IMAAGEN trial update is consistent with the safety profile from previously reported studies of abiraterone acetate 1000mg in combination with either 5mg or 10mg prednisone. [1]ASCO 2014 IMAAGEN primary endpoint poster presentation Clinical trial information: NCT 01314118.

5054 Poster Session (Board #47), Sat, 1:15 PM-4:45 PM

Tumor-directed PET imaging of metastases in metastatic castration-resistant prostate cancer (mCRPC) using Zr-89 labeled antiprostate-specific membrane antigen (PSMA) antibody J591. *First Author: Jarett L. Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There is no standard imaging (SI) modality that specifically and accurately images prostate cancer (PC) metastases, hampering prognostication and response assessment. J591 is a humanized antibody that targets the external domain of PSMA. We have previously reported on the feasibility, PK and biodistribution of ^{89}Zr-J591 in 10 patients (pts) (Pandit-Taskar et al, Eur J Nuc Med Img 2014). We now report on the targeting/accuracy in 50 pts with mCRPC. **Methods:** Following standard CT/MRI, bone scan (BS), and FDG PET imaging, 5 mCi of ^{89}Zr-J591 was administered IV. ^{89}Zr-J591 was imaged 6-8 days after injection. Positive (pos) scan findings were confirmed, where possible, with biopsies (bxs) in the following preference: concordant ^{89}Zr-J591 and FDG pos, ^{89}Zr-J591 and FDG mismatch, and a mismatch between SI and any PET. **Results:** Imaging: A total of 703 lesions in 50 pts were identified using all imaging modalities. *Bone*:538 total bone lesions were detected. 491(91%) lesions were present on J591 of which 99 were only evident by J591. BS identified 339 (63%), CT 301 (56%), and FDG 207 (38%). *Soft Tissue:* 165 total soft tissue lesions were detected. 90 (55%) were seen on J591 of which 17 were only evident by J591. CT identified 124 (75%) and FDG 88 (53%). Pathology:46 bx's were evaluable (21 bone, 25 soft tissue) in 34 pts. Of the unique J591 lesions bx'd, 5/7 were pos for PC. *Bone*: We bx'd 19 J591 pos lesions and 2 J591 neg sites. Overall, path concordance with J591 was: 89% true pos, 100% true neg, 11% false pos, and 0% false neg. *Soft tissue*: We bx'd 16 J591 pos lesions and 9 J591 neg sites. Of these, we found 88% true pos, 11% true neg, 13% false pos, and 89% false neg. **Conclusions:** J591 PET identifies additional disease in bone not seen using other imaging modalities. These lesions are highly likely to correspond to disease by bx. The data also continues to affirm that J591 appears to be superior at identifying bony disease than soft tissue lesions. Clinical trial information: NCT01543659.

5055 Poster Session (Board #49), Sat, 1:15 PM-4:45 PM

Molecular characterization of clinically defined aggressive variant prostate cancer (AVPCa) in prospectively collected tissues and corresponding patient derived xenografts (PDX). *First Author: Ana Aparicio, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: AVPCa shares clinical features with small cell carcinoma (SCC) such as resistance to androgen signaling inhibition and frequent visceral metastases. A prospective clinical trial of platinum doublets (NCT00514540; Aparicio, Clin Can Res 2013;19) gave confidence that clinically defined AVPCa also shares chemotherapy sensitivity with SCC, irrespective of morphology. Here we screen for links between the clinical phenotype and molecular profile of AVPCa and corresponding PDX. **Methods:** 59 PC samples from 40 men (10 with SCC) registered to NCT00514540, and 8 PDX from 6 of them, were stained for RB, p53, AR, NKX3-1, ASCL1, AURKA, UBE2C and Ki67. We examined relationships between markers. We subjected DNA from 36 of the PC samples and all PDX to OncoScan to determine copy number alterations (CNA). We compared findings to reported TCGA data. We examined associated and downstream molecular events in the PDX. **Results:** The 40 men with tissues available for study were similar to remaining NCT00514540 patients except for higher ECOG PS and LDH values. 67% stained negative for RB and 32% for AR. Nuclear (N)-AR showed strong positive correlations with RB, NKX3-1, N-AURKA, as did p53 with N-UBE2C and Ki67 with UBE2C. Most common CNA across morphologies were 8q24 amplification, PTEN loss (largely gene-specific) and RB1 loss (often regional). Clustering segregated samples by CNA rate and associated with Tp53 mutational status but not histology. CNA in RB1, PTEN and MYC carried the highest weight in linear discriminant analyses distinguishing AVPCa from TCGA samples. Seven of 8 PDX bore Tp53 mutations. 2 of 3 RB-positive PDX had high levels of hyperphosphorylated RB. Only AR-negative PDX expressed pro-neural transcription factors, albeit heterogeneously. **Conclusions:** Clinically defined AVPCa of varied morphologies share molecular profile with SCC and are characterized by combined alterations in RB, p53 and/or PTEN. Analysis of corresponding PDX contributed biological insight. The ability of this signature to distinguish AVPCa is being evaluated in an independent prospective clinical trial (Abstract #152334).

5056 Poster Session (Board #50), Sat, 1:15 PM-4:45 PM

A molecular and clinico-pathological model for predicting abiraterone acetate/prednisone (AA/P) efficacy in metastatic castrate resistant prostate cancer (mCRPC). *First Author: Manish Kohli, Mayo Clinic, Rochester, MN, Rochester, MN*

Background: There are no known markers for predicting AA/P efficacy in chemo-naïve mCRPC stage. We explored a model for predicting the 12-week efficacy outcome after initiation of AA/P in a prospective clinical trial (NCT# 01953640). **Methods:** mCRPC patients initiating AA/P underwent biopsy of metastases at baseline (pre AA/P) and at week 12. Somatic whole exome DNA sequencing; gene expression for AR full length (ARFL) and splice variants (ARVs) was performed of baseline metastases. Composite progression on AA/P at week 12, (primary endpoint) was evaluated with PSA, RECIST, bone scan and symptoms (based on PCWG2 criteria). Candidate molecular factors (RNA expression of ARFL, ARV3, ARV7, ARV9, ARV23, ARV45, Chromogranin-A (CGA)) were explored in a multivariate Cox Proportional Hazard Regression (CPHR) model. Additionally, PSA/testosterone levels, Gleason Score (GS:2-6;7;8-10) at initial diagnosis; time from starting hormone therapy to mCRPC stage (years), serum CGA levels were also included. A final CPHR model fitted only those factors which exceeded an entry threshold in univariate analysis or were considered clinically relevant. **Results:** Between 6/2013 and 11/2014, 56/70 patients enrolled had disease assessed at the 12-week time point. The CPHR model includes 56 patients with complete sequencing and 12 week clinical outcomes. The median follow up for the cohort was 170 days (41-502 days). Progression at 12-weeks was observed in 23/56 patients. The final CPHR model included baseline expression of ARV45 (HR = 13.107, p-value = 0.017); CGA levels (HR = 0.998, p-value = 0.004); time from hormone therapy to mCRPC stage (HR = 0.782, p-value = 0.008); GS at initial diagnosis (HR = 0.004, p-value $<$ 0.001 for GS group 7 and HR = 0.008 p-value $<$ 0.001 for GS group 8-10) and ARFL, ARV3, ARV7, ARV9, ARV23. A C-statistic for the model was observed at 0.76 with an adjusted R^2 of 0.47 (likelihood ratio p-value $<$ 0.001). **Conclusions:** Clinical prediction rules are needed for developing precision medicine in mCRPC. An initial attempt to incorporate molecular and clinico-pathological factors appears feasible. Evaluation for model stability remains ongoing. Clinical trial information: NCT# 01953640.

5057 Poster Session (Board #51), Sat, 1:15 PM-4:45 PM

Validation of correlation of RECIST changes with survival in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Gregory Russell Pond, Ontario Clinical Oncology Group (OCOG), Hamilton, ON, Canada*

Background: In patients (pts) with mCRPC receiving chemotherapy, measurable disease response by World Health Organization criteria is prognostic for overall survival (OS). We now explored the association of changes in measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) with OS. **Methods:** Data from the control arm (n = 612) of the VENICE trial receiving docetaxel, prednisone and placebo (DPP) were available. Data on baseline clinical variables and outcomes were obtained. Cox proportional hazards regression was used to evaluate the prognostic ability of RECIST changes adjusting for known factors for OS using a 90-day landmark analysis. The association was validated using 388 patients in the DPP arm of the MAINSAIL trial who had RECIST measurements prior to day 90 and survival beyond day 90. **Results:** 363 pts in VENICE had measurable lesions, of whom 296 were evaluable for landmark analysis. 28 (9.5%) had progressive disease (PD) prior to day 90, while 58 (19.6%) had unconfirmed partial response (PR). In a multivariable analysis, the hazard ratio (HR) for OS for pts with PR was 0.64 (95% CI 0.42 – 0.99, $P = 0.045$) compared to those without PR, and 1.78 (95% CI 1.07 – 2.95, $P = 0.026$) for those with PD compared to those without PD. PD remained significant (HR = 1.85, 95% CI 1.10-3.12, $P = 0.020$) after adjusting for PSA changes, but PR was not ($P = 0.14$). The association of PR (HR 0.51, 95% CI = 0.22-1.18, p = 0.12) and PD (HR = 3.51, 95% CI 1.92-6.43, $p < 0.001$) with OS was externally validated in 388 pts in MAINSAIL who had measurable disease. After adjusting for PSA changes, PD was associated with poor OS (HR = 2.36, 95% CI 1.11-5.04, p = 0.026), but PR was not (p = 0.15). **Conclusions:** In men with mCRPC receiving first-line docetaxel-based therapy, RECIST changes within 90 days are associated with OS. Given the frequent detection of measurable disease with current imaging and the unclear association of PSA and bone scan changes with outcomes in the setting of new agents, the accrual of patients with measurable tumors in phase II trials to assess RECIST changes may provide a more objective signal of efficacy of new agents.

5058 Poster Session (Board #52), Sat, 1:15 PM-4:45 PM

Development of an imaging approach to detect splice variants of androgen receptor in prostate cancer. *First Author: Yusuke Imamura, Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada*

Background: Resistance to therapies that target androgen receptor (AR) ligand-binding domain (LBD) in prostate cancer patients may be due to expression of constitutively active AR splice variants that lack LBD. EPI small molecules bind to activation function-1 (AF-1) in the AR amino-terminal domain (NTD). Development of a radiolabeled analogue, ^{123}I-EPI, may be useful for imaging prostate cancer using single-photon emission computed tomography (SPECT). Currently AR is imaged with positron emission tomography with 16β-[^{18}F]-fluoro-5α dihydrotestosterone (^{18}F-FDHT) that binds to AR LBD. ^{18}F-FDHT cannot detect AR splice variants lacking LBD. Our approach would employ sequential imaging with ^{18}F-FDHT to detect solely full-length (fl)-AR and ^{123}I-EPI to detect NTD of both fl-AR and variant AR. Discordant distribution or level of uptake between ^{18}F-FDHT and ^{123}I-EPI may reveal expression of AR splice variants lacking LBD. **Methods:** Specific activity against AR by I-EPI was confirmed in cells using reporter gene constructs for AR and related steroid hormone receptors. Binding experiments were done using ^{123}I-EPI with recombinant AF-1 and fl-AR proteins, as well as to endogenous fl-AR and variant AR in cells. Evaluation of ^{123}I-EPI in whole-body distribution included dosimetry in xenografts by small animal SPECT imaging; and temporal evaluation of ^{123}I-EPI uptake and clearance by quantifying ^{123}I in harvested organs. **Results:** In cell-based assays, I-EPI was specific for AR and blocked the activity of an AR-driven reporter, while having no effect on transcriptional activities of other steroid hormone receptors. ^{123}I-EPI covalently binds specifically to AR in living cells and to recombinant fl-AR and AR AF-1. Whole body SPECT imaging showed preferential uptake in LNCaP95 human prostate cancer xenografts that express AR while negligible uptake was observed in PC3 xenografts that lack functional AR. **Conclusions:** An AR NTD-targeted molecular imaging probe such as ^{123}I-EPI may be useful to select patients for subsequent antiandrogen therapies, monitor treatment response, and provide insight into the role of all AR species in resistance mechanisms.

5059 Poster Session (Board #53), Sat, 1:15 PM-4:45 PM

Tissue-based genomics to augment post-prostatectomy risk stratification in a natural history cohort. *First Author: Ashley Ross, The Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Genomics has provided insight into the underpinnings of lethal prostate cancer and led to the development and clinical use of RNA expression based gene signatures. We performed genome wide expression profiling on tissue from a large natural history cohort of at risk men undergoing radical prostatectomy (RP). **Methods:** In an IRB approved study, we utilized a case-cohort design to identify 356 intermediate and high risk men who underwent RP and had no further treatment until the time of metastasis. RP specimens were regraded by 2005 ISUP criteria and index lesions were sampled. RNA was prepared, labelled and hybridized to Human Exon 1.0 ST microarrays from which expression signatures were analyzed. The study followed REMARK guidelines for prospective blinded evaluation and analysis of prognostic biomarkers. **Results:** Microarray quality RNA was obtained from 260 men (99 of whom metastasized) with a median follow up of 9 years (IQR 6-12). 34 gene signatures were evaluated, including 3 based on commercially available assays (genomic classifier [GC, Decipher], microarray derived [md]-CCP, and md-GPS). GC provided the highest c-index to predict metastasis free survival at 10 years post-RP (0.76). Cumulative incidence of metastasis among men with low (< 0.45), intermediate (0.45-0.6) and high (> 0.6) GC scores was 12, 31 and 47% respectively at 5 years post-RP ($p < 0.001$). GC was independently prognostic of metastasis on multivariable analysis. Stratification by GC was most notable among nomogram predicted intermediate risk men. For instance, among men with CAPRA-S score of 3-5, 10% with low GC scores would develop metastasis compared to 27% among those with high scores. Addition of expression signatures from other CLIA certified tests (md-CCP or md-GPS) or from the next best performing expression signature (md-Penney, c-index 0.74) did not improve the performance of the GC. **Conclusions:** Genomic expression signatures stratify metastatic outcomes and provide additional prognostic information in a natural history cohort of men undergoing RP. Of 34 expression signatures analyzed, GC had optimal performance and captured prognostic information provided via analysis of other signatures.

5060 Poster Session (Board #54), Sat, 1:15 PM-4:45 PM

Evaluation of the contribution of individual gene groups to a 17-gene prognostic prostate cancer signature. *First Author: Dejan Knezevic, Genomic Health, Inc., Redwood City, CA*

Background: A 17-gene biopsy-based RT-PCR assay (Onco*type* DX® Prostate Assay) has been validated as a predictor of adverse pathology and biochemical recurrence (BCR) in clinically very low to intermediate-risk prostate cancer patients. The assay measures expression of 12 cancer and 5 reference genes that are combined to calculate a Genomic Prostate Score (GPS; scaled 0-100), providing a biologic measure of tumor aggressiveness. The cancer genes represent four biological pathways: androgen signaling, stromal response, cellular organization and proliferation. We examined the effects of variation in quantitative expression of individual gene groups on GPS results and prediction of clinical risk. **Methods:** The first 3,500 tumor specimens processed in the Genomic Health Inc.'s reference laboratory were included. Expression of individual genes was measured and the expression of the four gene groups and GPS calculated. For each gene group, GPS of patients with the lowest 5% expression levels were contrasted with GPS of patients with highest 5% expression levels. **Results:** Percentages of NCCN very low, low and intermediate patients were 28%, 37%, 30%; median age was 65. Mean and median GPS were 24.6 and 23 (range 0-90). Individual gene groups exhibited wide expression ranges (e.g. proliferation-16-fold difference (FD) vs. cellular organization > 8000 FD). Large differences in expression of each gene group were reflected in GPS values and, based on a prior clinical validation study, translate into large differences in BCR risk (Table). **Conclusions:** Each of the four gene groups show large variations in expression, meaningfully affect the GPS, and contribute to the prediction of PCa aggressiveness.

Gene groups	Median GPS for lowest 5% of expression (1st, 3rd quartiles)	Predicted 5-year BCR Risk for median GPS for lowest 5% of expression [95% CI]	Median GPS for highest 5% of expression (1st, 3rd quartiles)	Predicted 5-year BCR Risk for median GPS for highest 5% of expression [95% CI]
Stromal	12 (8, 19)	6% [3%, 10%]	43 (34, 53)	26% [20%, 33%]
Cell Organization	37 (27, 46)	20% [15%, 25%]	21 (15, 27)	9% [6%, 13%]
Androgen	50 (44, 58)	36% [27%, 46%]	9 (5, 13)	5% [3%, 9%]
Proliferation	16 (11, 22)	7% [4%, 11%]	35 (26, 43)	18% [14%, 23%]

5061 Poster Session (Board #55), Sat, 1:15 PM-4:45 PM

Effects of preoperative abiraterone acetate (AA) plus enzalutamide (E) and leuprolide acetate (LHRHa) versus AA and LHRHa in localized high-risk prostate cancer (LHRPC). *First Author: Eleni Efstathiou, Alexandra General Hospital of Athens, Oncology Department, Department of Clinical Therapeutics, University of Athens, Athens, Greece*

Background: High degree of heterogeneity in cytoreduction has been observed in LHRPC following AA+LHRHa and LHRHa (Taplin et al, *J Clin Oncol* 2014;32:3705; Efstathiou et al, *J Clin Oncol*2012:30 (suppl; abs 4556). Rationale exists for AA+E combination and promising efficacy is reported in mCRPC. This study aims to determine effects of AA+E vs AA and modulation of androgen signaling in LHRPC. **Methods:** Single-institution preoperative study of 24 wks of 1 g AA + 160 mg E + 5 mg prednisone (P) QD + LHRHa (Arm A) vs AA/P+LHRHa (Arm B) (randomized 2:1) in LHRPC pts (clinical stage T1c/T2; biopsy Gleason score ≥ 8, or ≥ T2b with Gleason ≥ 7 and PSA > 10 ng/mL). Safety and treatment effect on pathology stage, androgen metabolites, cellular density (% epithelial component of tumor volume), and link between molecular markers (by IHC) with clinical, pathology, and cellular response were assessed. **Results:** Study accrued 66 pts; 39 completed 24 wks therapy and had robot-assisted laparoscopic prostatectomy. Preliminary observations in evaluable pts: no perioperative ≥ Gr 3 adverse events (AEs); on-treatment Gr 3 AEs: liver function test elevation (7 Arm A, 2 Arm B), hypertension (5 Arm A, 1 Arm B), hypokalemia (1 Arm A), cognitive disturbance (1 Arm A), pulmonary embolism (1 Arm A), fatigue (1 Arm A). Fatigue Gr 1/2 in 38/55 evaluable pts (29/38 [76%] Arm A and 9/17 [53%] Arm B). Preoperative PSA was ≤ 0.1 ng/mL in 23/26 (89%) Arm A pts vs 10/11 (91%) Arm B pts; (p = ns). To date pathologic downstaging (≤ ypT2N0) occurred in 11/27 (41%) in Arm A vs 7/12 (58%) in Arm B (p = ns); pCR (2 Arm A, 1 Arm B). Tumors segregated by low (≤ 30%) (range 0-30%, median 5%) vs high (≥ 45%) (range 45-80%, median 55%) cellular density; low density in 63% Arm A and 77% Arm B. Preoperative testosterone was undetectable in 33/39; when detectable (range 1-10 pg/mL). Tumors with pathology stage ≤ ypT2N0 had higher AR-N terminal expression (85% vs 58% and AR-C/AR-N ratio; p = 0.008). **Conclusions:** Tumor cytoreduction is dichotomised despite universal serum PSA decline at 6 ms preoperative treatment. Planned Comprehensive molecular characterization of androgen biosynthesis will inform marker-driven LHRPC treatment strategy. Clinical trial information: NCT01946165.

5062 Poster Session (Board #56), Sat, 1:15 PM-4:45 PM

Genomic characterization of primary and metastatic prostate cancer (PC) using a targeted next-generation sequencing assay. *First Author: Wassim Abida, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Genomic alterations in PC have been described across the disease continuum, creating opportunities for selective clinical trial enrollment of patients (pts) with high-risk or metastatic disease based on their tumor profile. MSK-IMPACT is an exon capture-based sequencing assay performed in a CLIA-certified laboratory that targets 341 cancer-associated genes, many of which are potential drug targets. We assessed mutations and copy number alterations (CNAs) in primary and metastatic samples from untreated, hormone-treated and castration resistant pts. **Methods:** Pts with localized and metastatic PC were enrolled on an IRB-approved protocol for tumor genomic profiling. Fixed tumor and matched germline samples were subjected to DNA sequencing analysis using MSK-IMPACT for the identification of somatic mutations and CNAs. **Results:** 135 tumor samples from 124 pts were successfully sequenced, including 83 primary and 52 metastatic tumors. Metastatic sites include LN (22), bone (12), liver (6), lung (2) and other soft tissue (10). 5 tumors were pathologically classified as neuroendocrine. Common alterations in the metastatic tumors include *TP53* deletion/mutation (44%), *AR* amplification/mutation (38%), *PTEN* deletion/mutation (29%), *RB1* deletion/mutation (17%), *BRCA2* deletion/mutation (13%), *FOXA1* mutation (12%) and *SPOP* mutation (8%). Common alterations in the primary tumors (67% with Gleason > 7) include *TP53* mutation (20%), *SPOP* mutation (11%) and *PTEN* deletion/mutation (10%). Among metastatic samples, tumors from pts with castration resistant disease have higher CNA burden when compared to tumors from untreated or castration-sensitive pts (0.30 vs. 0.19 fraction genome altered, p < 0.05, unpaired *t*-test) as well as higher rates of *AR* amplification/mutation (50% vs. 7%, p < 0.01, Fisher's exact test). **Conclusions:** Genomic profiling of primary and metastatic prostate tumors is feasible with the targeted MSK-IMPACT assay and recapitulates findings from broader whole exome-based studies. This will facilitate genomic biomarker development and the rational selection of single-agent or combination therapy trials for pts with high-risk and metastatic disease.

5063 Poster Session (Board #57), Sat, 1:15 PM-4:45 PM

Ra-223 experience in pretreated patients: EAP setting. *First Author: A. Oliver Sartor, Tulane Cancer Center, New Orleans, LA*

Background: The early-access program aimed to monitor acute and long-term Ra-223 safety. Herein the number of Ra-223 cycles was examined in relation to prior therapy with abiraterone (abi) and/or enzalutamide (enza). These agents were not approved at the time of the ALSYMPCA trial, the basis for Ra-223 approval. **Methods:** Symptomatic bone metastatic CRPC patients (pts) and no visceral mets were enrolled in the US if they were ineligible for (or refused) docetaxel (Doc), or had prior Doc. Ra-223 at 50 kBq/kg IV q 4weeks was planned for 6 cycles concomitant with "standard of care". We assessed the baseline characteristics and number of cycles administered in pts naïve to, with prior use of either/or, and abi + enza. **Results:** Of 184 pts; 39 had prior abi + enza; 65 had abi or enza; 47 were naive. Notable differences in baseline demographics were seen in the prior abi + enza group with higher baseline median values for PSA, alk phos, and a higher % of pts with prior Doc (85%). The abi + enza pre-treated group had a lower median number of cycles (4; ALSYMPCA 6) and a significantly lower percentage of pts (36%; P=0.0115) completed > 4 cycles. Naïve pts had the lowest % of prior DOC (28%), the highest median number of cycles (n=6) and the highest percentage (62%) of pts completing > 4 cycles. 57%, 43%, and 31% of pts had 6 cycles in the naïve, either/or, and abi + enza group, respectively. The number of pts receiving all 6 cycles in the naïve compared with prior abi + enza group was significant (P=0.0134). **Conclusions:** A trend was observed, pts with less prior treatment completed more cycles of Ra-223 treatment. Using Ra-223 later in the current sequencing paradigm may limit the number of pts able to receive 6 cycles of treatment, as recommended in the Ra-223 label. Clinical trial information: NCT01516762.

	EAP								
	N=184								
	Prior Abi + Enza			Prior Abi or Enza			No Prior Abi or Enza		
	No=145	Yes=39		No=119	Yes=65		No=137	Yes=47	
Age, median, yrs	70	70		69	72		70	70	
Weight, median, kg	87	83		87	84		85	88	
ECOG, ≤ 1, %	90	90		92	86		90	89	
Baseline PSA, median	121	270		129	150		161	109	
Baseline Alk phos, median	139	223		159	147		159	120	
Total ALP ≥220 U/L, %	25	51		32	28		34	19	
Prior docetaxel, yes, %	53	85		57	65		71	28	
Median number of cycles	5	4		5	5		5	6	
% receiving ≤ 4 cycles	41	64	0.0115*	45	48	0.7634*	49	38	0.2082*
% receiving > 4 cycles	59	36		55	52		51	62	
% receiving 6 cycles	48	31	0.0604*	45	43	0.8487*	39	57	0.0317*

*Chi-square.

5064 Poster Session (Board #58), Sat, 1:15 PM-4:45 PM

Interim performance of a non-DRE urine exosome gene signature to predict Gleason ≥7 prostate cancer on initial prostate needle biopsy from patients enrolled in a prospective observational trial. *First Author: Michael J. Donovan, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: PSA and DRE are used for biopsy decisions; however, limited sensitivity and specificity have resulted in the over-diagnosis and treatment of low risk prostate cancer (PCa). Non-invasive screening tools that add predictive value for identifying high-grade, Gleason score (GS) ≥ 7, should impact the current paradigm. We sought to evaluate performance of a gene signature that differentiated GS7+ from GS6 + benign disease by evaluating patients with first-time biopsy results and gray zone PSA (4-10ng/mL) from an ongoing prospective clinical trial. **Methods:** 499 sequentially obtained first-catch non-DRE urine specimens (standard cups) from 15 urology practices were collected from patients presenting for biopsy. Exosomes were isolated and RNA extraction performed. RT-qPCR RNA copy numbers of ERG and PCA3, normalized to SPDEF, were measured to generate a three-gene signature, defined to yield a score discriminating GS7+ vs. GS6 and benign lesions, evaluating NPV, Sensitivity and Specificity relative to standard of care. **Results:** Urine samples from 205 men of 499 total (PSA 4-10 ng/mL, first biopsy, < 50 mL donation volume; median age 64 years, median PSA 5.46 ng/mL, 80% negative DRE, 74% no family history, 68% Caucasian), were evaluated. With 50% and 33% prevalence of positive biopsy for any cancer or GS7+ disease, respectively, a dichotomous gene signature + standard of care demonstrated good clinical performance in predicting biopsy result. For GS7+, with a 90% fixed sensitivity, the NPV and PPV were 92% and 48%, respectively compared to 79% and 35% for the prostate cancer prevention trial risk calculator (PCPTRC). A continuous score alone had an AUC of 0.74 for discriminating GS7+ from GS6 and benign disease and the results were significantly better than PCPTRC, AUC 0.64(p = 0.026). **Conclusions:** We confirmed a novel, non-invasive urine exosome gene signature demonstrated independent, negative predictive value for the diagnosis of GS7+ from first biopsy patients with 'gray zone' PSA. Its use in the biopsy decision process should result in fewer prostate biopsies pending completion of the prospective trial.

5065 Poster Session (Board #59), Sat, 1:15 PM-4:45 PM

Contemporary national trends of prostate cancer screening among privately insured patients in the United States. *First Author: Simon P. Kim, Yale University, New Haven, CT*

Background: Little is known about the degree to which prostate cancer (PC) screening with prostate-specific antigen (PSA) testing has changed in the face of recent clinical research data and the Grade D against screening from the U.S. Preventive Services Task Force. We used a large private health insurance database to determine the national trends of PSA screening and to investigate which patient characteristics are associated with PSA testing. **Methods:** Using Optum Labs Data Warehouse, a large private health insurance claims database, we identified males age 40-80 years who underwent PC screening from 2008 to 2013. The primary outcome was use of PSA testing among a privately insured population-based cohort. Demographic covariates included age, census region, race, education level and household income range. The Charlson/Deyo comorbidity index was calculated to assess comorbidity burden. Rates were calculated based on member-years and reported per 1,000 member-years. **Results:** Among 11.6 million eligible enrollees, we identified 2.9 million (25%) men who underwent PSA screening from 2008 to 2013 ($>$ 800,000 screened per year). The majority of the screened population were white males, age 50-59 years residing in the Southern census region. The rate of men undergoing PSA screening remained stable from 190.4 per 1,000 member-years in 2008 to 196.4 in 2013 ($p = 0.66$). Among enrollees aged 50 to 74 years old, PSA screening rates were relatively stable. However, enrollees who were $>$ 75 years old had a marked decrease in PSA screening from 201.5 to 124.1 per 1,000 member-years from 2008 to 2013 ($p = 0.04$). PSA screening rates did not vary by racial groups or geographic region over time. **Conclusions:** In this large population-based cohort of privately insured men, we found little effect of new data and change in clinical practice guidelines on the overall rate of PSA screening. However, older men ($>$ 75) showed a significant reduction in screening over time.

5066 Poster Session (Board #60), Sat, 1:15 PM-4:45 PM

Safety and efficacy of everolimus (E), bevacizumab (B), and docetaxel (D) for castration resistant prostate cancer (CRPC). *First Author: Mitchell E. Gross, University of Southern California, Beverly Hills, CA*

Safety and efficacy of Everolimus (E), bevacizumab (B), and docetaxel (D) for castration resistant prostate cancer (CRPC) Background: Based on studies suggesting co-targeting mTOR and angiogenic pathways potentiates chemotherapy, we studied combining mTOR (E, formerly RAD001) and VEGF (B) inhibition with D in CRPC. **Methods:** Eligible patients (pts) had progressive, metastatic, chemo-naive CRPC. D+B was given IV day 1 with E PO daily on a 21 d cycle at level 1 (D 75 mg/m^2, E 2.5 mg), level 2 (D 75 mg/m^2, E 5 mg), or level 3 (D 65 mg/m^2, E 5 mg). B 15 mg/kg was given at all levels. B/E without D (B/E-D) was allowed after $\geq$ 6 cycles. Prophylactic growth factor support was allowed only after cycle 1, if required The primary endpoint was response, defined as maximal confirmed PSA decline and RECIST criteria. **Results:** Dose level 1 was identified as the recommended phase 2 dose (Gross et al, 2009) thus 37 of 43 patients received level 1 dosing. Median age was 65 (50-79) years, PSA 76.6 (0-1847) ng/mL, alkaline phosphatase 114 (37-768) U/L, hemoglobin 12.5 (0.0-15.7) g/dl. Metastatic sites included: bone 38 (88%), lymph nodes 19 (44%), and viscera in 8 (19%) pts. Median cycles delivered was 10 (3-21) which included B/E-D maintenance in 24 pts for 3 (1-10) cycles. Maximal PSA decline $\geq$ 30% and $\geq$ 50% was achieved in 33 (79%) and 31 (74%) of pts. RECIST responses were assessable in 25 pts with best response complete or partial in 20 (80%) of pts. Hematologic toxicities were the most common treatment related grade $\geq$ 3 adverse events including: febrile neutropenia 12 (28%), lymphopenia 12 (28%), leukocytes 10 (23%), neutrophils 9 (21%), and hemoglobin 2 (5%). Non-hematologic grade $\geq$ 3 AEs included: hypertension 8 (19%), fatigue 3 (7%), pneumonia 3 (7%), and mucositis 4 (5%). There was 1 treatment related death due to neutropenic fever and pneumonia on a pt treated at dose level 3 despite dose modifications and prophylactic growth factor support. **Conclusions:** The combination of E/B/D demonstrates significant clinical activity against mCRPC which must be balanced against hematologic and other toxicities. Correlative biomarker studies are ongoing to better define patient subsets which may be more likely to benefit from this therapy. Clinical trial information: NCT00574769.

5067 Poster Session (Board #61), Sat, 1:15 PM-4:45 PM

Detecting predictive androgen receptor modifications in circulating prostate cancer cells. *First Author: Julie Steinestel, Clinic of Urology, University Hospital Muenster, Münster, Germany*

Background: Molecular modifications of the androgen receptor (AR) can cause resistance to androgen deprivation therapy (ADT) and chemotherapy in prostate cancer patients. When resistance to therapy ensues, lack of representative tumor samples hinders therapy adjustments according to emerging AR-modifications and some patients may thus receive ineffective therapy. **Methods:** We devised a single-tube assay to detect the two most common AR-modifications (AR-V7 splice variants and *AR*point mutations) in circulating tumor cells (CTC) using immunomagnetic CTC isolation followed by quantitative real-time PCR and DNA pyrosequencing. We prospectively investigated 47 prostate cancer patients with PSA progression and molecularly uninformed therapy switch. Comparison of newly administered therapy and CTC-AR-status allowed effect size estimation. **Results:** Nineteen (51%) of 37 patients with detectable CTCs carried AR-modifications. Specifically, 17 patients carried the AR-V7 splice variant, one harbored a p.T878A point mutation and one harbored both AR-V7 and a p.H875Y mutation. We found a positive predictive value for response and non-response to therapy by AR status in CTCs of ~94%. We estimated the overall benefit from molecularly informed therapy switch by subtracting the molecularly uninformed (31%) and the AR-status unmatched (6%) response rates from the AR-status matched response rate (72%). Thus, for prospective clinical trial planning our data suggest an estimated effect size of ~33%. **Conclusions:** In summary, the ability to detect key resistance-mediating AR modifications in CTCs has the potential to considerably improve prostate cancer treatment.

5068 Poster Session (Board #62), Sat, 1:15 PM-4:45 PM

Androgen receptor (AR) amplification in patients (pts) with metastatic castration resistant prostate cancer (mCRPC) resistant to abiraterone (Abi) and enzalutamide (Enz): Preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDT). *First Author: Rahul Raj Aggarwal, UC San Francisco, San Francisco, CA*

Background: Mechanisms of resistance to Abi or Enz in mCRPC pts are poorly understood. AR amplification (AR amp) is observed in Abi/Enz naive mCRPC pts, but its role in mCRPC pts who develop resistance to Abi/Enz is not known. As part of the WCDT project, which aims to identify genetic pathways underlying resistance to Abi and Enz, AR amp status was assessed in metastatic tumor biopsies from mCRPC pts. **Methods:** Eligible mCRPC pts underwent biopsy (bx) at one of 5 WCDT sites, using a uniform bx and clinical follow-up protocol. Formalin fixed, paraffin-embedded tissue underwent pathologic review and fluorescence in situ hybridization (FISH) for assessment of AR amp in a CLIA laboratory. AR amp by FISH was corroborated with array comparative genomic hybridization (aCGH) in select cases. **Results:** 150 mCRPC pts have undergone bx to date. To date, 92 have been evaluated by FISH for AR amp, including 36 from bone, 35 from lymph nodes, 16 from liver, and 5 from other soft tissues. Overall, 64% of mCRPC tumors were AR amplified by FISH and were corroborated by aCGH in 16/21 cases (76%). AR amp was seen in similar proportions in liver, bone, or nodal bx, and was present in $>$ 50% of tumors with small cell histology. AR amp was observed in 16/19 pts (84%) naïve to both Abi + Enz compared to 17/36 pts (47%) who were resistant to Abi ($p = 0.008$). 4/6 (67%) of Enz resistant tumor biopsies were AR amplified. In pts that received Abi or Enz post-bx, the PSA response rate (PCWG2 criteria) was 9/17 (53%) in AR amp and 5/12 (42%) in AR non-amplified tumors respectively. **Conclusions:** AR amplification status can be assessed by FISH from mCRPC biopsies. AR amplification was common in Abi/Enz-naïve tumors including those with small cell histology. AR amp was less frequent in pts with Abi resistance, suggesting that Abi may select for non-AR amplified cells. Sequential (paired) biopsies from the same pts are being evaluated to test this hypothesis. Preliminary data suggest higher rates of AR amp in pts who are resistant to Enz. The predictive utility of AR amp status and AR splice variants is currently being evaluated.

TPS5069 **Poster Session (Board #63a), Sat, 1:15 PM-4:45 PM**

Androgen receptor modulation optimized for response: Splice variant (ARMOR3-SV)–Randomized, open-label, multicenter, controlled study of galeterone vs enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC) expressing AR-V7 splice variant. *First Author: Mary-Ellen Taplin, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: mCRPC patients with tumors expressing the androgen receptor (AR) splice variant-7 (AR-V7), a constitutively-active truncated form of the AR lacking the ligand-binding domain, have been shown to have worse clinical outcomes after AR-targeting drugs than those without detectable AR-V7. Galeterone, a small molecule drug, disrupts AR signaling via selective inhibition of CYP17 lyase, AR blockade, and enhanced degradation of the AR protein. In preclinical models, galeterone showed activity against the full-length AR and AR alterations including AR-V7 and AR^{v567es} splice variants, and against activating AR mutations (eg, AR-T878A, AR-F876L). Given the encouraging results in patients with AR C-terminal loss in the galeterone Phase 2 ARMOR2 trial, further research is warranted in this patient subset. **Methods:** ARMOR3-SV is a Phase 3, randomized, open-label, multicenter study of galeterone vs enzalutamide in men with mCRPC expressing AR-V7 mRNA in circulating tumor cells (CTCs). Among other inclusion criteria, eligible patients must continue medical castration or have had surgical castration, and must not have received prior chemotherapy, abiraterone, or enzalutamide. Eligible patients will be prescreened and subsequently enrolled only if AR-V7 is detected in CTCs using a CLIA-certified, analytically-validated assay. A total of 148 patients will be randomized (1:1) to receive once-daily oral galeterone 2550 mg or enzalutamide 160 mg. The primary endpoint is radiographic progression-free survival determined by independent blinded, central radiologic review. Secondary endpoints include time to cytotoxic therapy or next anticancer intervention and overall survival. Other endpoints include time to first skeletal related event, decline in PSA, time to PSA progression, and best objective response rate (in men with measureable soft tissue disease [RECIST1.1]). Safety and pharmacokinetics of galeterone will also be assessed. CTCs will be enumerated and characterized molecularly in an exploratory fashion.

TPS5070 **Poster Session (Board #63b), Sat, 1:15 PM-4:45 PM**

Autologous dendritic cell vaccination (DCVAC/PCa) added to docetaxel chemotherapy in a double-blind, randomized phase III trial (VIABLE) in men with advanced (mCRPC) prostate cancer. *First Author: Nicholas J. Vogelzang, Carolina Urologic Research Center, The US Oncology Network, Myrtle Beach, SC*

Background: Prostate cancer (PCa) is the second most common cancer, and the fifth leading cause of cancer related death among men worldwide. Immunotherapy designed to induce tumor cell specific immune responses capable of destroying tumor cells has emerged as a promising treatment modality in solid malignant tumors. Clinical and preclinical trials have shown that docetaxel chemotherapy can be combined with vaccine without impairing the immune response. **Methods:** VIABLE is a randomized, double-blind, placebo-controlled, parallel-group, international phase III study to evaluate the efficacy and safety of DCVAC/PCa (active cellular immunotherapy based on dendritic cells) versus placebo in patients with mCRPC eligible for first-line docetaxel chemotherapy. The study was initiated in May 2014 and plans to enroll almost 1200 patients at approximately 300 sites globally. Eligible patients are required to present with metastatic castrate-resistant PCa defined by both presence and progression of the disease, maintenance of a castrate state with serum testosterone level less than 50 ng/dl, ECOG score 0-2, and adequate hematologic, hepatic and renal functions. All patients will receive standard of care docetaxel plus prednisone, and will be randomized 2:1 to DCVAC/PCa or placebo. Patients will be stratified by region (US vs other), previous therapy (enzalutamide and/or abiraterone) and ECOG score (0, 1 vs 2). The primary endpoint is overall survival (OS). Secondary objectives include assessments of safety, radiographic progression free survival, time to PSA progression, time to the first occurrence of skeletal related events (SRE), and quality of life (QoL) assessments based on the FACT-P questionnaire. Clinical trial information: Registration number NCT02111577, EudraCT number 2012-002814-38. Clinical trial information: NCT02111577.

TPS5071 **Poster Session (Board #64a), Sat, 1:15 PM-4:45 PM**

A phase 3 randomized, placebo-controlled double-blind study of ARN-509 plus abiraterone acetate (AA) in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC). *First Author: Dana E. Rathkopf, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: ARN-509, a potent and selective androgen receptor (AR) antagonist, inhibits AR nuclear translocation and DNA binding (Clegg, *Cancer Res.* 2012). AA directly inhibits androgen biosynthesis and has been approved for the treatment of mCRPC. Although ARN-509 and abiraterone both target the AR, each works through a different mechanism: the former blocks ligand binding, the latter inhibits ligand synthesis. Importantly, lack of sensitivity to one AR-targeted therapy does not necessarily imply resistance to another (Rathkopf, AACR 2014). Inhibiting the AR through multiple mechanisms simultaneously may be more effective than single pathway inhibition and has the potential to have a significant impact on the mCRPC field. This phase 3 trial will compare radiographic progression-free survival (rPFS) in pts with chemotherapy-naïve mCRPC treated with ARN-509 in combination with AA + prednisone/prednisolone (P) vs placebo + AA + P. **Methods:** This multicenter, double-blind, placebo-controlled trial is enrolling men with mCRPC with progressive disease and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Pts will be stratified by presence or absence of visceral metastases, ECOG PS, and region (European Union, North America, and rest of world) and randomized (1:1) to ARN-509 (240 mg QD) + AA (1000 mg po QD) + P (5 mg po BID) or placebo + AA + P. The primary end point is rPFS using RECIST 1.1 or PCWG2 criteria. Secondary end points are overall survival, time to long-term opioid use, time to initiation of cytotoxic chemotherapy, and time to pain progression. Population pharmacokinetics of AA and biomarker analyses will be performed. The study uses a group sequential design, including 2 interim analyses. The stratified log rank test will be used for the time-to-event analysis. An independent data monitoring committee will review safety and efficacy data. Approximately 960 pts will be randomized over 2 years in 225 sites in 18 countries. (ClinicalTrials.gov Identifier: NCT02257736) Clinical trial information: NCT02257736.

TPS5072 **Poster Session (Board #64b), Sat, 1:15 PM-4:45 PM**

A phase 1/2 open-label study of safety and antitumor activity of EPI-506, a novel AR N-terminal domain inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC) with progression after enzalutamide or abiraterone. *First Author: Robert B. Montgomery, University of Washington Oncology, Seattle, WA*

Background: EPI-506 is a first-in-class, highly specific small molecule inhibitor of the androgen receptor (AR) N-terminal domain (NTD). *In vitro* and in *vivo* studies have shown activity against full length AR and constitutively active AR splice variants, including AR-V7 (associated with resistance to abiraterone and enzalutamide). EPI-506 is expected to be effective in mCRPC driven by both canonical and aberrant AR signaling by targeting the NTD common to full length and splice variant AR. Initial clinical development of EPI-506 will target mCRPC with progression after prior enzalutamide and abiraterone. **Methods:** This open-label, single-arm, phase 1/2 study will evaluate the benefit of 12 week once-daily dosing with EPI-506, after establishing the safety, pharmacokinetics (PK), and optimal dose of EPI-506 in single- and multiple-dose escalations. The study will involve ~20 investigational sites in the US and Canada, and is expected to launch in Q2 2015. The planned enrollment is 150 patients. Inclusion criteria include mCRPC with progression after one or more lines of hormonal therapy or chemotherapy, and progression on enzalutamide or abiraterone. Exclusion criteria include hematologic, hepatic or renal insufficiency. The phase 2 portion of the study will evaluate activity in 3 patient populations: post-enzalutamide mCRPC, post-abiraterone mCRPC, and enzalutamide/abiraterone naïve mCRPC. Primary endpoints include PSA response at week 12, defined as a $\geq$ 50% PSA decrease from baseline. Secondary endpoints include: PK, objective RECIST response, time to PSA progression, radiographic progression-free survival, and safety/tolerability. Exploratory endpoints include evaluation of AR splice variants and AR mutations from CTC-based and ctDNA-based methodologies, as well as molecular characterization of optional tissue biopsies. This trial will be the first to evaluate the novel NTD inhibitor EPI-506 in men with enzalutamide- and/or abiraterone-failure mCRPC, and is the first agent with the potential to inhibit both canonical and variant-mediated AR signaling.

TPS5073 **Poster Session (Board #65a), Sat, 1:15 PM-4:45 PM**

Phase II multicenter study to analyze the predictive value of fusion gene TMPRSS2-ETS assessed both in tumor and blood sample, as a marker of response to enzalutamide in patients with metastatic castration resistant prostate cancer (CRPC) pre-chemotherapy: PREMIERE-SOGUG Trial. *First Author: Enrique Grande, Hospital Universitario Ramon y Cajal, Medical Oncology Department, Madrid, Spain*

Background: Enzalutamide (E) is a newly authorized drug for metastatic CRPC. E inhibits binding of androgens to androgen receptors, nuclear translocation of activated receptors and DNA transcription. E decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. The presence of TMPRSS2-ETS fusion gene rearrangement correlates with the effectiveness of abiraterone (Danila DC, et al 2011). This molecular alteration may also influence E clinical outcome. The aim of this study is to determine whether the efficacy and safety of E when administered to mCRPC before chemotherapy, is influenced by the presence or not of TMPRSS2-ETS fusion gene rearrangement both in primary tumor and circulating blood. **Methods:** This is a phase II open-label study conducted in chemotherapy naïve mCRPC patients older than 18 years, ECOG 0-1, testosterone $<$ 50 ng/dL and adequate, hematologic, hepatic, and renal function, that progressed to previous castration treatment documented by PSA (PCWG2), radiographic progression (modified RECIST 1.1) or bone scan progression. Patients will receive E treatment (160 mg/d) until clinical and/or radiographic disease progression. Primary objective is to assess the predictive value of the expression of TMPRSS2-ETS gene fusion in primary tumor tissue and circulating tumor cells correlated with progression free survival. Secondary objectives include assessing relationship between the presence of TMPRSS2-ETS fusion gene rearrangements with time to PSA response, overall soft tissue response rate, time to beginning of cytotoxic chemotherapy, safety of E treatment and circulating tumor cells (CTC) conversion rate. In this study is planned to include 98 patients. Sample size has been calculated using a Cox proportional hazards regression model with alpha 0.05, power 80% and 20% drop out rate. Patients will be included in 17 sites in Spain and it is expected to start in February 2015. Clinical trial information: NCT02288936.

TPS5074 **Poster Session (Board #65b), Sat, 1:15 PM-4:45 PM**

A randomized phase II study of androgen deprivation therapy with or without PD0332991 in RB-positive metastatic hormone-sensitive prostate cancer. *First Author: Phillip Lee Palmbos, University of Michigain Health System, Ypsilanti, MI*

Background: Androgens drive proliferation of prostate cancer cells via upregulation of cyclin D which complexes with the CDK4/6 kinases, resulting in phosphorylation of Rb and G1/S progression. Perturbations in this pathway (loss of Rb, upregulation of cyclin D) are felt to promote castration-resistance. PD0332991 (palbociclib) is a novel specific inhibitor of CDK4 and 6. Preclinically PD0332991 inhibited proliferation and promoted G1 arrest in an RB and Cyclin D-dependent manner. 80-90% of early metastatic hormone-sensitive prostate cancers are estimated to retain wild-type RB expression. Addition of PD0332991 to hormonal therapy in ER+ breast tumors demonstrated statistically significant improvements in progression-free survival. Hypothesis: Addition of PD0332991 to initial ADT in patients with newly metastatic RB-positive prostate cancer will significantly increase the efficacy of ADT. **Methods:** A multicenter randomized phase II study of PD0332991 was initiated (NCT02059213) in which patients (n = 60) with new metastatic hormone sensitive prostate cancer and RB intact tumors based on metastatic biopsy are stratified by disease extent and randomized (1:2) to ADT or ADT plus PD0332991. Primary endpoint is PSA response ($<$ 4 ng/mL) after 7 months of therapy. With 20 patients randomized to ADT and 40 randomized to ADT plus PD0332991 there will be a 64.2% power to detect a 20% difference in proportions with a one-sided type I error of 0.10 using the mid p-value method of the Fisher's exact test. Secondary endpoints: safety and tolerability of ADT + PD0332991, rate of undetectable PSA ($<$ 0.2ng/mL), biochemical and clinical progression-free survival, overall PSA and radiographic response rates, assessment of biomarkers which predict therapy response (circulating DNA and tumor cells, tumor protein and transcriptome analysis) and to establish a repository of metastatic hormone sensitive prostate tumor samples. Support: Movember-PCF Challenge Award, Pfizer. Clinical trial information: NCT02059213.

TPS5075 **Poster Session (Board #66a), Sat, 1:15 PM-4:45 PM**

A prospective, multicenter, randomized phase II trial of best systemic therapy (BST) or BST plus definitive treatment (Surgery or Radiation) of the primary tumor in metastatic prostate cancer. *First Author: Brian Francis Chapin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment for metastatic (M1) prostate cancer (PC) is centered on the use of systemic therapy. Evidence suggests that definitive treatment of the primary tumor (DTPT) may improve outcomes of men with advanced disease. In addition to prevention of symptomatic local progression there is evidence that local therapy may alter disease biology. Thus, DTPT may delay local and distant progression, prolong time to castration resistant PC (CRPC) and fatal metastatic burden. We sought to test the hypothesis that DTPT added to BST will delay time to CRPC in men presenting with M1 PC. **Methods**: After completing 6 months of BST (any standard therapy for M1 PC) 120 men will be randomized 1:1 to continue BST +/- DTPT. Patients are stratified by PSA nadir at randomization ($\leq$ 4 and $>$ 4) and by treatment center. Type of DTPT is based on patient preference and physician recommendations. Patients are evaluated every 3 months with a history and physical exam and serum PSA. Progressive disease is defined per the PCWG2. A Bayesian design with interim monitoring will be implemented. After a minimum of 60 patients have been randomized, if at any time, the probability of one arm (A) is better than the other arm (B) is greater than 97.5%, the trial will be stopped early and A will be selected as superior. Patients will be followed for a minimum 24 months before a final analysis is conducted. **Eligibility**: Prostate adenocarcinoma with documented evidence of M1 disease per AJCC v6. Patients must have castrate sensitive disease at randomization and have not received BST for $>$ 6 months prior to randomization. Exclusions include small cell carcinoma, brain metastases or CRPC within 6 months of initiating BST. **Enrollment:** 35 patients are enrolled to date and 20 have been randomized. 8 patients developed CRPC prior to the 6 month time point. The protocol is scheduled to open at 3 additional sites by spring 2015. **Correlative Studies:** Characterization of the prostate tumor and tumor microenvironment (stromal and immunologic components) and associated changes on magnetic resonance imaging will be used to identify a biomarker panel to predict benefit from DTPT. Clinical trial information: NCT01751438.

TPS5076 **Poster Session (Board #66b), Sat, 1:15 PM-4:45 PM**

Randomized phase-2 study of sipuleucel-T with or without radium-223 in men with asymptomatic/minimally symptomatic bone-metastatic castrate-resistant prostate cancer (CRPC). *First Author: Jong Chul Park, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Sipuleucel-T is an autologous cellular immunotherapy indicated for men with asymptomatic/minimally symptomatic metastatic CRPC. Recent analysis of immune responses in men treated with sipuleucel-T showed that antigen-specific immune responses to sipuleucel-T may be associated with survival, confirming the immune-based mechanism of action and suggesting the possibility that producing a stronger immune response may translate into the better clinical outcomes. Radiopharmaceutical agents have been shown to enhance immune modulation through a variety of mechanisms including enhanced display of tumor-associated antigens. Based on the immunomodulatory effects of radiopharmaceutical drugs, we hypothesized that combined use of radium-223 and sipuleucel-T may enhance the sipuleucel-T-induced immune response and improve clinical outcomes. **Methods:** This is a randomized phase 2 study comparing antigen-specific immune responses of sipuleucel-T used alone versus sipuleucel-T plus radium-223 in CRPC patients with bone metastases but no visceral involvement. Patients will be randomly assigned (1:1) to receive sipuleucel-T plus radium-223 (Arm 1) or sipuleucel-T alone (Arm 2); men in Arm 2 will receive 3 infusions of sipuleucel-T alone, while men in Arm 1 will receive 6 infusions of radium-223 plus 3 infusions of sipuleucel-T starting after the second radium-223 dose. The primary study objective is to determine whether addition of radium-223 to sipuleucel-T enhances immune response, as measured by peripheral PA2024-specific T-cell proliferation using a tritiated thymidine incorporation assay at 6 wks after the first sipuleucel-T infusion. With 15 men per arm, there is 80% power to detect a 3.6-fold increase in mean proliferation response between the two arms. PSA responses and radiographic responses (in men with measurable disease) will also be assessed. Incidence and severity of AEs will be graded according to CTCAE v4.0. Various immune parameters, both humoral and cellular, will be analyzed at multiple time points during the treatment period, and an exploratory assessment of antigen spread will also be performed.

TPS5077 **Poster Session (Board #67a), Sat, 1:15 PM-4:45 PM**

Randomised phase 3 trial of enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: the ANZUP ENZAMET Trial (ANZUP 1304). *First Author: Ian D. Davis, Monash University Eastern Health Clinical School, Box Hill, Australia*

Background: Androgen deprivation therapy (ADT) with a luteinising hormone releasing hormone analogue (LHRHA) or surgical castration, either alone or combined with conventional non-steroidal anti-androgen (NSAA), is widely used as initial treatment for hormone-naive, metastatic prostate cancer (PC). Meta-analysis of RCTs showed a 3% absolute improvement in 5 year survival with the addition of NSAA to ADT. Residual, low level androgen receptor (AR) signalling or agonist activity from conventional NSAA may provide a stimulatory signal to hormone-sensitive PC cells. We hypothesize that early use of enzalutamide, a more potent and effective androgen receptor blocker, will reduce residual AR signalling, and improve survival. The aim is to determine the effectiveness of ADT + enzalutamide versus ADT + conventional NSAA, as 1st line endocrine therapy for M1 PC. **Methods:** DESIGN Open label, randomised, stratified, 2-arm, intergroup, phase 3 trial including ANZ, Canada, UK and USA. ELIGIBILITY Metastatic PC starting 1stline ADT. STRATIFICATION Volume of disease, anti-resorptive therapy, comorbidities, early docetaxel use, study site. ENDPOINTS Overall survival (primary), PSA progression free survival (PFS), clinical PFS, health related quality of life, adverse events, cost-effectiveness. SAMPLE SIZE 1100 participants recruited over 2 years + 3.5 years minimum f/up for 80% power to detect a 25% reduction in the hazard of death assuming an OS rate at 3 years of 65% in control group. TREATMENT LHRHA or surgical castration plus either enzalutamide 160mg daily orally, or conventional oral NSAA until disease progression or prohibitive toxicity. ASSESSMENTS Baseline, days 29 and 85 then 12 weekly until clinical progression; imaging prior to randomisation and on progression (PSA and clinical). Tertiary correlative objectives include identification of prognostic/predictive biomarkers from archival tumour tissue and fasting bloods collected at baseline, week 24 and progression (PSA and clinical). Email: enzamet@ctc.usyd.edu.au Website: http://www.anzup.org.au/ Clinical trial information: ACTRN12614000110684.

TPS5078 **Poster Session (Board #67b), Sat, 1:15 PM-4:45 PM**

Randomised phase 3 trial of enzalutamide in androgen deprivation therapy with radiation therapy for high risk, clinically localised prostate cancer: The ANZUP ENZARAD Trial (ANZUP 1303). *First Author: Scott G. Williams, Peter MacCallum Cancer Centre, East Melbourne, Australia*

Background: Adjuvant androgen deprivation therapy (ADT) including a luteinising hormone releasing hormone analogue (LHRHA) is standard of care given before, during, and after radiotherapy for localised prostate cancer (PC) at high risk of recurrence. Enzalutamide is a new, second generation androgen receptor (AR) inhibitor that is more potent and binds with a higher affinity to the AR than conventional non-steroidal anti-androgens (NSAA), and improves survival in metastatic, castration-resistant PC. We hypothesise that the incorporation of enzalutamide in adjuvant ADT, given before, during, and after radiation therapy for localised PC at high risk of recurrence will further improve outcomes.The aim is to determine the effectiveness of enzalutamide as part of adjuvant ADT with a LHRHA in men planned for radiotherapy for localised PC at high risk of recurrence **Methods:** DESIGN Open label, randomised, stratified, 2-arm, phase 3 intergroup trial. ELIGIBILITY Localised PC, high risk of recurrence, suitable for EBRT with curative intent. STRATIFICATION Gleason 8-10, T3-4, PSA $>$ 20, study site ENDPOINTS Overall survival (primary), cause-specific survival, PSA progression free survival (PFS), clinical PFS, health related quality of life, adverse events, cost-effectiveness. SAMPLE SIZE 800 participants accrued over 2 yrs + 5.5 years minimum f/up for 80% power to detect a 33% reduction in the hazard of death assuming a 5-year survival rate of 76% amongst controls. TREATMENT LHRHA for 24 months and EBRT (78Gy/39F) starting after week 16 plus either enzalutamide 160mg daily during months 1-24, or conventional NSAA during months 1-6. ASSESSMENTS Baseline, weeks 4, 12, 16, 20 and 24, then 3-4 monthly until year 5, 6-monthly until year 7, then annually. Imaging at baseline and then as clinically indicated. Tertiary correlative objectives include the identification of prognostic and predictive biomarkers from archival tumour tissue, and from fasting bloods collected at baseline, 24 weeks, 5 years, and first evidence of progression. Email: enzarad@ctc.usyd.edu.au Website: http://www.anzup.org.au/ Clinical trial information: ACTRN12614000126617.

TPS5079 **Poster Session (Board #68a), Sat, 1:15 PM-4:45 PM**

A randomized phase II study comparing bipolar androgen therapy vs. enzalutamide in asymptomatic men with castration resistant metastatic prostate cancer: The TRANSFORMER trial. *First Author: Benjamin A. Teply, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Prostate cancer can progress despite androgen deprivation therapy through overexpression of the androgen receptor (AR) and expression of AR splice variants. Almost paradoxically, testosterone given to cancer cells in this state can cause growth inhibition. The AR is normally degraded during progression through the cell cycle, but androgen-bound AR is stabilized, thus arresting the cell cycle and inducing DNA strand breaks through interaction with topoisomerase-IIb. Clinically, supraphysiologic testosterone given to men with castration-resistant prostate cancer was found to be safe in a pilot clinical trial, producing responses and re-sensitizing patients to subsequent anti-androgen therapy. In this context, we designed a randomized phase II study comparing bipolar androgen therapy (BAT) to enzalutamide for patients who have experienced progression on abiraterone. **Methods:** In this multi-center randomized study, funded by a grant from the Department of Defense, eligible patients have asymptomatic metastatic castration-resistant prostate cancer that has radiographically or biochemically progressed after treatment with abiraterone. Patients are enzalutamide-naïve and have not received docetaxel for castration-resistant disease. Patients randomized to BAT will continue on androgen deprivation therapy and receive monthly intramuscular testosterone at the FDA-approved dose of 400mg. This dose produces initial supraphysiologic testosterone levels with return to castrate levels after one month. Patients randomized to enzalutamide will receive 160mg daily. Crossover is encouraged. The primary endpoint is radiographic progression-free survival (rPFS). The trial is powered to detect a 50% improvement in median rPFS in the BAT arm compared to the enzalutamide arm (expected to be ~6 months), with planned accrual of 90 patients in each arm. The arms will be stratified for time to progression on abiraterone. Secondary endpoints include PSA response rates, safety, and quality of life. Correlative studies include the effect of BAT on AR variant expression. Enrollment opened in February 2015. Clinical trial information: NCT02286921.

TPS5080 **Poster Session (Board #68b), Sat, 1:15 PM-4:45 PM**

ARAMIS trial: Efficacy and safety phase 3 trial of ODM-201 in men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). *First Author: Karim Fizazi, Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, Villejuif, France*

Background: There is no standard treatment for nmCRPC besides continuing androgen deprivation therapy (ADT). Preventing metastatic disease in nmCRPC is a major unmet need. Patients with nmCRPC who have shorter PSA doubling time (PSADT) are at high risk for metastatic disease or death (Smith et al. J Clin Oncol. 2013;31:3800-6). ODM-201, a novel second-generation oral androgen receptor inhibitor, has shown an excellent safety profile and promising anticancer activity in progressive CRPC (Fizazi et al. Lancet Oncol. 2014;15:975-85). The ARAMIS trial aims to evaluate the efficacy and safety of ODM-201 in high-risk nmCRPC. **Methods:** This international, randomized, double-blind, placebo-controlled phase 3 trial (NCT02200614) involves over 300 sites in more than 30 countries. 1500 patients on ADT will be randomized 2:1 to ODM-201 600 mg or placebo twice daily. Patients will be stratified by PSADT and baseline use of bone-targeting agent. Eligibility criteria include nmCRPC, PSADT $\leq$ 10 months, and screening PSA $\geq$ 2 ng/mL. The primary endpoint is metastasis-free survival based on central independent review of bone scan and CT/MRI every 16 weeks; progression of regional disease is not considered metastasis. Secondary endpoints are OS, time to first symptomatic skeletal event (SSE), initiation of first cytotoxic chemotherapy for prostate cancer, pain progression, and first opioid use. Additional endpoints are PFS, time to first prostate cancer–related invasive procedure, initiation of subsequent antineoplastic therapy, PSA progression, change in ECOG status, and changes in health-related QoL. Endpoints will be analyzed using a stratified log-rank test, accounting for stratification. The trial has 90% power to detect a target hazard ratio of 0.75 based on a 2-sided log-rank test at an overall significance level of 0.05. Kaplan-Meier estimates will be produced for both treatment groups. The ARAMIS trial is open and recruiting, with the first patient randomized in October 2014. Clinical trial information: NCT02200614.

TPS5081 **Poster Session (Board #69a), Sat, 1:15 PM-4:45 PM**

Prospect: A randomized double-blind phase 3 efficacy study of PROSTVAC-VF immunotherapy in men with asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer. *First Author: James L. Gulley, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: PROSTVAC, a targeted active immunotherapy, is being studied in men with asymptomatic to minimally symptomatic mCRPC in PROSPECT, a global double-blind, randomized phase 3 study. PROSTVAC is a prime-boost regimen consisting of subcutaneous administrations of poxvirus-based PROSTVAC-Prime (a modified vaccinia vector) and PROSTVAC–Boost (a modified fowlpox vector) that encode prostate specific antigen (PSA) as the target antigen with three T-cell co-stimulatory molecules (B7.1, ICAM-1, and LFA-3) also known as TRICOM. A statistically significant overall survival (OS) benefit of 8.5 months (P= 0.0061) with a hazard ratio of 0.56 (95% CI, 0.37 to 0.85), and a favorable risk-benefit profile were reported in a randomized, phase 2 study in mCRPC (Kantoff et. al. 2010 J Clin Onc 28:1099-1105). **Methods:** In PROSPECT, 1200 subjects have been randomized in a double-blind fashion to three arms: PROSTVAC, PROSTVAC plus GM-CSF, or Placebo at a 1:1:1 ratio. The 5 month treatment regimen comprises one PROSTVAC-Prime injection followed by 6 PROSTVAC-Boost injections. Enrolled subjects have asymptomatic/minimally symptomatic mCRPC and are chemotherapy-naïve. Subjects with rapidly progressing disease and visceral metastases are excluded. The primary endpoint is OS and pre-specified interim analyses are integrated in the statistical plan. Secondary efficacy endpoints include the proportion of event-free subjects at 6 months (radiographic progression, pain progression, chemotherapy initiation, or death) compared to placebo. Exploratory endpoints are planned, including immune responses. An immune monitoring program would inform future immunotherapy studies and potential identification of biomarkers. The trial is fully enrolled. ClinicalTrials.gov registry number: NCT01322490. Clinical trial information: NCT01322490.

TPS5082 **Poster Session (Board #69b), Sat, 1:15 PM-4:45 PM**

ERA 223: A phase 3 trial of radium-223 dichloride (Ra-223) in combination with abiraterone acetate (abiraterone) and prednisone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients (pts) with bone predominant metastatic castration-resistant prostate cancer (mCRPC). *First Author: Matthew Raymond Smith, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Ra-223, a first-in-class alpha-emitting radiopharmaceutical targeting bone metastases, reduced risk of death by 30% and delayed time to first symptomatic skeletal event (SSE) versus placebo (15.6 vs 9.8 mo; HR = 0.66) in phase 3 ALSYMPCA (Parker et al. *NEJM* 2013, Sartor et al. *Lancet Oncol* 2014). Ra-223 favorable safety profile and lack of significant toxicity support combining it with other agents. Abiraterone improved radiologic progression-free survival (rPFS) and overall survival (OS) (Ryan et al. *NEJM* 2012) in chemotherapy-naïve men with mCRPC; it has no overlapping toxicity with Ra-223. This study investigates efficacy and safety of Ra-223 + abiraterone versus abiraterone alone in chemotherapy-naïve pts with mCRPC to bone. **Methods:** This phase 3, double-blind, placebo-controlled, multinational trial (ERA 223, NCT02043678) will randomize ~ 800 pts with asymptomatic or mildly symptomatic chemotherapy-naïve, bone-predominant mCRPC 1:1 to receive abiraterone (oral 1000 mg daily) and prednisone (oral 5 mg twice daily) + Ra-223 (50 kBq/kg IV) q 4 wk for 6 cycles or matching placebo until an SSE or death. Stratification is by geographic region, concurrent use of denosumab or bisphosphonates, and total alkaline phosphatase. The primary end point is SSE-free survival. Secondary end points include OS; time to opiate use for cancer pain, pain progression, and cytotoxic chemotherapy; rPFS; and acute and long-term safety. Pts are assessed at each treatment visit for efficacy, safety, and health-related quality of life, and every 3 months for progression and long-term safety. Pts who complete all study treatment and have no SSE enter active follow-up. Long-term follow-up begins after pts experience an SSE and ends 7 years after the last Ra-223 dose or at death, loss to follow-up, or withdrawal. SSE-free survival will be analyzed using a stratified log-rank test, accounting for stratification. Kaplan-Meier estimates will be produced for both treatment groups. As of January 15, 2015, 118 pts were screened. Clinical trial information: NCT02043678.

TPS5083 **Poster Session (Board #70a), Sat, 1:15 PM-4:45 PM**

The PRESIDE trial: A randomized, double-blind, placebo-controlled phase III efficacy and safety study of continued enzalutamide plus docetaxel after disease progression on enzalutamide alone in patients with metastatic castration-resistant prostate cancer. *First Author: Simon Chowdhury, Guy's King's and St Thomas Hospitals, London, United Kingdom*

Background: Enzalutamide (ENZA) is an oral androgen receptor inhibitor approved in the US for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) (US PI, 2014) and in the EU for the treatment of asymptomatic/mildly symptomatic men with mCRPC after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, or those whose disease has progressed on or after doxetaxel (DTX) therapy (EU SmPC, 2014). The PRESIDE study (NCT02288247) will evaluate the efficacy and safety of continued ENZA treatment vs placebo (PBO) when starting docetaxel plus prednisolone (PRED) after disease progression on first-line ENZA in chemotherapy-naïve mCRPC patients. **Methods:** PRESIDE will consist of an open-label treatment period with ENZA (period 1), followed by a randomized double-blind treatment with continued ENZA or PBO in addition to DTX plus PRED (period 2). Eligibility criteria include confirmed prostate adenocarcinoma, metastatic disease, prostate-specific antigen (PSA) progression on androgen deprivation or surgical castration, Eastern Cooperative Oncology Group performance status 0–1, testosterone $\leq$ 50 ng/dL, and minimally symptomatic patients (Brief Pain Inventory Short Form, question 3, $<$ 4 in the absence of opiate analgesia). In period 1, all patients will receive open-label ENZA 160 mg/day until radiographic progression and/or PSA progression with rapid PSA doubling time. In period 2, patients with confirmed disease progression on ENZA alone will be randomized to continue ENZA 160 mg/day or receive PBO. All patients will also receive therapy with DTX 75 mg/m^2 every 3 weeks plus PRED 10 mg/day. The primary end point is radiographic progression-free survival. Secondary end points include PSA and pain progression, PSA and radiographic response, opiate use for cancer-related pain, skeletal related events and quality of life. Planned enrolment is 650 patients in 90 sites across Europe for period 1, with $\geq$ 137 patients in each randomized arm for period 2. Recruitment commenced in December 2014. Clinical trial information: NCT02288247.

TPS5084 **Poster Session (Board #70b), Sat, 1:15 PM-4:45 PM**

The role of highly selective androgen receptor (AR) targeted therapy in men with biochemically relapsed hormone sensitive prostate cancer. *First Author: Rahul Raj Aggarwal, UC San Francisco, San Francisco, CA*

Background: Androgen deprivation therapy (ADT) is frequently applied in men with a rising PSA after surgery and/or radiation, often on an intermittent basis (Crook et al. NEJM 2012). Yet, progression to castration-resistant prostate cancer (CRPC) is a near universal event and many ultimately succumb from their disease, especially those with a short PSA doubling time (PSADT) (Freedland et al. JAMA 2005). Furthermore, ADT is associated with an adverse impact on quality of life (QOL), decreased bone density (BMD), and insulin resistance (Keating et al. JCO 2006). Potent AR antagonists have proven beneficial in metastatic CRPC but their role in castration-sensitive disease is unknown. We hypothesize that compared to standard ADT with luteinizing hormone releasing hormone (LHRH) agonist monotherapy: (1) potent AR antagonist monotherapy may have less detrimental impact on QOL and metabolic effects yet preserved efficacy, and (2) LHRH agonist + potent AR blockade may lead to more durable PSA suppression thereby allowing longer treatment-free intervals and hence improved QOL within an intermittent treatment framework. **Methods:** In the ongoing, open-label, phase 2 study (NCT01790126), patients are randomized 1:1:1 to receive ARN-509 monotherapy (240 mg/day), ARN-509 + LHRH agonist, or LHRH agonist monotherapy. Patients are treated for 12 months, then observed until the time of PSA progression. Eligibility criteria include prior definitive local therapy, rising PSA with PSADT $\leq$ 12 months, minimum PSA $>$ 1 if prior surgery (nadir + 2 if radiation alone), serum testosterone (T) $>$ 150 ng/dL, no prior ADT for biochemical relapse, and no metastases. The primary study endpoint is the percent change from baseline to 12 months in QOL as measured by FACT-P. Secondary endpoints include PSA nadir on treatment and PSA progression-free survival, median time to T recovery, and percent change from baseline in bone density, fasting insulin/glucose/lipids, and serum T and estradiol levels. Correlative studies include analysis of AR mutations in circulating tumor DNA and association with clinical outcomes. Thus far, 34 out of 90 planned patients have been accrued across five investigational sites. Clinical trial information: NCT01790126.

5500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A randomized phase II study of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus and ixabepilone/carboplatin/bevacizumab as initial therapy for measurable stage III or IVA, stage IVB or recurrent endometrial cancer, GOG-86P. *First Author: Carol Aghajanian, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Paclitaxel (PC) is a standard initial therapy for advanced endometrial cancer (EC). We evaluated efficacy and tolerability of incorporating three novel agents into initial therapy. **Methods:** Patients (pts) had received no prior chemotherapy. Randomization (1:1:1) was stratified by measurable disease, recurrent disease, prior pelvic RT. Primary endpoint was progression-free survival (PFS). GOG 209 was used as historical control. **Results:** At least 70% received 6 cycles of C (70-83%) or P (74-82%); 68% received 6 cycles of I. Pts on arm 1 received a median of 12 cycles (0 - 78) of Bev compared with 9 cycles (0-53) on arm 3. A median of 8 cycles (0-62) of Tem was given on arm 2. Hypertension (G 3/4) was more common in the Bev arms (16%) than in the Tem arm (3%), $p = 0.001$. Pneumonitis ($p = 0.004$) and oral mucositis ($p < 0.001$), were more common in the Tem arm. PFS, compared using a log-rank test on data grouped by time intervals, was not significantly increased in any experimental arm ($p > 0.039$) when each arm was compared to historical control. HR (92% CI) for arms 1, 2 and 3 was 0.81 (0.63-1.02), 1.22 (0.96-1.55) and 0.87 (0.68-1.11), respectively. Overall survival (OS) censoring at 36 months, a secondary endpoint, was statistically significantly ($p < 0.039$) increased in arm 1 relative to control but was not significantly increased in arms 2 or 3 (HR (92% CI) arms 1, 2 and 3 was 0.71 (0.55-0.91), 0.99 (0.78-1.26) and 0.97 (0.77-1.23)). **Conclusions:** PFS is not significantly increased in any Arm. OS is significantly increased in the PC + Bev arm. Clinical trial information: NCT00977574.

	Arm 1 PC + Bev	Arm 2 PC + Tem	Arm 3 IC + Bev
Enrolled (N = 349)	116	115	118
Eligible and Treated (N = 329)	108	111	110
Median Age	62	63	65
PS			
0-1	106 (91%)	109 (95%)	113 (96%)
Stage			
III	12 (10%)	13 (11%)	10 (9%)
IV	58 (50%)	58 (51%)	62 (52%)
Recurrent	46 (40%)	44 (38%)	46 (39%)
Prior Pelvic RT			
No	99 (85%)	95 (83%)	98 (83%)
Yes	17 (15%)	20 (17%)	20 (17%)
Measurable Disease			
No	27 (23%)	30 (26%)	33 (28%)
Yes	89 (77%)	85 (74%)	85 (72%)
Histology			
Endometrioid G 1	17 (15%)	13 (11%)	15 (13%)
Endometrioid G 2	36 (31%)	24 (21%)	27 (23%)
Endometrioid G 3	30 (26%)	30 (26%)	22 (19%)
Serous	16 (14%)	26 (23%)	31 (26%)
Clear Cell	6 (5%)	4 (3%)	6 (5%)
Other	11 (9%)	18 (16%)	17 (14%)
RR (GOG209 51%)	60%	55%	53%

5501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer: Toxicity and quality-of-life results of the randomized PORTEC-3 trial. *First Author: Carien L. Creutzberg, Leiden University Medical Center, Leiden, Netherlands*

Background: PORTEC-3 is an intergroup trial investigating survival improvement with adjuvant chemotherapy given during and after pelvic RT (CTRT) versus RT alone (RT) for women with high-risk endometrial cancer (HR-EC). Primary endpoints are overall and failure free survival, secondary endpoints toxicity and health-related quality of life (HRQL). Accrual was completed Dec 2013. Toxicity and 2-year HRQL results are presented. **Methods:** 686 women with HR-EC were allocated to RT (48.6 Gy in 1.8 Gy fractions) or CTRT (2 cycles of cisplatin 50 mg/m^2 during RT, followed by 4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2). Adverse events (AE) were graded using CTCAEv3.0. HRQL was evaluated using EORTC QLQ-C30 and symptom scales from CX 24 and OV28 at baseline, after RT and at 6-12 month follow up (FU) intervals. **Results:** 674 patients met eligibility criteria, and 572 (85%) were evaluable for HRQL. Median FU was 30 months. Rates of AE were significantly higher for CTRT vs RT. During RT, grade ≥ 2 AE were found in 79 vs 44%, and grade ≥ 3 in 36 vs 13% of patients, both $p < 0.001$. During FU, any grade ≥ 3 AE were reported in 67% (CTRT) vs 32% (RT), especially hematologic (32 vs 8%), neurologic (10 vs 2%) and GI AE (14 vs 5%, all $p < 0.001$). AE decreased over time; at 1 yr differences for CTRT vs RT were only significant for grade ≥ 2 neurologic (12 vs 1%, $p < 0.001$) and musculoskeletal AE (3 vs 0%, $p = 0.015$). Rates of any grade ≥ 2 and ≥ 3 AE were 47 vs 39% ($p=0.06$) and 12 vs 8% (ns). At 2 years, grade ≥ 2 neurologic AE persisted (10 vs 2%, $p<0.001$) without differences in grade ≥ 3 AE. QLQC30 functioning scores were lower and HRQL symptom scores were higher for CTRT vs RT after RT and at 6 months, improving with time. At 1 and 2 years, small (mean 5-6 points) but significant differences in physical, role, emotional and social functioning remained. Most striking differences at 2 years were tingling/numbness (24 vs 7%, $p < 0.001$) and weakness arm/legs (14 vs 9%, $p < 0.001$). **Conclusions:** CTRT for high-risk endometrial cancer causes significantly higher AE and symptom ratings and reduced HRQL during and after treatment as compared with RT, but with recovery over time, without differences in grade ≥ 3 AE at 2 years. Clinical trial information: NCT00411138.

5502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Randomized phase II trial of carboplatin-paclitaxel (CP) compared to carboplatin-paclitaxel-bevacizumab (CP-B) in advanced (stage III-IV) or recurrent endometrial cancer: The MITO END-2 trial. *First Author: Domenica Lorusso, MITO and Fondazione IRCCS National Cancer Institute, Milan, Italy*

Background: The prognosis of advanced or recurrent endometrial cancer (AEC) is dismal. The antiangiogenic drug Bevacizumab (B) has reported activity in AEC with response rates ranging from 13 to 22% and 6-month disease control up to 40%. The This randomized phase II trial was designed to compare CP vs CP-B in the treatment of AEC in terms of progression free survival (PFS).(EUDRACT Number 003301-16) **Methods:** Eligible pts had advanced (stage III-IV) or recurrent (progression $>$ 6 months after completion of previous platinum chemotherapy) endometrial cancer, and ≤ 1 prior CT lines. All patients had measurable or evaluable disease and both type 1 and 2 endometrial cancers were eligible. Pts were randomized 1:1 to receive CP standard dose for 6-8 cycles with or without Bevacizumab 15 mg/kg in combination and maintenance until progression or unacceptable toxicity. **Results:** From January 2012 to October 2014, 108 pts were randomized (CP: 54 pts; CPB 54 pts). Overall, 2 out of 3 of pts presented with recurrent disease; almost 60% of cases had endometrioid histology, and 55% were G3. PS was $<$ or 1 in 83% and 15% of case, respectively. Vascular comorbidity was documented in 57% of pts. There was no difference in clinico-pathological features according to arm allocation. As on March 2015, median duration of follow up was 13 months; outcome data are summarized in the table. As far as toxicity, Grade 3 cardiac toxicity was documented in 4 cases in arm B versus no cases in arm A. 13 serious adverse events (SAE) were documented in 8 patients: 3 DVTs, 3 retinal artery thrombosis, 2 intracardiac thrombus, 1 silent myocardial infarction, and 1 cerebrovascular accident. **Conclusions**: The addition of B to CP significantly increased PFS in recurrent endometrial cancer. Cardiovascular toxicity should be carefully evaluated in a population with pre-existing cardiovascular risk factors. Clinical trial information: EUDRACT Number 003301-16.

	CP (N = 48)		CP-B (N = 48)
PFS (IRC*)			
Events, n (%)	31 (35.4)		27 (43.8)
HR (95% CI)		0.57 (0.34, 0.96) Log-rank p = 0.036	
Median, mo (95% CI)	8.7 (6.3-11.2)		13.0 (9.2-16.8)
ORR (IRC), %	(54.3)§ (39.9-68.7)		(72.7)° (59.5-85.9)

§Calculated on 46 cases; ° calculated on 44 cases.

5503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Impact of trebananib plus weekly paclitaxel on overall survival (OS) in patients (pts) with recurrent ovarian cancer and ascites: Results from the phase III TRINOVA-1 study. *First Author: Bradley J. Monk, Department of Obstetrics and Gynecology, University of Arizona Cancer Center Creighton University School of Medicine at Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ*

Background: Trebananib is an antiangiogenic peptibody that inhibits angiopoietin 1 and 2 binding to the Tie2 receptor. TRINOVA-1 showed significantly longer progression-free survival (PFS) in the trebananib arm (Monk et al, *Lancet Oncol* 2014;15:799). We evaluated OS, including clinically important subgroups, and postprogression PFS (PFS2). **Methods:** 919 women with recurrent epithelial ovarian cancer (platinum-free interval $<$ 12 mo) were randomized to paclitaxel (P) 80 mg/m^2 IV QW (3 wks on/1 wk off) plus either blinded trebananib 15 mg/kg IV QW (T+P) or placebo (P alone). Treatment continued until progression, toxicity or consent withdrawal. PFS was the primary, intent to treat (ITT) OS a key secondary endpoint. Exploratory PFS2 analysis followed the EMA guidance (EMA/CHMP/27994/2008/Rev.1; 13 Dec 2012). **Results:** After median follow-up of 17.7 mo and 628 OS events, median OS (ITT) was 19.3 mo with T+P vs 18.3 mo with P alone (HR = 0.95, 95% CI, 0.81–1.11; $p = 0.55$). Prespecified subgroup analysis of OS also evaluated 295 (32%) pts with ascites at baseline. Characteristics did not differ between pts with and without ascites, and pts with ascites randomized to T+P vs P alone. There was a difference in median OS of 2.2 mo between pts with ascites receiving T+P vs P alone (14.5 vs 12.3 mo; HR = 0.72, 95% CI 0.55–0.93; $p = 0.011$). After on-study progression, 684 (74%) pts received a median of 2 (range, 1–8) additional lines of therapy. Median PFS2 in the T+P arm increased by 1.6 mo (12.5 vs 10.9 mo with P alone; HR = 0.85, 95% CI 0.74–0.98; $p = 0.024$). Analysis of time to second subsequent therapy confirmed the PFS2 result (median 13.4 vs 11.7 mo with P alone; HR = 0.83, 95% CI, 0.72–0.96; $p = 0.012$). The incidence of grade ≥ 3 adverse events (AEs) was 60% for T+P vs 56% for P alone. T+P was associated with more AE-related treatment discontinuations (22% vs 8%) and localized edema events (any grade, 59% vs 27%). **Conclusions:** Despite multiple additional lines of therapy, OS was longer with T+P among pts with ascites but not in the ITT population (no decrement). The initially reported PFS benefit was sustained through next subsequent anticancer therapy, translating into longer PFS2. Clinical trial information: NCT01204749.

5504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Efficacy and safety of chemotherapy (CT) ± pertuzumab (P) for platinum-resistant ovarian cancer (PROC): AGO-OVAR 2.20/ENGOT-ov14/PENELOPE double-blind placebo-controlled randomized phase III trial. *First Author: Christian Kurzeder, AGO and Kliniken Essen Mitte, Essen, Germany*

Background: Adding P to gemcitabine (GEM) for PROC improved progression-free survival (PFS) in a subset of patients (pts) with low tumor HER3 mRNA expression [Makhija 2010]. **Methods:** Eligible pts had recurrent PROC (progression [PD] during/within 6 mo of completing ≥ 4 platinum cycles) with centrally tested low tumor HER3 mRNA expression (concentration ratio ≤ 2.81 by qRT-PCR on cobas z480) and ≤ 2 prior CT lines. Investigators (INVs) chose CT (topotecan [TOP], paclitaxel [PAC] or GEM); recruitment was capped to ensure similarly sized CT cohorts. Pts were stratified by chosen CT, prior anti-angiogenic therapy and platinum-free interval (< 3 vs 3–6 mo) and randomized 1:1 to CT with either placebo or P 840→420 mg q3w until PD/unacceptable toxicity. The primary objective was to determine if independent review committee (IRC)-assessed PFS was superior with P + CT vs placebo + CT. The prespecified primary PFS analysis after 109 blinded IRC-assessed PFS events in 154 planned pts provided 95% power to detect a PFS hazard ratio (HR) of 0.50 (median 1.4→2.8 mo) with 2-sided log-rank $\alpha = 0.05$. Other endpoints include overall survival, INV-assessed PFS, objective response rate, safety and translational research. **Results:** From Oct 2013 to Sep 2014, 156 pts were randomized. Adding P to CT improved PFS (median 4.3 mo vs 2.6 mo for placebo + CT); however, significance was not achieved for the primary endpoint analysis. Subgroup analyses by CT showed inconsistent results. No new safety signals were seen. **Conclusion:** Although the primary objective was not met, subgroup analyses showed trends favoring P in the GEM and PAC cohorts, potentially explaining the significant findings in one of the sensitivity analyses. These results merit further exploration of P in ovarian cancer. Clinical trial information: NCT01684878.

PFS analysis	No. of events/pts	Stratified HR (95% CI)
Primary	126/156	0.74 (0.50–1.11); p = 0.14
Sensitivity		
IRC in first 109 PFS events	109/156	0.61 (0.39–0.94)
IRC backdating PD due to missing tumor assessment	126/156	0.82 (0.55–1.21)
CT subgroup, primary		
GEM	45/53	0.63 (0.34–1.14)
PAC	41/54	0.56 (0.29–1.09)
TOP*	40/49	1.19 (0.63–2.25)

*Recruitment to TOP was slowest.

5505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Retrospective analysis of candidate predictive tumor biomarkers (BMs) for efficacy in the GOG-0218 trial evaluating front-line carboplatin–paclitaxel (CP) ± bevacizumab (BEV) for epithelial ovarian cancer (EOC). *First Author: Michael J. Birrer, Massachusetts General Hospital/Dana Farber Cancer Center, Boston, MA*

Background: In EOC, the double-blind placebo (PLA)-controlled randomized phase 3 GOG-0218 trial showed significantly improved progression-free survival (PFS) (but not overall survival [OS]) with BEV added to front-line CP and continued alone. Plasma BM correlative analyses identified no predictive BMs for efficacy. Tumor BM evaluation was an exploratory objective. **Methods:** Patients (pts) with stage III (incompletely resected) or IV OC were randomized to receive 6 cycles of CP with: PLA (CPP); BEV 15 mg/kg q3w → PLA (CPB15); or BEV for 15 mo (CPB15+). Five tumor BMs (CD31, tVEGF-A, VEGFR-2, NRP-1, MET) with a biologic rationale for evaluation were assessed by immunohistochemistry (IHC). The BM-evaluable population (BEP; all pts with an evaluable BM sample and ≥ 1 post-baseline efficacy assessment) was analyzed using 1st, 2nd and 3rd quartile (Q) expression levels for each BM as the cutoff for high vs low BM subgroups. Correlations between tumor BM levels and PFS and OS were analyzed. **Results:** The BEP, comprising 1455 (78%) of 1873 pts in the ITT population, had very similar baseline characteristics and efficacy to the ITT population. No prognostic or predictive association was seen for VEGFR-2, NRP-1 or MET. However, when comparing CPB15+ vs CPP (control), higher microvascular density (MVD) measured by CD31 IHC showed prognostic (not shown) and potential predictive value for PFS (> Q3 MVD HR 0.38 [95% CI 0.25–0.58]; ≤ Q3 MVD HR = 0.68 [95% CI 0.54–0.86]; interaction p = 0.018) and OS (> Q3 MVD HR 0.57 [95% CI 0.39–0.83]; ≤ Q3 MVD HR 1.03 [95% CI 0.83–1.27]; interaction p = 0.0069). tVEGF-A showed potential predictive value for OS (and PFS) for CPB15+ vs CPP with a Q3 cutoff (> Q3 tVEGF-A OS HR 0.62 [95% CI 0.43–0.91]; ≤ Q3 tVEGF-A OS HR 1.01 [95% CI 0.82–1.25]; interaction p = 0.023). **Conclusions:** These retrospective tumor BM analyses suggest a positive correlation between expression levels of molecular (tVEGF-A) and cellular (endothelial cell) targets of anti-VEGF and magnitude of PFS and OS improvement from BEV in EOC. The predictive value of these candidate efficacy BMs requires validation in other relevant datasets. Clinical trial information: NCT00262847.

5506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

An international, biomarker-directed, randomized, phase II trial of AZD1775 plus paclitaxel and carboplatin (P/C) for the treatment of women with platinum-sensitive, *TP53*-mutant ovarian cancer. *First Author: Amit M. Oza, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Data suggest synthetic lethality when *TP53*-deficient cells are exposed to genotoxic drugs plus the Wee1 inhibitor AZD1775 (MK-1775). AZD1775 plus C was well tolerated in patients (pts) with advanced solid tumors (NCT00648648). This current two-part study (NCT01357161) evaluated the efficacy of AZD1775 plus P/C compared with P/C alone in women with *TP53*-mutant OC. **Methods:** After confirming a dose of AZD1775 (225 mg bid; capsules) in 15 pts in part 1, pts in part 2 received AZD1775 or placebo bid for 2.5 days plus P (175 mg/m^2; IV) and C (AUC5; IV) on day 1 per 21-day treatment cycle, until progression or the completion of six cycles. Primary objectives: PFS (enhanced [volumetric] RECIST v1.1, criterion for superiority = $P < 0.1$), safety and tolerability (CTCAE v4.0). Secondary objectives: PFS (RECIST v1.1), ORR (enhanced RECIST v1.1, CA-125 levels) and OS. **Results:** 121 pts with confirmed *TP53* mutations were randomized, 59 and 62 to AZD1775/P/C and P/C, respectively. PFS by independent central review (~57% maturity) was greater with AZD1775/P/C compared with P/C alone (enhanced RECIST: HR 0.63, 80% CI 0.45, 0.89, 95% CI 0.38, 1.06, $P = 0.080$, median 34.14 vs 31.86 weeks; RECIST: HR 0.55, 80% CI 0.39, 0.79, 95% CI 0.32, 0.95, $P = 0.030$, median 42.86 vs 34.86 weeks). ORRs were 81.4% vs 75.8% (difference 5.6%, 95% CI for difference –9.4, 20.2, $P = 0.459$) with AZD1775/P/C vs P/C, respectively. Best response rates based on CA-125 criteria were 81.35% vs 74.19% with AZD1775/P/C vs P/C, respectively. OS data are immature. Most common adverse events (AEs) were nausea (78.0% vs 60.0% for AZD1775/P/C vs P/C, respectively), diarrhea (74.6% vs 36.7%), alopecia (54.2% vs 66.7%) and fatigue (54.2% vs 55.0%). 85 pts had grade ≥ 3 AEs (78.0% vs 65.0% for AZD1775/P/C vs P/C, respectively), 36 pts had serious AEs (40.7% vs 20.0%) and 25 pts had AEs resulting in discontinuation (20.3% vs 21.7%). **Conclusions:** AZD1775/P/C was associated with a significant increase in PFS when compared with P/C alone, met the preset primary and secondary PFS efficacy bar for clinical importance, and showed acceptable tolerability in women with *TP53*-mutant OC. Clinical trial information: NCT01357161.

5507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A phase I study of continuous veliparib in combination with IV carboplatin/paclitaxel or IV/IP paclitaxel/cisplatin and bevacizumab in newly diagnosed patients with previously untreated epithelial ovarian, fallopian tube, or primary peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study. *First Author: Katherine M. Bell-McGuinn, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Veliparib, a poly-(ADP-ribose)-polymerase inhibitor, increases anti-tumor activity when combined with platinum chemotherapy and has monotherapeutic activity in *BRCA1* or *BRCA2* deficient tumors. This study was done to determine the recommended phase II dose (RP2D) of continuous veliparib in combination with initial treatment for epithelial ovarian, fallopian tube, or primary peritoneal cancer. **Methods:** Eligible patients had newly diagnosed, untreated, stage II-IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma or carcinosarcoma. Three regimens (six 21 day cycles) were evaluated: 1, IV q3week carboplatin (AUC 6) and paclitaxel (175mg/m^2); 2, IV q3week carboplatin (AUC 6) and weekly paclitaxel (80mg/m^2); and 3, IV paclitaxel (135mg/m^2, day 1), IP cisplatin (75mg/m^2, day 1 or 2) and IP paclitaxel (60mg/m^2, day 8). Bevacizumab 15mg/kg started in cycle 2 and continued as monotherapy for cycles 7-22. Veliparib continuous oral BID dosing in cycles 1-6 started at 30mg. A 3+3 dose escalation design evaluated dose-limiting toxicities (DLTs) in cycles 1 and 2. Once <2/6 patients experienced a DLT, that dose level was expanded to evaluate feasibility over 4 cycles. **Results:** We enrolled 189 patients; 32 were not evaluable. DLTs at ≥RP2D levels were as seen in the table. **Conclusions:** The RP2D for all regimens is veliparib 150mg BID. Clinical trial information: NCT00989651.

Veliparib dose (mg BID)	No. Evaluable Patients	No. Patients with DLTs	DLT (grade)[no. patients]
Regimen 1			
150	**17**	**2**	febrile neutropenia (3) hyponatremia (3) febrile neutropenia (3)[2] thrombocytopenia (4)[2] >3 week delay for thrombocytopenia
200	**16**	**6**	syncope (3)
250	17	7	febrile neutropenia (3)[3] thrombocytopenia (4)[4]
300	6	2	febrile neutropenia (3) thrombocytopenia (4)
Regimen 2			
150	17	1	headache (3)
200	3	0	significant early cycle delays
Regimen 3			
150	31	9	febrile neutropenia (3) sepsis (4) pulmonary embolism (3,4)[2] myocardial infarction (4) cerebrovascular event (4) mucositis & extremity pain (3) syncope (3) abdominal pain (3) headache (3) sepsis (5)
200	6	2	

5508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Results of ARIEL2: A Phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis. *First Author: Iain A. McNeish, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland*

Background: At least 50% of high-grade serous ovarian cancers (OC) may have homologous recombination deficiency (HRD). Germline *BRCA1* and *BRCA2* mutations (*gBRCA*^{mut}) account for ~1/3. Identification of *BRCA*^{wt} HRD tumors likely to respond to a PARP inhibitor remains challenging. ARIEL2 prospectively tested a novel next generation sequencing-based HRD assay and algorithm to predict rucaparib sensitivity by assessing tumor *BRCA* status and genome-wide loss of heterozygosity (LOH). **Methods:** ARIEL2 enrolled pts with platinum-sensitive, recurrent, high-grade serous or endometrioid OC. The primary objective was to evaluate clinical activity of 600 mg BID rucaparib in 3 pre-defined HRD subgroups: tumor BRCA^{mut}, BRCA^{wt}/LOH^{high} and BRCA^{wt}/LOH^{low}. Known *gBRCA*^{mut} pt enrollment was limited. Tumor HRD status was assessed in pre-treatment biopsies and archival tumor. Response was assessed by RECIST and GCIG CA-125 criteria. **Results:** In 206 treated pts: median age=64 [range 31-86]; 64% ECOG=0; 96% high-grade serous; 46% with ≥2 prior regimens. Treatment-related AEs in ≥15% of pts were GI symptoms (nausea, dysgeusia, ↓ appetite, vomiting, constipation, diarrhea), fatigue, ↓ Hgb, and transient ALT/AST elevations with no other evidence of liver dysfunction. Efficacy data for 135 pts indicate RECIST + CA125 ORRs of 69%, 39%, and 11% in BRCA^{mut}, BRCA^{wt}/LOH^{high}, and BRCA^{wt}/LOH^{low} pts, respectively (Table 1, p<0.0001, Cochran-Armitage trend test). Responses occurred in both *gBRCA*^{mut} (14/19, 74%) and somatic *BRCA*^{mut} (10/16, 63%) tumors. Only 15/161 (9%) BRCA^{wt} tumors had a loss-of-function mutation or homozygous deletion in a HR gene; 4/15 (27%) alterations were in *RAD51C*. All 4 tumors were LOH^{high}and responded to rucaparib, suggesting a potential HRD mechanism. Importantly, matched archival and screening tumor analysis revealed an increase in genomic LOH over time in a subset of tumors. **Conclusions:** ARIEL2 data indicate a tumor HRD assay and algorithm combining *BRCA* analysis and genomic LOH identifies OC pts likely to respond to rucaparib. Clinical trial information: NCT01891344.

Response by HRD status.

HRD Subgroup	# of Pts	RECIST, %	RECIST & CA-125, %
BRCA^{mut}	35	66	69
BRCA^{wt}/LOH^{high}	56	32	39
BRCA^{wt}/LOH^{low}	44	11	11

5509 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with previously treated, recurrent or refractory ovarian cancer: A phase Ib, open-label expansion trial. *First Author: Mary L. Disis, University of Washington School of Medicine, Seattle, WA*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab (proposed INN) (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Here we present results from a cohort of patients (pts) with recurrent or refractory ovarian cancer in an ongoing phase Ib study (NCT01772004). **Methods:** Pts with ECOG PS 0-1 received avelumab at 10 mg/kg Q2W. Best overall response (BOR) and progression-free survival (PFS) were assessed according to RECIST 1.1. Adverse events (AEs) were evaluated by CTCAE v4.0. A prespecified analysis of 23 pts with follow-up of ≥ 2 months showed confirmed and unconfirmed partial responses (PRs), leading to cohort expansion to 75 pts. **Results:** Seventy-five pts were enrolled from November 2013 to November 2014 (median age 62 [range 38-84]; ECOG PS 0 [41%] or 1 [59%]; median of four prior lines of therapy). As of January 2015, median duration of treatment with avelumab was 10 weeks (range 2-54 weeks), and 27 pts remained on treatment. Efficacy data from the 23 pts followed-up for ≥ 2 months (range 2–8 months) demonstrated 4 pts (17.4%, [95% CI, 5.0%, 38.8%]) achieved an unconfirmed BOR of PR,11 (47.8%) had stable disease, and 2 pts had >30% tumor shrinkage after progression was reported. Median PFS was 11.9 weeks (95% CI, 5.9, not reached), and the PFS rate at 24 weeks was 33.3% (95% CI, 11.5, 57.2). Drug-related treatment-emergent AEs (TEAEs; all grades) were reported in 18 pts (78.3%), and 2 pts (8.7%) experienced grade ≥ 3 drug-related TEAEs (increased lipase [1] and elevated creatine kinase and autoimmune myositis that led to discontinuation [1]). No drug-related serious TEAEs occurred. The most commonly reported drug-related TEAEs (> 10%) were fatigue, nausea, and diarrhea. **Conclusions:** These data represent the largest reported dataset of pts with recurrent ovarian cancer treated with anti-PD-L1 therapy. Avelumab demonstrated an acceptable safety profile and is clinically active in this heavily pretreated ovarian cancer pt population. Clinical trial information: NCT01772004.

5510 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study. *First Author: Andrea Varga, Gustave Roussy Institute, Villejuif, France*

Background: Pembrolizumab is a potent, highly selective humanized monoclonal antibody against PD-1 designed to block interaction with PD-L1 and PD-L2 and remove the inhibition of T-cell activation against cancer. PD-L1 was found to be overexpressed in ovarian cancer and can contribute to malignancy. We assessed the safety and efficacy of pembrolizumab in pts with PD-L1^{+}advanced ovarian cancer. **Methods:** KEYNOTE-028 (NCT02054806) is a nonrandomized, multicohort phase Ib trial of pembrolizumab in pts with PD-L1^{+} advanced solid tumors. Key eligibility criteria for the ovarian cancer cohort included advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma; failure of prior therapy; PD-L1 expression in ≥ 1% of cells in tumor nests or PD-L1^{+} bands in stroma as determined by a prototype IHC assay at a central laboratory; and ECOG PS 0-1. Pembrolizumab 10 mg/kg was given every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity. Primary end points: safety, tolerability, and preliminary efficacy. Response assessed per RECIST v1.1 by investigators every 8 weeks for the first 6 months and every 12 weeks thereafter. **Results:** 26 pts were enrolled. Mean (SD) age was 58.1 (7.5); 57.7% were white. 84.6% received prior therapies for recurrent/metastatic disease (38.5% received ≥ 5 therapies), and 50% received prior adjuvant therapies. One pt achieved complete response and 2 pts experienced partial response; 6 pts had stable disease. Of the 3 patients who responded, all remain in response with duration of response ≥ 24 weeks at the time of analysis. The best overall (confirmed) response was 11.5% (95% CI, 2.4-30.2). 6/26 (23.1%) had evidence of tumor reduction; 3 had a tumor reduction of at least 30%. All pts experienced ≥ 1 adverse event (AE) (regardless of treatment); most common were fatigue (42.3%), anemia (30.8%), and decreased appetite (30.8%). Drug-related AEs occurred in 69.2% of pts (grade ≥ 3, 1/26 pts). Currently, 6 pts remain on pembrolizumab treatment. **Conclusions:** PD-1 blockade with pembrolizumab is well tolerated and has antitumor activity in pts with advanced ovarian cancer. This preliminary signal for clinical efficacy will be further investigated. Clinical trial information: NCT02054806.

5511 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Association of *POLE*-mutated and MSI endometrial cancers with an elevated number of tumor-infiltrating and peritumoral lymphocytes and higher expression of PD-L1. *First Author: Brooke E. Howitt, Brigham and Women's Hospital, Boston, MA*

Background: TCGA identified two groups of endometrial cancers with high mutation frequency: an ultramutated group of tumors which harbored mutations in polymerase e (POLE) and a hypermutated group with microsatellite instability (MSI). We hypothesized that these hypermutated tumors may harbor more neoantigens and thus stimulate a stronger immune response compared to tumors with low mutation frequency. In this regard, we evaluated whether hypermutated tumors are associated with an elevated number of tumor-infiltrating lymphocytes (TILs) and peritumoral lymphocytes and higher expression of the immune modulatory molecule PD-L1. **Methods:** We evaluated 4 *POLE*-mutated (determined via Sanger sequencing of mutational hotspots), 28 MSI-tumors and 32 microsatellite stable (MSS) endometrioid endometrial tumors. MSI status was determined using immunohistochemistry (IHC). IHC was performed for CD3, CD4, CD8, CD20, PD-1 and PD-L1 using standard protocols. For evaluation of TILs, a photomicrograph (40X) of the area of maximum CD3+ intraepithelial lymphocytes was obtained with corresponding photomicrographs for the additional stains. For peritumoral lymphocytes, a semi-quantitative scoring method was utilized. **Results:** *POLE*-mutated and MSI tumors exhibited significantly elevated CD3+ ($p = 0.001$), CD4+ ($p = 0.078$) and CD8+ ($p < 0.001$) TILs compared to MSS tumors. CD20+ TILs were not statistically significantly different between MSI/POLE tumors and MSS tumors. Expression of PD-1 ($p < 0.001$) and PD-L1 ($p = 0.022$) was higher in TILs of POLE and MSI tumors compared to MSS tumors. Furthermore, POLE and MSI tumors harbored more peritumoral T-lymphocytes ($p < 0.001$) and higher expression of PD-1 ($p = 0.001$) and PD-L1 ($p < 0.001$) compared to MSS tumors. There were no significant differences in TILs, peritumoral lymphocytes and PD-1/PD-L1 expression between *POLE*-mutated and MSI tumors. **Conclusions:** *POLE*-mutated and MSI endometrial cancers are associated with an elevated number of TILs and peritumoral lymphocytes, and higher expression of PD-1 and PD-L1. These data support trials of immune-checkpoint inhibitors in hypermutated endometrial cancers.

5512 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Tumor infiltrating and peritumoral T cells and expression of PD-L1 in BRCA1/2-mutated high grade serous ovarian cancers. *First Author: Kyle Strickland, Brigham and Women's Hospital, Boston, MA*

Background: Previous studies have shown that the presence of CD3+ and CD8+ tumor-infiltrating lymphocytes (TILs) and a high CD8+/CD4+ ratio are associated with favorable overall survival in ovarian cancer. Given that BRCA1/2 mutated ovarian cancers are also known to be associated with improved survival, we assessed whether the presence of CD3+, CD8+ and CD4+ TILs is enriched in these tumors compared to non-BRCA1/2 mutated ovarian cancers. Furthermore, we assessed the expression of PD-1 and PD-L1 in these tumors. **Methods:** In this pilot study, we evaluated 34 high grade serous ovarian cancers with germline BRCA1 (n = 28) and BRCA2 (n = 6) mutations and 18 tumors without germline or somatic mutations in BRCA1, BRCA2 or other homologous recombination (HR) genes. Immunohistochemistry (IHC) was performed for CD3, CD4, CD8, CD20, PD-1 and PD-L1 using standard protocols. For evaluation of TILs, a photomicrograph (40X) of the area of maximum CD3+ intraepithelial lymphocytes was obtained with corresponding photomicrographs for the additional stains. For peritumoral lymphocytes, a semi-quantitative scoring method was utilized. **Results:** The number ofCD3+ TILs was not significantly different between BRCA1/2-mutated and non-BRCA1/2-mutated ovarian cancers (p = 0.23). However, BRCA1/2-mutated tumors were associated with a strong trend for increased CD8+ TILs (p = 0.06) while demonstrating significantly less CD4+ TILs (p = 0.05) compared to non-BRCA1/2-mutated tumors. Overall, there was a significantly higher CD8+/CD4+ ratio in BRCA1/2-mutated tumors (p = 0.02). Furthermore, peritumoral CD3+ T-cells were significantly increased in BRCA1/2-mutated (p = 0.03) compared to non-BRCA1/2-mutated ovarian cancers. We did not detect statistically significant differences in the intensity or distribution of PD-1 and PD-L1 expression between BRCA1 and non-BRCA1/2-mutated tumors. **Conclusions:** In this pilot study, BRCA1/2-mutated tumors were associated with significantly higher CD8+/CD4+ ratio of TILs and significantly higher peritumoral T cells. These findings support an additional mechanism for the improved survival of patients with BRCA1/2-mutated ovarian cancers.

5513 Poster Discussion Session; Displayed in Poster Session (Board #71), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase II open-label, multicenter study of single-agent rucaparib in the treatment of patients with relapsed ovarian cancer and a deleterious BRCA mutation. *First Author: Ronnie Shapira-Frommer, Sheba Medical Center, Ramat Gan, Israel*

Background: Rucaparib is a potent oral PARP inhibitor that has shown robust activity in patients (pts) with homologous recombination deficient (HRD) tumors, with the highest response rates observed in ovarian and breast cancer pts harboring deleterious germline BRCA mutations (gBRCA^{mut}). This phase II study (NCT 01891344) evaluated the efficacy and safety of rucaparib in pts with relapsed gBRCA^{mut} high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (EOC/FTC/PPC). **Methods:** Women with gBRCA-^{mut} EOC/FTC/PPC who received 2-4 prior chemotherapy (chemo) regimens and had a progression-free interval (PFI) $\geq$ 6 months after their last platinum dose were enrolled. ECOG PS 0-1 and adequate organ function were required. Pts received oral rucaparib 600 mg BID in 21 day cycles until disease progression. The primary endpoint was objective response rate (ORR) by RECIST 1.1. **Results:** 35 pts have been enrolled. Median age was 55 years (range 44-84). The median number of prior chemo regimens was 2 (range 2– 4). Fifteen pts (43%) had received $\geq$ 3 prior chemo regimens. RECIST/CA-125 ORR was 81% (21/26); RECIST ORR was 65% (17/26). RECIST ORR was 88% (7/8) and 56% (10/18), respectively, in pts with PFI 6-12 mo or $>$ 12 mos. In pts with $\geq$ 3 prior chemo regimens, 58% (7/12) achieved a RECIST response. The median duration of response and PFS have not been reached. The most common treatment-related AEs (generally grade 1/2) were nausea (55%), anemia (41%), ALT/AST elevations (41%), fatigue (41%), and asthenia (35%). The ALT/AST elevations are transient with no other evidence of liver dysfunction. No pts discontinued treatment due to an AE. No secondary malignancies have been observed. **Conclusions:** Rucaparib demonstrated robust activity in heavily pretreated EOC/FTC/PPC pts with gBRCA^{mut} tumors with 81% of pts achieving RECIST/CA-125 responses. Rucaparib was well tolerated and AEs did not result in any treatment discontinuations. The ongoing pivotal program in EOC/FTC/PPC pts is evaluating rucaparib in treatment (ARIEL2, NCT01891344) and maintenance (ARIEL3, NCT01968213) settings. Clinical trial information: NCT01891344.

5514 Poster Discussion Session; Displayed in Poster Session (Board #72), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase I/Ib study of the PARP inhibitor (PARPi) olaparib (O) with carboplatin (C) in heavily pretreated high-grade serous ovarian cancer (HGSOC) at low genetic risk (NCT01445418). *First Author: Victoria L. Chiou, Natl Cancer Inst, Bethesda, MD*

Background: O is a FDA-approved PARPi for advanced ovarian cancer with germline BRCA mutation (gBRCAm). O and C each have shown single agent activity in HGSOC. We hypothesize that addition of O to C to stress DNA repair machinery is tolerable and of clinical benefit in HGSOC pts without gBRCAm. **Methods**: 3x3 dose escalation examined O capsules (400 mg q12h, d 1-7) with C AUC 3, 4, or 5 on d1 or 2 every 21d over 3 dose levels. No more than 8 O + C cycles were given, followed by daily O maintenance. Safety was assessed every cycle. Response was assessed every 2 cycles. PBMCs were collected at baseline, d3, and post-cycle 1 for PAR incorporation. Tumor biopsies were performed in a 15 patient (pt) expansion cohort at maximum tolerated dose (MTD) pre-and post-cycle 1 for proteomics and apoptosis endpoints. **Results**: 30 women (median age 65 [49-71]) were treated over 3 dose levels of O + C AUC3 (3 pts), AUC4 (MTD, 21 pts), and AUC5 (6 pts). 24 pts had negative gBRCAm testing and 6 had BRCAPRO score $<$ 10% with negative family history. The median number of prior therapies was 7 (2-12). All pts received prior platinum (time from last platinum: median 17 mo [7-154]), with 11 platinum-sensitive and 19 platinum-resistant disease. Gr 3/4 AEs included neutropenia (23%), thrombocytopenia (20%), and anemia (13%). DLTs were gr 3 neutropenia/thrombocytopenia and gr 3 infection on AUC 5. 2 pts required C dose reduction and early discontinuation due to delayed marrow recovery. Of 28 evaluable pts, 5 PR (18%; median 4 [3-18] mo), and 10 SD $\geq$ 4 mo (36%; median 8 [4-11] mo) were observed, yielding a disease control rate of 54%. RR and median PFS were 36 % (4/11 pts) and 3.5 (1.5-10) mo in platinum-sensitive disease and 6% (1/17 pts) and 4 (1.5-18) mo in platinum-resistant disease. There was no significant difference in tissue apoptotic index pre-and post-cycle 1. PAR incorporation and proteomics results will be presented. **Conclusions**: Recommended phase 2 dose is O 400 mg capsules q12h d1-7 with C AUC4 on 21d cycles in heavily pretreated recurrent HGSOC pts without gBRCAm. Interactive marrow suppression was observed. Identification of biomarkers of response to O + C is needed in recurrent HGSOC without gBRCAm. Clinical trial information: NCT01445418.

5515 Poster Discussion Session; Displayed in Poster Session (Board #73), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Results of a phase I pharmacokinetic study of intraperitoneal bortezomib (B) and carboplatin (C) in patients with persistent or recurrent ovarian cancer (OC): An NRG/Gynecologic Oncology Group study. *First Author: Don S. Dizon, Massachusetts General Hospital, Boston, MA*

Background: Intraperitoneal therapy (IP) has been shown to improve survival outcomes for women with optimally cytoreduced, newly diagnosed, advanced OC, but whether IP has a role for recurrent OC is unknown. Preclinicial data show IP administration of the proteasome inhibitor bortezomib (B) prior to IP carboplatin (C) increased cellular platinum accumulation and results in synergistic cytotoxicity. Hence, we conducted this phase I trial of an IP regimen consisting of B+C in women with recurrent or persistent disease. **Methods:** We enrolled 33 pts with recurrent or persistent OC, GOG PS $\leq$ 2, with $\leq$ 4 prior regimens. After DLT at DL1 (B 0.5 mg/m^2]/C AUC 5), the protocol was amended to fixed C AUC4 with dose escalation of B: DL-1 (0.5); 1a (0.9); 2a (1.3), 3a (1.7), 4a (2.1), 5a (2.5). Treatment was delivered every 21 days for six cycles. Pharmacokinetics (PK) of B (by LC-MS/MS) and C (ultrafilterable, by AAS) were studied in cycle 1. **Results:** Of enrolled pts, 32/33 were evaluable for safety. Two patients experienced DLT at DL1 (G3 abdominal pain, G4 thrombocytopenia and G3 lung infection). At C AUC4, we escalated BTZ to DL5a without DLT. Grade 3/4 related toxicities included fatigue, abdominal pain, nausea, vomiting, and diarrhea; however, all were relatively infrequent. The overall response rate in patients with measurable disease (n = 21) was 19% (1 CR, 3PR). At DL5a (n = 5), the ORR was 20% (0CR, 1PR). PK revealed IP and peripheral blood plasma B C_{max} and AUC increased linearly with dose. The B IP to peripheral geometric mean ratios (range) were (N = 26): C_{max} 304 (317-2840), and AUC 139 (15-1867) and appeared independent of dose. Ultrafilterable platinum IP to peripheral geometric mean ratios (range) were (N = 9): C_{max} 49 (18-101) and AUC 17 (6-54). **Conclusions:** IP administration of B+C was feasible and showed promising activity in this phase I trial of heavily pre-treated women with OC. PK analysis showed a favorable exposure ratio of the peritoneal cavity relative to peripheral blood plasma. Further evaluation of this novel IP combination should be conducted. Clinical trial information: NCT01074411.

5516 Poster Discussion Session; Displayed in Poster Session (Board #74), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase Ib dose-escalation study of binimetinib (MEK162) in combination with weekly paclitaxel in patients with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. *First Author: Rachel N. Grisham, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Ovarian cancer is associated with key genetic alterations, including those that lead to activation of the RAS/RAF/MEK/ERK pathway. Binimetinib (BINI) is a potent, selective, allosteric inhibitor of MEK1/2. This study determined the recommended phase II dose (RP2D) of BINI administered on 2 dosing schedules in combination with weekly paclitaxel (PAC) and assessed the safety, pharmacokinetics (PK) and preliminary antitumor activity in female patients (pts) with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. **Methods:** BINI was administered orally either on a continuous (CONT) schedule at 30 mg twice daily (BID; dose level 1 [DL1]) or 45 mg BID (DL2), or on an intermittent (INTERM) schedule on Days (D) 1-5 weekly for 3 of every 4 weeks (q3/4w) at 45 mg BID, in combination with PAC 80 mg/m^2 IV on D1 weekly q3/4w. **Results:** Thirty-four pts were enrolled and treated, with 22 pts on the CONT schedule (14 at DL1; 8 at DL2) and 12 pts on the INTERM schedule. The median age was 63 years (range 42-77), baseline ECOG PS was 0 or 1 (97%), median number of prior systemic therapies was 4 (range 1-14) and the majority of tumors were high-grade serous (HGS; 74%) or low-grade serous (LGS; 18%). On the CONT schedule, dose-limiting toxicities (DLTs) of fatigue, nausea, neutropenia, rash and stomatitis were observed; the RP2D was declared as BINI 30 mg BID CONT with weekly PAC. On the INTERM schedule, a DLT of asthenia was observed; the RP2D was confirmed as BINI 45 mg BID INTERM with weekly PAC. The most common Grade 3/4 AEs included anemia (18%), vomiting (12%), and fatigue, nausea, neutropenia, pulmonary embolism, small intestinal obstruction and stomatitis (9% each). When administered in combination, no clinically relevant differences in BINI or PAC exposures were observed. Of the 29 pts with measurable disease, the response rate was 17% with 1 complete response (LGS) and 4 partial responses (1 LGS, 3 HGS). **Conclusions:** In this pt population, the combination of BINI on both the CONT and INTERM schedules with weekly PAC had an acceptable safety and PK profile at the RP2Ds. Responses were observed in HGS and LGS pts. Clinical trial information: NCT01649336.

5517 Poster Discussion Session; Displayed in Poster Session (Board #75), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Randomized phase III study comparing paclical-carboplatin with paclitaxel-carboplatin in patients with recurrent platinum-sensitive epithelial ovarian cancer. *First Author: Ignace Vergote, University Hospital Leuven, Leuven, Belgium*

Background: Paclical (Pcal), a CremophorEL-free formulation of paclitaxel (Oasmia Pharmaceutical AB) was compared with Paclitaxel (Pxel). Pcal can be administered without anti-allergic premedication as an iv infusion over 1 hour. **Methods:** Primary objective: To show non-inferiority between Pcal and Pxel in PFS using CT scans (RECIST) in platin-sensitive recurrent ovarian, fallopian tube or peritoneal carcinoma. To obtain 379 events of progression 850 were estimated to be accrued (non-inferiority HR = 1.2; α = 0.25 (one-sided); β = 0.8). Patients were randomized to Pcal 250 mg/m^2 iv 1 hr or Pxel 175 mg/m^2 iv 3 hrs, both followed by Carboplatin, AUC 5-6, q 3 wks. Stratification factors: CA 125 value ($<$ 250 U/L or $\geq$ 250 U/L) and relapse (1st or 2nd). CT scans were done before treatment, after 3 and 6 cycles and at the time of clinical symptoms or CA125 progression. A subset of 243 patients had CTs done every 3rd month until progression. Main inclusion criteria: response to prior platin containing treatment, $>$ 6 months platin-free interval (PFI), and CA 125 $>$ 2 x UNL. Patients with a history of severe allergy to study drugs were excluded. **Results:** 789 patients were 1:1 randomized in the period 2009 to 2012 in 81 centers. Inclusion was stopped when 437 patients showed progression. Main baseline characteristics were similar (PFI 6-12 months: 40% vs 43 %, $>$ 12 months 58% vs 57%; second line: 76% vs 76% for Pcal and Pxel, respectively). Non-inferiority of PFS for Pcal (10.3 months) compared to Pxel (10.1 months) was observed (HR:0.86 CI:0.72-1.03 p = 0.0938). In the subgroup of patients with CTs performed every 3rd month during follow-up the PFS was 12.2 versus 10.2 months, respectively (HR:0.76 CI:0.56-1.03 p = 0.0798). Response according to RECIST: 67% vs 65%; according to GCIG CA125 criteria: 86% vs 85%, respectively. AEs were noted in 90% in the Pcal group and 87% in the Pxel group. All grade peripheral neuropathy were 29% vs 32% and myalgia 11% vs 13%, respectively (NS). Severe allergic reactions were seen in 2% vs 1%. **Conclusions:** Pcal-treatment is as effective and safe as Pxel, without standard use of premedication and a shorter infusion time. Clinical trial information: NCT00989131.

5518 Poster Discussion Session; Displayed in Poster Session (Board #76), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Preliminary single agent activity of IMGN853, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in platinum-resistant epithelial ovarian cancer (EOC) patients (pts): Phase I trial. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: IMGN853 (mirvetuximab soravtansine) is a FRα-targeting ADC that comprises a FRα-binding antibody conjugated with the potent maytansinoid, DM4. **Methods:** This phase I trial evaluates the safety, pharmacokinetics, pharmacodynamics and anti-tumor activity of IMGN853 in pts with FRα-positive solid tumors. A recommended phase II dose (RP2D) of 6.0 mg/kg, administered once every three weeks using adjusted ideal body weight was established in the dose-finding phase. Preliminary evidence of antitumor activity is being investigated at the RP2D in disease-specific cohorts of pts with platinum-resistant EOC and relapsed/refractory endometrial carcinoma. Here we report preliminary clinical activity (partial PR or complete CR response, CA125 response, SD $\geq$ 6 cycles) at the RP2D in pts with platinum-resistant EOC. **Results:** To date, 14 platinum-resistant EOC pts have been treated at the RP2D: 2 in dose escalation; 12 in the expansion cohort. All pts were heavily pretreated (mean: 4.5; range 2-12 prior treatments), all had prior taxane exposure, and all had progressed on their most recent regimen. All pts had FRα-positive tumor expression by IHC in archival tissue. Clinical benefit was observed in 5 /10 evaluable patients (4 have not reached 1st assessment): 4 PRs and 1 confirmed CA125 response, for an objective response rate (ORR) of 40% and clinical benefit rate (CBR) of 50%. In each pt with a PR, tumor regression had begun early on treatment (cycle 2 evaluation). Shrinkage of visceral metastases was seen: a PR pt had a 45% reduction in a 5 cm liver mass. One additional pt had an unconventional response: the disappearance of a non-target lesion with development of new lesions. The majority of adverse events (AEs) were CTCAE grade 1 or 2, with diarrhea, ocular events, cough, fatigue, decreased appetite, neuropathy and nausea reported in $>$ 20 % of pts. Nine of the 14 pts remain on study; enrollment continues. **Conclusions:** IMGN853 demonstrates promising preliminary clinical activity with an ORR of 40% and CBR of 50%, in heavily pretreated platinum-resistant ovarian cancer pts with a manageable AE profile. Clinical trial information: NCT01609556.

5519 Poster Discussion Session; Displayed in Poster Session (Board #77), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Autologous oxidized whole-tumor antigen vaccine in combination with angiogenesis blockade to elicit antitumor immune response in ovarian cancer. *First Author: Janos L. Tanyi, University of Pennsylvania, Philadelphia, PA*

Background: Personalized tumor lysate vaccines can encompass all putative antigens in tumors. **Methods:** A pilot clinical trial was conducted using an autologous oxidized whole tumor cell lysate dendritic cell (DC) based vaccine (vx) injected intranodally, alone or in combination with bevacizumab (Bev) with or without low-dose IV cyclophosphamide (Cy) and/or oral aspirin (ASA), in recurrent ovarian cancer patients (pts). Pts were treated every 3 weeks. Most of the pts were platinum-resistant and heavily pretreated. Adverse events (AEs) were graded by CTCAE v4.0 and clinical responses by RECIST v1.1. **Results:** To date, 35 pts (cohort 1 (vx only; n = 5), 2 (vx+bev; n = 10), 3 (vx+bev+Cy; n = 10) and 4 (vx+Bev+Cy+ASA; n = 10) have received over 392 vx doses. The treatment was well tolerated without serious AEs. Immune response to autologous antigen was seen mainly in cohorts 3 and 4, which received low-dose Cy. An increase in the frequency of T cells recognizing known tumor associated antigens (Her2, WT1, mesothelin, NY-ESO-1) was observed post-vx. Moreover, it is demonstrated for the first time that vaccination with whole tumor lysate-loaded DCs elicited a CD8 T cell response against mutated peptides derived from private non-synonymous somatic tumor mutations. Six pts achieved a partial response or were disease-free at end of treatment. The median progression-free survival (PFS) of cohort 1, 2, 3 and 4 were 4, 3.8, 11.1 and 10.1 mos, respectively. The median overall survival (OS) of cohorts 1 and 2 were 35.3 and 11.4 mos, while for cohorts 3 and 4 it has not been reached, with median potential follow up of 19 mos. A historic population (HP) of 16 pts from the same institution who received Bev+Cy (without vx) had PFS and OS of 4.1 and 26.4 mos respectively. Estimated PFS at 6 mos was 70% for cohorts 3 and 4 and 31% in the HP. The OS at 20 mos was 100% and 90% for cohorts 3 and 4, respectively and 61% for the historic cohort. **Conclusions:** Clinical benefit was demonstrated only in pts who exhibited an immune response against whole tumor lysate or autologous tumor. The use of oxidized whole tumor lysate DC vaccine is safe, effective in eliciting a broad antitumor immunity including private neoantigens. Clinical trial information: NCT01132014.

5520 Poster Discussion Session; Displayed in Poster Session (Board #78), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

MITO (Multicentre Italian Trials in Ovarian cancer): CERV 2 trial—A randomized phase II study of carboplatin and paclitaxel +/- cetuximab, in advanced and/or recurrent cervical cancer. *First Author: Sandro Pignata, MITO and Istituto Nazionale Tumori di Napoli, Napoli, Italy*

Background: Carboplatin (C) plus paclitaxel (P) is among standard options for treatment of advanced or recurrent cervical cancer (ARCC) patients (pts). Cervical cancer cells often express Epidermal Growth Factor receptor (EGFR). Cetuximab (CET), an anti-EGFR monoclonal antibody, can be safely combined with CP. MITO-CERV 2 is a comparative randomized phase 2 study, testing the addition of CET to CP. **Methods:** ARCC pts, < 2 previous chemotherapy, ECOG PS$\leq$1, were randomized to CP (C AUC5 + P 175 mg/m^2, d1q21) for 6 cycles +/- CET (400 mg/m^2 one week before starting CP, then 250 mg/m^2 weekly) until disease progression or unacceptable toxicity. Primary endpoint was event-free survival (EFS), i.e. time from randomization to progression, death, definitive discontinuation of the whole treatment or loss to follow-up, whichever occurred first. With a 4.5 mos expected median EFS and a 6.4 mos auspicated EFS (HR 0.70), 0.20 one-tailed α and 80% power, 89 events were required for the final intent-to-treat analysis. **Results:** 108 pts were randomly assigned to CP (n = 53) or to CP-CET (n = 55). Median age was 50, 69% were PS0, 76% had recurrent disease, 91% had distant metastasis and 57% had received previous chemotherapy. A median number of 6 CP cycles was given in both arms. After a median follow-up of 23 mos (95% CI:20-26), 102 pts had an event, 97 progressed and 61 died. Median EFS was 4.7 and 6.0 mos (one-tail p = 0.43), median PFS was 5.2 and 7.6 mos (one-tail p = 0.20) and median OS was 17.7 and 17 mos (one-tail p = 0.27), with CP and CP-CET, respectively. One patient died for a stroke during standard treatment. There was no difference in the occurrence of severe side-effects, except grade 3-4 skin toxicity reported only with CP-CET (8 cases, 6 with acneiform rash, p = 0.004). Out of 86 patients eligible for RECIST, objective response rate was 43% and 38% with CP and CP-CET respectively (p = 0.63). **Conclusion**: The addition of CET to CP is not worthy of further investigation in unselected ARCC pts. Efforts are ongoing to retrospectively collect tumor samples for an exploratory biomarker analysis. ClinicalTrials.gov NCT00997009. Partially supported by Merck Serono. Clinical trial information: NCT00997009.

5521 Poster Discussion Session; Displayed in Poster Session (Board #79), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Effect of sentinel lymph-node biopsy alone on the morbidity of the surgical treatment of early cervical cancer: Results from the prospective randomized study Senticol2. *First Author: Patrice Mathevet, CHU Vaudois, Lausanne, Switzerland*

Background: Sentinel lymph node (SLN) biopsy is now part of the management of early cervical cancer. Feasibility and low false negative rate in case of bilateral detection have been demonstrated by several studies. However, patients' benefits have not been demonstrated after SLN biopsy only. **Methods:** A multicenter prospective randomized study comparing SLN biopsy alone (Arm A) versus SLN biopsy + pelvic lymph-node dissection (Arm B) in early cervical cancer, has been carried out in France. Patient's eligibility criteria were: 1) FIGO stage IA/IB1/IIA1 cervical cancer, 2) squamous or adenocarcinoma histology, 3) non pregnant patients aged $>$ 18. All patients underwent SLN identification with a combined method (technetium + Patent blue). Patients with negative SLN at per-operative assessment were randomized. The primary objective was to compare the surgical morbidity of the 2 arms. The planned sample size was 124 patients per arm for a type I error rate of 5% and a one sided test. The protocol has been funded by the French NCI and has been reviewed by an Ethical Committee. **Results:** 267 patients were included between March 2009 and July 2012, and 61 patients were not randomized due to: unilateral or no SLN detection, positive SLN at frozen sections and other reasons. Of the remaining 206 patients, 105 were in arm A and 101 in arm B. The analysis was performed in intention-to-treat. The median number of SLN was 3 per patient and 1 per side. No false negative case was identified in arm B. The surgical morbidity related to the lymph-node dissection was largely and significantly reduced in arm A: 33 cases (31.4%) vs 52 cases (51.5%) in arm B, (p = 0.0046, X2test) and major morbidity related to the lymph-node dissection was also reduced: 1 case in arm A vs 6 cases in arm B (p = 0.06). The rate of early post-operative neurological symptoms was significantly reduced in arm A (7.8% vs 20.6% in arm B, p = 0.01). **Conclusions:** SLN biopsy may improve the management of early cervical cancer, as it induced less surgical morbidity than full pelvic lymphadenectomy. This study leads to morbidity-sparing approaches in cervical cancer treatment incorporating SLN biopsy alone in negative SLN patients. Clinical trial information: NCT01639820.

5522 Poster Discussion Session; Displayed in Poster Session (Board #80), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

CT perfusion as an early biomarker of treatment efficacy in advanced ovarian cancer: An ECOG-ACRIN and NRG GOG study. *First Author: Ting-Yim Lee, Lawson Health Research Institute, London, ON, Canada*

Background: GOG-0262 is an advanced stage ovarian cancer phase III trial comparing standard paclitaxel (q3 week)/carboplatin to dose-dense paclitaxel (weekly)/carboplatin with and without bevacizumab per physician choice. ACRIN 6695's primary objective was to determine whether CT perfusion (CTP) parameters are prognostic of progression-free survival (PFS) at 6 months (PFS-6) in a cohort of GOG-262 patients. **Methods:** FIGO stage III or IV patients with suboptimal surgical cytoreduction or undergoing neoadjuvant therapy were recruited and underwent CTP studies before (T0) and at 3- (T1) and 4-weeks (T2) after chemotherapy initiation. Target lesion blood flow (BF) and blood volume were derived with CTP software (GE Healthcare). The association of BF changes from baseline to T2, dichotomized at zero ($\Delta BF_{\pm}$), and the response rate (best confirmed response by RECIST criteria) and PFS-6 rate were assessed with Fisher's exact tests. Cox regression model was used to assess the association between $\Delta BF_{\pm}$ and time-to-progression (TTP) and overall survival (OS). **Results:** From August 2011 to July 2013, 120 patients were screened, yielding 76 evaluable (with both T0 and T2 CTP studies analyzable) patients from 19 centers. The median age and TTP of those 76 patients were 61 (range 25-87) years and 427 (95% CI: 372-505) days. Overall response and PFS-6 rates were 74% (56/76) and 96% (73/76), respectively. 11/76(14%) patients had increase in tumor BF from baseline to T2 (positive $\Delta BF_{\pm}$). Positive $\Delta BF_{\pm}$ were significantly associated with lower response rate (45% vs. 78%, p = 0.03) and shorter TTP (median TTP 335 vs. 457 days, HR 2.9, 95% CI: 1.3-6.4, p = 0.008); and a trend towards lower PFS-6 rate (82% vs. 98%, p = 0.053). The significant association between $\Delta BF_{\pm}$ and TTP remained after adjusting for age, baseline tumor volume, change in tumor volume or surgery status (adjuvant vs. neoadjuvant) individually ($p < 0.02$). $\Delta BF_{\pm}$ was not significantly associated with OS (p = 0.28). **Conclusions:** CTP parameters measured within 4 weeks of initiating therapy may provide early prognostic information for treatment response and TTP, and could be used to refine treatment interventions for advanced ovarian cancer in future clinical trials. Clinical trial information: NCT01167712.

5523 Poster Discussion Session; Displayed in Poster Session (Board #81), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

The role of PET-CT in treatment decision making for women with locally advanced cervical cancer. *First Author: Lorraine Margaret Elit, McMaster University, Hamilton, ON, Canada*

Background: Women with locally advanced cervical cancer (LACC) are treated with concurrent chemotherapy and radiation therapy (CRT) with curative intent. Pre-treatment staging is important to define the extent of disease and guide therapy. Staging with ^{18}FDG PET-CT may detect more extensive disease compared to usual CT. Although promising, the existing data on PET-CT for this indication is based on small retrospective studies. OCOG conducted a randomized trial to address this question. Our objective was in patients with LACC, to determine the added value of staging with PET-CT over usual CT abdomen-pelvis in terms of the treatment received. **Methods:** Women with FIGO Stages IB-IVA carcinoma of the cervix who were candidates for CRT were randomized 2:1 to PET-CT or CT abdomen-pelvis. Stratification was by center, MRI, and Stage (1B1-2A and 2B – 4A). Treatment delivered was classified as standard pelvic CRT of curative intent; more extensive CRT of curative intent e.g. extended-field radiation (CRT-EF); or palliative treatment of non-curative intent (e.g. symptom management, radiation, chemotherapy or both). Treatment received was adjudicated by experts unaware of arm. **Results:** 171 women were randomized to PET-CT (113) or CT (58) between Apr 2010 and Jun 2014. The arms were well-balanced with a slightly higher rate of Stage 3B in the PET-CT arm (21%) compared to the CT (14%) arm. MR staging was performed in 68%. In the PET-CT arm, 59.8% of subjects had standard pelvic CRT, 34.8% had CRT-EF, and 5.4% had palliative/non-curative therapy. The corresponding data for CT arm was 73.2%, 21.4% and 5.4%. There was no difference detected in the rates of more extensive CRT of curative intent or palliative treatment between PET-CT (40.2%) versus CT (26.8%), OR 1.90, 95%CI 0.92, 3.92, p = 0.08). At a median FUP of 25.8 months, there have been 13 deaths (11.5%) in the PET-CT arm and 7 (12.0%) in the CT arm. **Conclusions:** We were unable to detect a difference in treatments received with the addition of PET-CT. Improvement in CT quality and use of MRI may explain the negative result. In an era of cost constraint, the additional benefit from PET appears to be limited in women with LACC. Clinical trial information: NCT00895349.

5524 Poster Discussion Session; Displayed in Poster Session (Board #82), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in high risk endometrial cancer. *First Author: Mostafa Atri, University Health Network, Toronto, ON, Canada*

Background: To assess if PET-CT improves accuracy of CT to detect lymph node (LN) metastasis in high risk endometrial cancer. **Methods:** This was a prospective HIPAA compliant ACRIN/GOG multicenter trial. Patients underwent contrast enhanced PET-CT followed by pelvic and abdominal lymphadenectomy. Seven independent blinded readers reviewed PET-CT and CT only images in different sessions at least one month apart. Region correlation was performed between pathology and review results for abdomen (right and left para-aortic, right and left common iliac) and pelvis (right and left external iliac and right and left obturator) regions. Abdomen and pelvic regions were combined, respecting laterality, to calculate accuracy values at participant level. Reference standard was pathology of surgically removed LNs. Reader average sensitivities/specificities of PET-CT vs CT were compared with generalized linear mixed models. Reader average AUCs were compared with Obuchowski's method. Fleiss' kappa was used to assess reader agreement. **Results:** A total of 207 patients had PET/CT and pathology proof in the abdomen from 215 patients enrolled between January 2010 and June 2013.Twenty-three of 207 patients had metastasis to abdominal LNs. All 23 abdominal positive and 26 randomly selected abdominal negative patients were used for reader study. Reader study cases were from 36 to 81 years old (mean; 62.7±9.6). Cancer stages were: I = 30, II = 14, III = 5; sixteen endometrioid, 17 serous, 6 carcinosarcoma or MMT, 6 mixed epithelial carcinoma, and 4 others. Three were 5 grade 2, 20 grade 3, and 24 unknown. Mean sensitivities of PET-CT/CT alone in abdomen were 0.65 (CI:0.57,0.72)/0.50 (CI:0.43,0.58) (p = 0.01) and in pelvis 0.65 (CI:0.57,0.72)/0.48 (CI:0.41,0.56) (p = 0.004). Corresponding mean specificities were 0.88 (CI:0.83,0.92)/0.93 (CI: 0.89,0.96) (p = 0.11) and 0.93 (CI:0.86,0.96)/0.89 (CI:0.82,0.94) (p = 0.27). Mean AUCs were 0.78 (CI:0.66,0.89)/0.74 (CI:0.63,0.86) (p = 0.39) and 0.82 (CI:0.71,0.92)/0.73 (CI:0.63,0.84) (p = 0.02). Agreement for PET/CT was 0.81in both abdomen and pelvis. **Conclusions:** Addition of PET to diagnostic CT significantly increased diagnostic accuracy to detect LN metastasis in abdomen and pelvis. Clinical trial information: ACRIN6671GOG0233.

5525 Poster Session (Board #83), Sat, 1:15 PM-4:45 PM

Randomized phase III trial of carboplatin/paclitaxel alone (CP) or in combination with bevacizumab followed by bevacizumab (CPB) and secondary cytoreduction surgery in platinum-sensitive recurrent ovarian cancer: GOG0213, an NRG Oncology/GOG Study—Analysis of patient reported outcomes (PRO) on chemotherapy randomization. *First Author: Karen Basen-Engquist, The University of Texas MD Anderson Cancer Center, Houston, TX*

Purpose: GOG 213 is a bifactorial, phase III, randomized trial studying the efficacy and tolerability of the incorporation of B and secondary cytoreduction in women with platinum sensitive recurrent EOC. The primary endpoint was OS. Here we report intervention related PROs. **Methods:** PRO's were assessed using the ovarian Functional Assessment of Cancer Therapy-Trial Outcome Index (FACT-O TOI, QoL endpoint for chemotherapy objective), treatment side effects related to B (TSE-B), physical function (PF) subscale of the Rand SF-36 (QoL endpoint for surgical randomization), and treatment side-effects related to surgery (TSE-Surg). Assessment time points were baseline, prior to cycles 1, 3 and cycle 6, 6 mo. after cycle 1, and 12 mo. after cycle 1. QoL scores were compared using a linear mixed model adjusting for baseline score, age, and assignment to secondary surgery. Mixed effects mixed distribution model evaluated treatment differences in physical functioning on the RAND SF-36. **Results:** Patients randomized to CT (n = 298 (88%)) or CTB (n = 302 (90%)) were evaluable for QoL. Treatment compliance was 93% at baseline, 88% at cycle 3, 83% at cycle 6, 82% at 6 months and 78% at 12 months. More CTB patients completed PRO assessments (P = 0.037). FACT-O TOI scores at baseline were similar. Subscales of FACT-O showed no differences in TSE-Bev, except pre-cycle 3 physical well-being, which was negatively impacted by treatment (p = 0.028). CPB patients had significantly worse physical functioning (P = 0.0156): treatment difference of 3.4 points (95% CI: 0.05-6.7, p = 0.048) at cycle 3 and 6.8 points (95%CI: 3.0-10.6, p = 0.0004) at cycle 6. **Conclusion**: Treatment with CPB was not associated with a significant difference in health-related QoL measured by the FACT-O TOI. While receiving CPB, patients may experience lower physical functioning with recovery to baseline during maintenance B. Clinical trial information: NCT00565851.

5526 Poster Session (Board #84), Sat, 1:15 PM-4:45 PM

Clinical characteristics and survival outcomes in *BRCA1*-methylated epithelial ovarian cancer (Bmeth-OC): A pooled analysis of data for 1,278 patients across five studies. *First Author: Roshni Deepa Kalachand, Department of Medical Oncology, Beaumont Hospital, Dublin, Ireland*

Background: *BRCA1/2* mutations render ovarian cancers (OC) homologous recombination deficient (HRD) and thus sensitive to platinum and PARP inhibitors. Data on *BRCA1* promoter methylation in OC, another potential biomarker of HRD, are conflicting and limited. **Methods:** We searched PubMed and ASCO/ESMO abstracts for studies with survival outcomes in Bmeth-OC. Individual patient data were obtained from 5 studies. Associations between clinical characteristics and Bmeth-OC were determined using the Cochran-Mantel-Haenszel test. Progression-free (PFS) and overall survival (OS) differences between Bmeth-OC and non-Bmeth-OC (and between Bmeth-OC, *BRCA1/2*-mutated OC and *BRCA1/2*-wild type non-Bmeth-OC where data available) were estimated with Kaplan-Meier analysis, adjusting for cohort. **Results:** We obtained data for 164 patients (pts) with Bmeth-OC and 1114 pts with non-Bmeth-OC (Bmeth-OC frequency = 12.8%). Median age was 59 (range 26-93) and median follow-up was 31 months (range 0-203). 72.7% of OCs were high grade serous. 91.3% of pts received adjuvant platinum-based chemotherapy. Bmeth-OC was associated with high grade (85.4% vs 80.7% of non-BmethOC, p = 0.016) and younger age (< 59: 58.5% vs 47.1% of non-BmethOC, p = 0.012), but not stage, histology, cytoreduction or platinum sensitivity. There was no difference in median PFS (18.7 vs 19.1 months, p = 0.42) or OS (44.3 vs 46 months, p = 0.62) between Bmeth-OC and non-Bmeth-OC. *BRCA1/2* mutation status was assessed in 3 cohorts (639 pts). *BRCA2*-mutated OC had a better median PFS and OS compared to *BRCA1*-mutated OC, Bmeth-OC, and *BRCA1/2*-wild type non-Bmeth-OC (PFS: 26 vs 17.6, 15.6, 15.8 months, p = 0.025; OS: 74.3 vs 49.3, 41.9, 44mths, p = 0.003).On multivariate Cox analysis including clinical variables, *BRCA2* mutation but not *BRCA1* mutation/methylation had a significant effect on OS/PFS (p = 0.001, HR = 0.44 95%CI [0.27-0.70]/p = 0.001, HR = 0.5 95%CI [0.33-0.77]). **Conclusions:** *BRCA1* methylation occurs in OC in younger pts, but has no impact on survival. *BRCA2* mutation, in contrast to *BRCA1* mutation/methylation, is an independent prognostic factor for improved survival in OC.

5527 Poster Session (Board #85), Sat, 1:15 PM-4:45 PM

Efficacy and safety comparison between belotecan and topotecan in patients with recurrent or refractory ovarian cancer: A multi-center, randomized, open-labelled, parallel-group phase IIb trial. *First Author: Hee Seung Kim, Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, South Korea*

Background: Belotecan is a camptothecin derivative with anti-tumor properties. Previous studies suggested the feasibility of belotecan-based chemotherapy for patients with primary or recurrent ovarian cancer. Thus, we conducted a phase IIb trial to compare the efficacy and safety between belotecan and another derivative of camptothecin, topotecan, in patients with recurrent or refractory ovarian cancer. **Methods:** Patients with recurrent or refractory ovarian cancer were randomized to receive belotecan 0.5 mg/m^2 (B-arm) or topotecan 1.5 mg/m^2(T-arm) intravenously for 5 consecutive days every 3 weeks till 6 cycles or disease progression. The primary endpoint was overall response rate based on RECIST or GCIG criteria, and secondary endpoints were progression-free survival (PFS), overall survival (OS) and adverse events according to NCI-CTCAE version 4.0. **Results:** One hundred and forty one patients were randomized from January 2011 to June 2014. Among all patients, 140 were eligible in full analysis (FA) set where patients received at least one dose (B-arm, n = 71; T-arm, n = 69), and 130 were eligible in per protocol (PP) set where patients completed the study protocol (B-arm, n = 66; T-arm, n = 64). Clinico-pathologic characteristics were not different between the two arms. ORR was not different between B- and T-arms in FA and PP sets (29.6% vs. 26.1%, p = 0.645; 30.3% vs. 25%, p = 0.499). Median values of PFS in B- and T-arms were 26.4 vs. 17.3 months in FA (HR = 0.69; 95% CI 0.41-1.16) and PP sets (HR = 0.68; 95% CI 0.39-1.16) without significant difference. However, OS was improved in B- versus T-arm in FA set with marginal significance (median values, 37.1 vs. 21.3 months, log-rank p = 0.053; HR = 0.60; 95% CI 0.35-1.01), and PP set (median values, 37.1 vs. 24.9 months, log-rank p = 0.023; HR = 0.53; 95% CI 0.31-0.93). Grade 3 or 4 adverse events were not different between the two arms. **Conclusions:** Belotecan may have a similar response and toxicity rates to topotecan in patients with recurrent or refractory ovarian cancer. Moreover, belotecan may prolong OS when compared with topotecan in these patients. Clinical trial information: NCT01630018.

5528 Poster Session (Board #86), Sat, 1:15 PM-4:45 PM

Multicentre trial of carboplatin/paclitaxel versus oxaliplatin/capecitabine, each with/without bevacizumab, as first line chemotherapy for patients with mucinous epithelial ovarian cancer (mEOC). *First Author: Martin Eric Gore, Royal Marsden Hosp NHS Trust, London, United Kingdom*

Background: Advanced mEOC responds poorly to standard therapy. It comprises < 8% pts in ovarian cancer trials, so it is difficult to examine treatment effects in this subgroup. We conducted the first ever randomised trial specific for this rare subgroup (4 regimens). **Methods:** mEOC/GOG 241 is a multi-centre randomised phase II trial (UK, USA) in chemo- naive pts with advanced/recurrent disease. Six 21-day cycles of chemotherapy were given to each of 4 arms: (A) carboplatin (AUC 5/6) + paclitaxel (175mg/m^2); (B) oxaliplatin (130 mg/m^2) + capecitabine (850mg/m^2 bd; D1-14); (C) carboplatin/paclitaxel with bevacizumab (15mg/kg); (D) oxaliplatin/capecitabine with bevacizumab. Bevacizumab was given concurrently, then alone 3-weekly for 12 more cycles. 332 pts required to detect 5 month increase in median PFS for oxaliplatin/capecitabine (B+D), or adding bevacizumab (C+D). **Results:** Trial stopped early (2013) due to poor accrual (median follow up 23 months; 31 progressions/deaths). 50 pts recruited: n = 13, 13, 11, 13 in arms A-D. Median age 54 yrs; FIGO stage II (n = 15), III (n = 25), IV (n = 4), recurrent (n = 6); ECOG 0 (n = 34), 1 (n = 15), 2 (n = 1). 62, 85, 82, 69% in arms A-D completed 6 cycles of combination therapy, and 36, 46% completed 12 maintenance cycles of bevacizumab (arms C,D). 2,2,4,2 pts (arms A-D) had complete/partial response. Median PFS 10.1 (B+D) vs 15.4 (A+C) months; hazard ratio (HR) 1.08, 95% CI 0.53-2.19, p = 0.83. Median PFS 17.4 (C+D) vs 8.8 (A+B) months, HR 0.88 95% CI 0.43-1.79, p = 0.72. Grade 3-4 toxicities (most common: neutropenia, & hypertension for bevacizumab) were seen in 62, 62, 55, 92% pts in arms A-D (total 4 pts with grade 4). After specialist pathology review n = 36 so far, 19 were considered to not have primary mEOC (many metastatic disease). **Conclusions:** Setting up & conducting this international trial was challenging in this rare group; correctly assigning histological diagnosis was difficult. Bevacizumab may delay progression (ITT analyses), but without sufficient pts no conclusions can be made. Primary mEOC is rarer than previously thought so different approaches are needed to evaluate new therapies. Clinical trial information: NCT01081262.

5529 Poster Session (Board #87), Sat, 1:15 PM-4:45 PM

Efficacy and safety of olaparib monotherapy in a subgroup of patients with a germline *BRCA1/2* mutation and advanced ovarian cancer from a Phase II open-label study. *First Author: Susan M. Domchek, Basser Research Center for BRCA at the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: Olaparib (Lynparza), an oral PARP inhibitor, has demonstrated antitumor activity in patients (pts) with *BRCA*-mutated(m) ovarian cancer. Data from the overall cohort of pts in this Phase II study (NCT01078662) have been reported (Kaufman *et al. JCO* 2014). Presented here are data from a subgroup of pts with germline (g)*BRCA*m ovarian cancer, stratified by prior lines of chemotherapy (< 3 or ≥ 3) and platinum sensitivity. **Methods:** Pts were treated with olaparib 400 mg twice daily (bid; capsule formulation) monotherapy until disease progression according to RECIST v1.1. Objective response rate (ORR) and duration of response (DoR) were assessed for pts with measurable disease at baseline (n=167). Safety and tolerability were assessed for all pts (n = 193). **Results:** Of the pts with measurable disease at baseline, 30 and 137 had received < 3 and ≥ 3 prior lines of chemotherapy, respectively. Adverse events (AEs) most commonly causally related to olaparib were nausea (107/193 pts, 55%), fatigue (99 pts, 51%) and anemia (60 pts, 31%; grade ≥ 3 in 36/193 [19%]). Twenty pts (10%) had a serious AE causally related to olaparib. Two pts developed leukemia and one pt myelodysplastic syndrome; all three had been heavily pretreated. **Conclusions:** Olaparib 400 mg bid (capsule form) monotherapy demonstrated notable antitumor activity in g*BRCA*m pts with advanced ovarian cancer, including heavily pretreated, platinum-resistant pts. No new safety signals were identified. Clinical trial information: NCT01078662.

Platinum sensitivity	Confirmed responders, n/N	ORR, % (95% CI)	Median DoR, mths (95% CI)	Confirmed responders, n/N	ORR, % (95% CI)	Median DoR, mths (95% CI)
		< 3 prior lines			≥ 3 prior lines	
Total	14/30	47 (28, 66)	6.2 (3.9, 9.2)	46/137	34 (26, 42)	7.9 (5.6, 9.6)
Sensitive*	6/9	67 (30, 93)	5.7 (3.7, 9.2)	17/38	45 (29, 62)	8.2 (5.6, 13.5)
Resistant	4/8	50 (16, 84)	8.3 (3.9, NC)	22/77	29 (19, 40)	8.0 (4.8, 14.8)
Refractory	0/1	0 (0, 98)	0	2/14	14 (2, 43)	6.4 (5.4, 7.4)
Unknown	4/12	33 (10, 65)	5.4 (3.8, 6.8)	5/8	63 (24, 91)	7.9 (4.7, NC)

*Platinum sensitive but ineligible to receive further platinum-based chemotherapy; n, response; N, total pts with measurable disease; NC, not calculated

5530 Poster Session (Board #88), Sat, 1:15 PM-4:45 PM

A GINECO phase I study evaluating lenalidomide (Le) combined with pegylated liposomal doxorubicin (PLD) and carboplatin (C) in late (>6 months) recurrent ovarian cancer (LROC) patients (pts). *First Author: Frédéric Selle, Medical Oncology, Hôpital Tenon, Paris, France*

Background: Le is a thalidomide analogue with both immunomodulatory and anti-angiogenic properties. Le has shown efficacy and good tolerability as single agent for LROC pts (Selle F, et al. Ann Oncology 2014). **Methods:** LROC pts were enrolled in cohorts of 3 to 6 pts and treated with PLD 30 mg/m2 and C AUC 5 day (d)1 q4 weeks in combination with daily oral escalation dose of Le (15, 20 and 25 mg/d) according to different schedules (A: 21 consecutive days from d1; B: 21d from d2; C: 21d from d7; D: 14d from d2). Dose limiting toxicities (DLT) were defined as: treatment delay (> 14d), grade (Gr) 3 febrile neutropenia, Gr 4 neutropenia or Gr 4 thrombocytopenia lasting more than 7 d, bleeding with platelet transfusion and all other Gr ≥ 3 toxicity (except vomiting) occurring at cycle 1. Completion of the 6 planned cycles without inacceptable toxicity defined feasibility of the regimen. Secondary objectives were response, progression-free (PFS) and overall survival (OS) rates. **Results:** 22 pts were enrolled up to 01/2014 with a median age of 61.4 years (47-73). Pts characteristics were: serous (82%), previous lines (one 68%, two 32%), median platinum-free interval (PFI) 11.4 months and ECOG 0 (73%). Safety: all the 4 schedules were evaluated at a 15mg/d Le dose. With schedule A&B, 2DLT/3pts and 3DLT/4pts were observed. DLT was cycle delay > 14d for neutropenia (2pts) or neurotoxicity (1pt), Gr3 thrombosis (1pt) and Gr3 visual acuity decreased (1pt). With schedule C&D, 1DLT/9pts (Gr3 rash) occurred at cycle 1, only 1 pt completed the 6 planned cycles without dose reduction and 6 pts stopped early for toxicity (hematotoxicity for 5pts). Efficacy: complete and partial responses were observed in respectively 10% and 29% of pts. Median PFS and OS were 9.2 months (95% CI, 7.4-11) 28 months (95% CI, 18.9-37.1) respectively. **Conclusions:** Lenalidomide combined with PLD-C was not feasible at the dose and schedules evaluated, mainly due to cumulative hematologic toxicity. Clinical trial information: NCT01111903.

5531 Poster Session (Board #89), Sat, 1:15 PM-4:45 PM

Phase II randomized trial of neoadjuvant (NA) chemotherapy (CT) with or without bevacizumab (Bev) in advanced epithelial ovarian cancer (EOC) (GEICO 1205/NOVA TRIAL). *First Author: Yolanda García, Corporació Sanitaria Universitaria Parc Taulí, Universitat Autonoma de Barcelona, Barcelona, Spain*

Background: First-line carboplatin(C)-paclitaxel(P) and Bev has proved to be an active combination after primary debulking surgery and improved overall survival in suboptimal resected advanced EOC patients (pts). However, the role of Bev in the NA setting has not been well defined yet. **Methods:** We performed a phase II randomized open label multicentric study in 66 pts with high grade serous or endometroid EOC, FIGO stage III-IV, ECOG 0-2, considered unresectable in whom NA CT and interval debulking surgery (IDS) were planned. Main exclusion criteria were intestinal occlusion and contraindication for Bev therapy. Pts were randomized to four courses of triweekly C AUC 6 and P 175 mg/m2 iv alone or with at least 3 courses of bev 15 mg/kg i.v. every 3 w. in experimental arm. The primary endpoint was the complete macroscopic response rate at the time of IDS. Secondary objectives were safety, surgical feasibility, optimal surgery rate, RECIST 1.1 and GCIG response rate. Biomarker analysis were performed in pre and post biopsies. All pts received 3 additional courses of CT and Bev after IDS followed by maintenance Bev up to complete 15 month. **Results:** We report the preliminary data of 64 pts. Clinical pts characteristics were well balanced with median age 59.9 y.o and a 34.4% stage IV. No differences in the primary endpoint were found (1/32 Control Arm and 0/32 Bev Arm) but there was a higher rate of surgical feasibility in the Bev Arm (64 vs 88%). Optimal surgery rate also favored the Bev arm (77.7 vs 86.4%) and there wasn't any patient deemed unresectable at the time of surgery in the Bev arm (2 vs 0). None of these figures were statistically significant difference. There were lower rates of serious adverse events (grade 3-4) in bev arm (40.6 vs 18.8%, p = 0.055). Three Bev related adverse events of special interest were observed in 3 pts (1 G3 entero-vaginal fistulae, 1 surgical dehiscence, 1 deep venous thrombosis). **Conclusions:** Our preliminary data have shown that NA bev seems feasible and could improve the surgical outcomes in advanced EOC considered initially unresectable. Updated clinical and translational data will be provided. Clinical trial information: NCT01847677.

5532 Poster Session (Board #90), Sat, 1:15 PM-4:45 PM

Use of homologous recombination deficiency (HRD) score to enrich for niraparib sensitive high grade ovarian tumors. *First Author: Keith Matthew Wilcoxen, TESARO, Inc., Waltham, MA*

Background: The therapeutic potential of PARP inhibitors is predicted to extend beyond patients with germline BRCA mutations ($BRCA^{mut}$) to those with homologous recombination deficient (HRD) cancers. An HRD test is being applied to patient samples to identify BRCA mutated tumors, provide a categorical determination of tumor HRD, and determine an enrichment strategy for patients with tumors that are sensitive to niraparib treatment. **Methods:** Archival FFPE tumor tissue obtained from ovarian cancer patients enrolled in an ongoing Phase III clinical study (ENGOT-OV16/NOVA, NCT 01847274) and a living tumor bank was subjected to HRD testing. The final HRD score is a numeric output ranging from 0-100. A predefined cut-off score of 42 was utilized to determine HRD status of each tumor and classify it as HR deficient (HRD score $\geq$ 42) or non-deficient (HRD score $<$ 42). Classification of BRCA mutations from tissue was based on analysis criteria consistent with the laboratory's approved diagnostic BRCA testing. Niraparib efficacy was evaluated utilizing a living tumor bank of orthotopic patient-derived ovarian xenografts. Intraperitoneal tumorgrafts were monitored for tumor growth with twice-weekly transabdominal ultrasound imaging. **Results:** One hundred and six high grade serous ovarian tumors from a living tumor bank were evaluated for HRD, BRCA1/2 mutations, and BRCA1 promoter hypermethylation. Twenty six tumors (25%) were BRCA deficient (a deleterious BRCA1/2 mutation or BRCA1 hypermethylation with a concomitant loss of heterozygosity). All BRCA1/2 deficient tumors had an HRD score of 42 or greater, with the exception of one tumor. The in-vivo response to niraparib monotherapy has been evaluated in 20 unique tumor models across a range of HRD scores. All responding tumors had an HRD score of 42 or above, irrespective of BRCA deficiency. **Conclusions:** HRD testing of ovarian cancer was predictive of BRCA deficiency. Response to niraparibwas only observed in HRD positive (HRD+) tumors. Our data are supportive of the use of HRD testing to enrich for niraparib responders in high grade ovarian cancer.

5533 Poster Session (Board #91), Sat, 1:15 PM-4:45 PM

The influence of polypharmacy on grade III/IV toxicity, prior discontinuation of chemotherapy and survival in recurrent ovarian cancer patients: An individual participant data meta-analysis of the North-Eastern German Society of Gynecological Oncology (NOGGO) of 1,213 patients. *First Author: Hannah Woopen, Department of Gynecology, European Competence Center for Ovarian Cancer, Charité, University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany*

Background: In ovarian cancer patients prevalence of comorbidity and quantities of prescribed comedications increase with age. We aimed to evaluate the influence of polypharmacy on grade III/IV toxicity, prior discontinuation of chemotherapy and survival. **Methods:** Synthesized raw data of three phase II/III studies ("Tower", "Topotecan phase III" and "Hector") of the North-Eastern German Society of Gynecological Oncology (NOGGO) including 1213 patients were analyzed using logistic regression and cox regression analyses. **Results:** In our analysis 349 patients (28.8%) were older than 65 years at initial diagnosis. Most patients were in an advanced stage at the time of diagnosis (1047 patients FIGO III/IV, 86.3%). Hematological grade III/IV toxicity was documented in 715 cases (58.9%), non-hematological grade III/IV toxicity occurred in 531 cases (43.8%). While 110 patients (9.1%) were naive to comedication, 530 patients (43.7%) were prescribed less than five co-drugs, 683 patients (56.3%) were treated with five or more co-drugs, and 267 (22.0%) were treated with ten or more co-drugs. Most frequent comedications were beta-blockers (211 cases, 17.4%), diuretics (163 patients, 13.4%) and ACE-inhibitors (133 patients, 11.0%). In the multiple regression models, an increasing amount of comedications was associated with overall ($p < 0.001$; OR 1.120), hematological ($p < 0.001$; OR 1.056) and non-hematological ($p < 0.001$; OR 1.134) toxicity. Prior discontinuation of therapy was not associated with the amount of comedications ($p = 0.196$). Increasing number of comedication was not associated with overall survival ($p = 0.068$). **Conclusions:** Our synthesized data analysis suggests that polypharmacy in ovarian cancer recurrence may be a clinically useful predictor of increased risk of grade III/IV toxicity during chemotherapy. Patients with increasing amount of comedication had no disadvantage regarding survival. Hence, polypharmacy should not be a criterion for exclusion of clinical studies in ovarian cancer.

5534 Poster Session (Board #92), Sat, 1:15 PM-4:45 PM

Characteristics of homologous recombination deficiency (HRD) in paired primary and recurrent high-grade serous ovarian cancer (HGSOC). *First Author: Jai Narendra Patel, Levine Cancer Institute, Charlotte, NC*

Background: Defects in the HRD pathway, particularly those involving *BRCA1/2*, have a major impact on the response to DNA damaging platinum-based therapy used in patients with HGSOC. The objective of this study was to assess characteristics of HRD in paired primary and recurrent HGSOC specimens. **Methods:** HRD scores were determined in paired primary and recurrent specimens of HGSOC from 25 patients treated with adjuvant carboplatin and paclitaxel. *BRCA1/2* mutation and *BRCA1* methylation (including loss of heterozygosity (LOH) status), and HRD scores were characterized using tumor DNA-based assays. **Results:** All 50 samples analyzed yielded *BRCA1/2* mutation and *BRCA1* methylation assay data and 7 failed HRD analyses, leaving 19 primary-recurrent pairs available for comparative analysis of HRD. *BRCA1/2* mutations (3/25, 12%) comprised only *BRCA1*, and LOH at *BRCA1* was observed in all mutated tumors. All 3 mutant pairs had high HRD scores (range 46-76, 1 missing value in the primary). No reversion of mutations was observed in recurrent samples. In 3 primary-recurrent pairs with methylation and LOH at the *BRCA1* locus, high HRD scores (range 55-72) were observed. A fourth pair was below the methylation threshold in the primary tumor but had high HRD scores in both primary and recurrent. Two primary-recurrent pairs had high HRD scores with intact *BRCA1/2*. HRD scores between primary and recurrent samples were highly correlated ($r^2 = 0.91$). Scores were somewhat more likely to be higher in the recurrent tumor than in the primary, but the difference was not significant (mean = 2.6, paired t-test p-value = 0.11). Comparison of the genomic profile in paired samples revealed that while a number of tumors acquired additional genomic rearrangements that were different between the primary and recurrent sample, this did not significantly impact the HRD score. **Conclusions:** All markers of HRD examined were maintained between the primary and recurrent specimen. High HRD scores were prevalent (42%) and primarily linked to *BRCA1* mutation and methylation. These data suggest that characterization of recurrent tumors may not yield alternative treatment strategies compared to analysis of the primary tumor.

5535 Poster Session (Board #93), Sat, 1:15 PM-4:45 PM

Role of HE4, CA125, and ultrasound in risk assessment in pelvic mass patients: Results from a prospective, multicentric study. *First Author: Elena Ioana Braicu, Charité – Universitätsmedizin Berlin, Department of Gynaecology, European Competence Center for Ovarian Cancer, Charité Campus Virchow Klinikum, Berlin, Germany*

Background: Ovarian cancer (OC) lacks of specific symptoms and biomarkers for early diagnosis. Advanced stages are associated with poor survival. CA125 and HE4 are overexpressed in OC. Their role in early diagnosis is controversial discussed. Ultrasound criteria (e.g. IOTA algorithms) seem to improve the sensitivity and specificity for risk assessment. **Methods:** In a prospective, multicentric study performed in 676 pelvic mass patients, transvaginal ultrasound together with blood sampling and biomarker analysis were performed. All patients had an ovarian (including paraovarian and tubal) mass and underwent a standardized ultrasound examination, according to IOTA criteria, prior to surgery. ROMA algorithm combining CA125, HE4 and menopausal status, was used to distinguish between benign and malignant disease. An online data base was provided for the prospective documentation of clinical parameters, ultrasound, surgical methods and histology. Patients were included at 7 clinics in Berlin. All samples were analyzed centralized at Labor Berlin. These results represent the analysis of the training cohort. **Results:** From the 676 patients, 57% were premenopausal, 13.3% were diagnosed with OC, 4.3% with borderline tumors, 0.2% Krukenberg tumors and 0.8% rare malignancies of the ovary. The area under the receiver operating characteristic curve (AUC) for the discrimination between benign and malignant tumors was for CA125 0.840 and 0.899, for HE4 0.860 and 0.885 and for ROMA 0.863 and 0.930 in pre-and postmenopausal patients, respectively. The IOTA LR2 model includes one clinical and five ultrasound predictors: age, presence of ascites, presence of papillations with detectable blood flow, maximum diameter of largest solid component, irregular cyst walls and presence of acoustic shadows. IOTA LR2 reached an AUC of 0.971 in premenopausal and of 0.748 in postmenopausal patients. **Conclusions:** HE4 performed slightly better than CA125 in risk assessment in premenopausal patients, nevertheless ultrasound criteria could best discriminate between benign and malignant disease in premenopausal patients. In postmenopausal patients, ROMA reached the best sensitivity and specificity.

5536 Poster Session (Board #94), Sat, 1:15 PM-4:45 PM

Is it time to change the primary endpoint in clinical trials in recurrent ovarian cancer (ROC)?: Symptom burden and outcomes in patients with platinum resistant/refractory (PRR) and potentially platinum sensitive ROC receiving ≥ 3 lines of chemotherapy (PPS ≥ 3)—The Gynecologic Cancer Intergroup (GCIG) Symptom Benefit Study (SBS). *First Author: Michael Friedlander, Prince of Wales Cancer Centre, Randwick, Australia*

Background: The primary endpoint for clinical trials in PRR/PPS ≥ 3 ROC is progression free survival (PFS) and symptom benefit is not typically measured or reported. The primary aim of GCIG SBS is to validate a patient-reported outcome measure (PROM), the MOST (Measure of Ovarian Symptoms and Treatment concerns), to assess symptom benefit from palliative chemotherapy (PC). The SBS recruited 949 patients; the secondary aims provide insights into symptom burden, patients' and clinician's expectations of treatment and outcomes in a "real world" setting. **Methods:** Patients with PRR/PPS ≥ 3ROC completed 4 PROMs before each cycle of chemotherapy. They reported expectation of symptom improvement. Clinicians documented the indications for PC, symptoms at baseline, adverse events and estimated the number of cycles patients would receive. **Results:** Palliation was the major indication for chemotherapy. The mean number of prior regimens was 2.6 (range 1-10). 60% of patients had PRR and 40% had PPS > 3 ROC. At baseline, most patients were symptomatic; 75% rated at least one symptom as moderate (³5 on a 0-10 scale) and 30% rated > 5 symptoms as moderate or worse. The symptoms included pain, fatigue, anorexia, abdominal distension, dyspnea, and constipation. Many had symptoms related to prior chemotherapy (e.g. neuropathy in 28%). Most patients had high expectations of symptom benefit from chemotherapy. 36% of patients received the predicted number of cycles. 25% of patients with PRR-ROC stopped treatment in < 8 weeks mainly due to progression/death. The median number of cycles and median PFS were 4 and 5.6m in PPS≥3ROC, and 3 and 3.7m in PRR ROC respectively. **Conclusions:** Patients with PRR/PPS ≥ 3ROC reported a number of significant baseline symptoms. They had high expectations of symptom improvement and this should be measured. The results underscore the importance of incorporating PROMs and including symptom benefit as primary endpoints in trials in patients with PRR/PPS ≥ 3 ROC. Clinical trial information: ACTRN12607000603415.

5537 Poster Session (Board #95), Sat, 1:15 PM-4:45 PM

First-in-human phase I/II dose-escalation study of IMAB027 in patients with recurrent advanced ovarian cancer (OVAR): Preliminary data of phase I part. *First Author: Ugur Sahin, TRON GGmbHI, Mainz, Germany*

Background: Ovarian cancer (OC) is a high medical need disease. Most patients (pts) relapse following initial therapy with limited therapeutic options. IMAB027 is the first-in-class monoclonal antibody (mAB) directed against claudin 6 (CLDN6), a cancer cell specific, embryonic tight junction protein and cancer stem cell marker. CLDN6 is expressed in > 55% of OCs and frequently in other cancer types. In preclinical models, IMAB027 executes potent anti-tumor activity via AB-dependent cellular cytotoxicity and complement-dependent cytotoxicity without mediating off-target toxicity. **Methods:** This first-in-human, open-label, dose escalation Phase I/II trial assesses the safety/tolerability (NCI-CTCAEv4.0), pharmacokinetics (PK) and clinical efficacy (RECIST 1.1) of IMAB027 in pts with advanced, recurrent CLDN6$^+$ OC. Here we report preliminary data on 12 pts enrolled in the Phase I part of the study as of August 15, 2014. Pts received 100, 300, 600, or 1000 mg/m^2 IMAB027 (n = 3/group) q3w IV until disease progression. **Results:** Pts had a median age of 64 (54–75) years, platinum-resistant disease and had received a median of 4 (3–9) lines of previous chemotherapies. All administered doses were safe and well tolerated, no DLT was observed and the MTD was not reached. 108 AEs have been recorded, all but 5 (4 grade [gr] 3, 1 gr 4) were gr 1–2 (82 and 21 AEs, respectively). 29 AEs were considered IMAB027 related (22 gr 1, 6 gr 2, 1 gr 3 as deemed by investigator). Five AEs (all in 1 pt) were classified as SAEs incl. one gr 2 hypersensitivity (study drug-related SUSAR). IMAB27-related SAEs were manageable and fully resolved. IMAB027 PK was well described with a 2-compartment model (mean AUC: 20,770–86,160 μg/mL×h; mean C_{max}: 151–611 μg/mL for 300–1000 mg/m^2). First signs of IMAB027 clinical activity were observed. **Conclusions:** This is the first clinical study to show effects of a therapy targeting CLDN6. Based on these preliminary Phase I data, IMAB027 may present a safe and well tolerated treatment option for women with recurrent, advanced OC. This warrants further clinical evaluation of IMAB027 in this patient population with a high medical unmet need. Clinical trial information: NCT02054351.

5538 Poster Session (Board #96), Sat, 1:15 PM-4:45 PM

Correlation of baseline clinical characteristics and laparoscopic extent of carcinomatosis of women with initially unresectable ovarian, tubal or peritoneal adenocarcinoma, in ANTHALYA study: A randomized, open-label, phase II study assessing the efficacy and the safety of bevacizumab in neoadjuvant. *First Author: Roman Rouzier, Insitut Curie, Paris, France*

Background: ANTHALYA study is a randomized non comparative clinical trial to evaluate the efficacy and safety of neoadjuvant chemotherapy associated with bevacizumab. It was a 2:1 randomization to receive carboplatin, paclitaxel with (experimental arm) or without (control arm) bevacizumab in the neoadjuvant setting. The extent of initial carcinomatosis is a major determinant of complete resection but is rarely well described. We report here the extent of carcinomatosis explored by laparoscopy of patients included in Anthalya and its correlation with baseline characteristics. **Methods:** Non-optimally resectable stage IIIC or IV ovarian cancer patients were eligible for this study. Disease extent was evaluated by a standardized form and the Fagotti score was calculated. Baseline clinical characteristics were compared to trials comparing primary debulking surgery and IDS. **Results:** This multicenter study was conducted in 15 centers: 205 patients have been screened and 95 patients were included. Median age was 63 years, ECOG performance status 0/1 was 92%, FIGO stage IIIc and IV was 70% and 30% respectively. Lesions assessed were larger than 5 cm in diameter in 63% of patients and larger than 10 cm in 28%. Median CA-125 was 1045 U/ml (over 500U/mL in 71% cases). Carcinomatosis explored by laparoscopy was present on diaphragmatic peritoneum and digestive tract in 96% patients and 89% patients, respectively. Fagotti score > = 8 was 46%. There were more stage IV patients with low Fagotti score than stage IIIC. There was a correlation between carcinomatosis extent and tumor size > 100mm. Baseline characteristics were balanced between arms and similar to previous neoadjuvant trials. **Conclusions:** ANTHALYA aims to determine the efficacy and safety of neoadjuvant bevacizumab. 46% of patients had high Fagotti score (> = 8). The evaluation of the carcinomatosis by laparoscopy present in 99% of patients confirms advanced disease tumor. ANTHALYA tumor and patient characteristics were similar to previous neoadjuvant trials. Clinical trial information: NCT01739218.

5539 Poster Session (Board #97), Sat, 1:15 PM-4:45 PM

Tumor biopsies in high grade ovarian cancer: Clinical utility and challenges for biomarker-directed therapy. *First Author: Michelle K. Wilson, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Molecular profiling of tissue obtained with a biopsy aids detection of predictive and pharmacodynamic biomarkers to guide patient (pt) selection and treatment. This study assesses the safety and success rate of obtaining FFPE tissue for profiling in ARIEL2 - a large multi-center Phase II trial of rucaparib (oral PARP inhibitor) in high grade serous or endometrioid ovarian cancer (HGOC). **Methods:** Screening biopsy and archival tissue samples were required at study entry. Success was defined as the ability to obtain tissue with minimal pt risk and to complete Foundation Medicine's next generation sequencing-based comprehensive genomic profiling (NGS-based CGP), which requires tissue specimens with tumor nuclei ≥ 20% and volume ≥ 0.2 mm^3. Usability of tissue was assessed by biopsy site. **Results:** 201 pts were enrolled, with results available for 189 screening and 195 archival specimens. 8 pts had insufficient/inaccessible tissue at the time of biopsy. No serious biopsy-related adverse events were seen, with grade 1 pain in only 4 pts (2%). Omental/peritoneal disease was the most common site biopsied (table). Overall NGS-based CGP success rate was 83%. Greater success was seen with archival tissue (179; 92%) than screening biopsies (141; 75%). Unsuccessful profiling on biopsies was due to insufficient tumor nuclei in 36 pts (75%; med tumor nuclei 5%), inadequate volume in 10 (21%; med 0.08mm^3), and insufficient DNA yield in 2 (4%). Success was higher in nodal biopsies (84%) but lower in omental/peritoneal samples (63%). No pt tumors failed profiling on both screening biopsy and archival tissue. **Conclusions:** Research biopsies in HGOC are safe, feasible, and can be profiled with a NGS-based assay. Nodal biopsies had higher success rates compared to peritoneal/omental samples. Algorithms to guide biopsy site choice should be developed considering primary disease, radiologic appearance, and test in question. Clinical trial information: NCT01891344.

	Overall	Sufficient tumor nuclei and volume		Successful NGS-based CGP		
Site of biopsy	n	n	Success %	n	Success %	p*
Liver	25	18	72	18	72	0.81
Lymph node	45	38	84	38	84	0.12
Omentum/ peritoneum	57	37	65	36	63	0.03
Other	62	50	81	49	79	0.38

* Fisher's exact of success/fail rate for each biopsy site vs all other sites

5540 Poster Session (Board #98), Sat, 1:15 PM-4:45 PM

Molecular profiling of mucinous epithelial ovarian carcinomas (mEOC): Opportunities for clinical trials. *First Author: Michael Friedlander, Prince of Wales Cancer Centre, Randwick, Australia*

Background: mEOCs are an uncommon subset of epithelial ovarian cancers. Most patients have early stage disease at presentation and a good prognosis. However, patients with advanced stage disease at diagnosis are rare and can be difficult to distinguish from gastrointestinal metastases to the ovary. They have a poor prognosis and a low response to standard platinum /taxane chemotherapy. Rather than assigning chemotherapy according to the tissue of origin, selecting treatment based on the molecular characteristics of mEOC should be explored. Molecular profiling of mEOCs may help identify patients for clinical trials with targeted/novel therapies. **Methods:** 304 mEOCs referred to Caris Life Sciences (from 2009 - 2014) were evaluated. The diagnosis was based on reported pathology. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification (CISH or FISH), and/or RNA fragment analysis. **Results:** Alterations in the MAP Kinase pathway were common in mEOCs with the most frequent mutations observed in KRAS (49%). The mutation rate in BRAF was 3.5%. Alterations in the mTOR pathway occurred at a less frequent rate (PIK3CA 12% and PTEN 6%). PD-1 positivity was observed in 43% of tumor infiltrating lymphocytes and PD-L1 was positive in 14% of mEOCs. cMET overexpression was seen in 33% of cases, but no cMET amplification was seen. HER2 amplification (per ASCO-CAP guidelines) by FISH was observed in 11%. EGFR amplification occurred in 50% of cases and 57% had overexpression of EGFR by IHC.35% of mEOCs tested (37 of 105 cases) had P53 mutations. P53 mutated (n = 37) and wildtype (n = 68) mEOCs differed significantly in ER, PR and HER2 expression and BRAF, PIK3CA and PTEN mutation prevalence. **Conclusions:** Molecular profiling highlights the genomic heterogeneity and distinct molecular subsets in mEOCS and demonstrates the similarities with mucinous gastrointestinal cancers. There are a number of potential treatment targets and therapeutic options that could be investigated in phase 2 basket trials. Given the rarity of advanced stage mEOCs this will require international collaboration.

5541 Poster Session (Board #99), Sat, 1:15 PM-4:45 PM

Phase I study of intraperitoneal IL-12 plasmid formulated with PEG-PEI-cholesterol lipopolymer administered in combination with pegylated liposomal doxorubicin in recurrent or persistent epithelial ovarian, Fallopian tube, or primary peritoneal cancer patients: An NRG/GOG study. *First Author: Premal H. Thaker, Washington Univ School of Medicine, St. Louis, MO*

Background: EGEN-001 is an immunotherapeutic agent that comprises a human IL-12 plasmid that encodes for functional IL-12 and a synthetic DNA delivery system polyethyleneglycol-polyethyleneimine-cholesterol that facilitates plasmid delivery into cells. Ip injection of EGEN-001 is associated with increases in IL-12 levels and its downstream cytokines in the tumor environment without a significant increase in systemic circulation. The study's purpose was to assess safety and efficacy of escalating doses of EGEN-001 with pegylated liposomal doxorubicin (PLD) in recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer (EOC) patients. **Methods:** Patient eligibility criteria: Females age ≥ 18 years with persistent or recurrent EOC. Patients were not required to have measurable disease and could have a biochemical recurrence; must have had one prior platinum-based chemotherapeutic regimen and up to two additional cytotoxic regimens; have adequate organ function. The trial was a standard 3 + 3 phase I dose escalation with patients receiving PLD every 28 days and EGEN-001 ip on days 1, 8, 15, and 22 of a 28 day cycle (table 1). Cycles were repeated every 28 days until disease progression. **Results:** Sixteen evaluable patients enrolled on trial from 9/2012-7/2012. No DLTs were found during cycle one of each dose level. The adverse side effects were 3 grade 3 anemia; 2 grade 3 abdominal pain; 7 grade 3 neutropenia and 2 grade 4 neutropenia. There were minimal side effects of fever, flu-like symptoms, and infusion or injection site reactions. A clinical benefit of 57.1% (PR = 21.4%; SD = 35.7%) was found in the 14 patients with measurable disease. The highest number of PRs were found at dose level 3 (28.6%) along with SD at 57.1%. The MTD was not achieved. Translational studies are ongoing. **Conclusions:** EGEN-001 in combination with PLD has clinical benefit in recurrent or persistent EOC and warrants further investigation with escalating doses of EGEN-001. Clinical trial information: NCT#01489371.

Dose Level	EGEN-001 (mg/m^2 ip)	PLD (mg/m^2 iv)
1	24	40
2	36	40
3	36	50

5542 Poster Session (Board #100), Sat, 1:15 PM-4:45 PM

A phase I/II trial of multiple dose VB-111 and weekly paclitaxel in recurrent platinum-resistant Müllerian cancer. *First Author: Richard T. Penson, Massachusetts General Hospital and Harvard Medical School, Braintree, MA*

Background: VB-111 is a gene therapy agent consisting of a non-replicating adenovirus vector (Ad-5) with a modified murine pre-proendothelin promoter leading to apoptosis of tumor vasculature by expressing a fas-chimera transgene in angiogenic endothelial cells. One hundred and sixty five patients have been treated so far with VB-111 across different cancer indications including Recurrent GBM, advanced well differentiated thyroid carcinoma with preliminary evidence of anti-tumor activity with no significant safety issues. Safety of VB-111 in combination with paclitaxel was evaluated for patients with recurrent Müllerian cancers in a phase I/II dose-escalation study. **Methods:** VB-111 was administered as a single intravenous infusion at escalating doses from $3x10^{12}$ (DL1&2) to $1x10^{13}$ viral particles (VPs) (DL3), followed by repeat doses every 2 months. Paclitaxel was given at 40 mg/m2 (DL1), and 80mg/m2 weekly (DL2-3), with a planned dose expansion at DL3. Assessments included safety, pharmacokinetics, pharmacodynamics, tumor response (CA125 and RECIST criteria) and progression free survival (PFS). **Results:** Fourteen patients at 2 US centers received up to 6 repeat doses of VB-111. Of these 10 received the higher dose ($1x10^{13}$ VPs). Patients were relatively older (Median age 65 (41-74)) with poor prognosis disease. No DLTs were observed. VB-111 was associated with flu-like symptoms and mild infusion reactions. CTCAE grade ≥ 3 toxicity included infection (1), proteinuria (1), GI (2), and thrombosis (2) including a fatal MI, anaphylaxis (1), neutropenia (2), hypophosphatemia (2). 57% (8 /14) of the patients had a CA125 response (defined as 50% reduction), 62% (8/13) had clinical benefit (RECIST stable disease) on study. Median progression free survival was 2.0 months (1.6 to 12.0). **Conclusions:** The expansion cohort was defined as VB-111 1x1013 VPs in combination with weekly paclitaxel 80 mg/m2. VB-111 was safe and well tolerated in combination with paclitaxel in ovarian cancer patients. Anticipated toxicities and clinical benefit were observed. Clinical trial information: NCT01711970.

5543 Poster Session (Board #101), Sat, 1:15 PM-4:45 PM

Urinary acetylated polyamines in ovarian cancer. *First Author: Johanna Unelma Maenpaa, School of Medicine, University of Tampere, Tampere, Finland*

Background: Diacetylated polyamines have been detected in the urine of patients with malignant tumors since 1960s but methodological problems have hindered research. We have recently developed a liquid chromatography tandem mass spectrometry (LC-MS/MS) method for a simultaneous analysis of 14 polyamines in free, mono- and diacetylated forms in human urine, without any derivatization. The present study was undertaken to explore urinary polyamine profiles in the differential diagnostics of ovarian tumors in postmenopausal women. **Methods:** Forty-five postmenopausal women presenting with an abnormal adnexal mass, and as controls, 21 women with genital prolapse scheduled for surgery, were included prospectively. A morning urine sample was obtained before surgery. The urinary concentrations of 14 polyamines were analyzed simultaneously with LC-MS/MS. Preoperative serum CA12-5 concentrations were also determined, and the risk of malignancy indexes (RMI) calculated in the research arm. The statistical analysis was performed by Wilcoxon rank sum test. **Results:** There were 22 benign and 23 malignant ovarian tumors (16 low malignant potential and 7 high grade tumors). Of the urinary polyamines, N1,N12-diacetylspermine (DiAcSpm) was the best one to make the distinction between the benign and malignant tumors. The urinary levels of DiAcSpm were similar in controls and in women with benign tumors. However, DiAcSpm was elevated in malignant vs. benign tumors ($p = 0.0002$), in high grade vs. low grade cancers ($p = 0.0003$), and in Stage III-IV vs. Stage I-II cancers ($p = 0.0007$), respectively. Also the difference between benign tumors and early-stage cancer (Stage I-II) was statistically significant ($p = 0.006$). DiAcSpm had similar specificity (Sp) (65%) and better sensitivity (Se) (91%) (AUC 0.82) as CA12-5 (Sp 65% /Se 68 %, with a CA12-5 cut-off value 35, respectively) (AUC 0.75) and as RMI (Sp 70%/Se 68% with a RMI cut-off value 200, respectively) (AUC 0.72). **Conclusions:** DiAcSpm was elevated in the urine of patients with ovarian cancer as compared to women with benign tumors and to women with genital prolapse. It seems to be able to detect even early-stage cancer, and its performance seems to be at least comparable to CA12-5 and RMI.

5544 Poster Session (Board #102), Sat, 1:15 PM-4:45 PM

A phase I trial and pharmacokinetic study of non-pegylated liposome-encapsulated doxorubicin citrate (NPLD) plus carboplatin in patients with recurrent gynecological and primary peritoneal tumors. *First Author: Andres Poveda, Instituto Valenciano de Oncologia, Valencia, Spain*

Background: Pegylated liposomal doxorubicin (PLD) plus carboplatin is one of the standard treatments for platinum-sensitive recurrent ovarian patients (pts). PLD shortage during 2012 and 2013 was determining in the need to search for an alternative doxorubicin combination with carboplatin. Non-pegylated Liposome-Encapsulated Doxorubicin Citrate (NPLD, Myocet) has been developed in the past decades with proved activity and limited skin-cardiac toxicity. **Methods:** This open multicentric dose-escalation phase I trial aimed to determine the maximum-tolerated dose (MTD) and the pharmacokinetic (PK) profile of Carboplatin+NPLD using a traditional 3+3 design. Main eligibility criteria: measurable or evaluable recurrent gynecological and primary peritoneal cancer (ca), ECOG: 0-2, normal organ function, no limited number of prior regimens, left ventricular ejection fraction (LVEF) $>$ 50%. Prior anthracycline therapy permitted only for previous responders. Dose Limiting Toxicity (DLT) was defined as G4 hematologic and/or G3 febrile neutropenia and/or ^{3} G3 non-hematologic toxicity (NCI-CTCAE v4.03). If more than one DLT occurred at a specific dose level the previous dose level was defined as the MTD. **Results:** 22/23 evaluable pts were treated with NPLD (40, 50, 60, 70 mg/m^2) and carboplatin (AUC 5) every 21 days. ECOG 0:14, 1: 8, 2:1. Median age: 57y (40-79). 9 pts had epithelial ovarian, 9 cervical, 5 endometrial ca. Number of prior regimens: 3 (1-7). Previous anthracycline: 7/22. *MTD was LEDC 60mg/m^2 + Carboplatin AUC 5.* DLT were: NPLD 40mg/m2: G3 febrile neutropenia, (1/6); 50mg/m2: G4 thrombocytopenia (1/6); 60 mg/m2: G4 thrombocytopenia (1/6); 70mg/m2: G4 thrombocytopenia (1/4), G3 febrile neutropenia, (1/4). Other non-hematologic G2 toxicities were (%): asthenia (16), infection (7) and anorexia (5). No cardiotoxicity was reported. 1PR and 17SD at 8 weeks were observed. PK data will be presented at the Meeting. **Conclusions:** The MTD for NPLD when combined with carboplatin AUC 5 is 60mg/m^2. The regimen is well tolerated, antitumor activity was observed. A phase-II study is ongoing. Clinical trial information: EudraCT: 2012-003173-25.

5545 Poster Session (Board #103), Sat, 1:15 PM-4:45 PM

Comparison of metachronous epithelial ovarian carcinomas. *First Author: David Arguello, Caris Life Sciences, Phoenix, AZ*

Background: Epithelial ovarian carcinoma (EOC) is a relatively common malignancy with high, initial response rates to standard chemotherapy but frequent relapses. Next-generation sequencing (NGS) is a promising technology with the potential to alter how this disease is managed. However, much remains unknown regarding its applicability in ovarian carcinomas. The purpose of this study is to compare metachronous epithelial ovarian carcinoma specimens arising from different sites in an attempt to better understand how to apply NGS in the management of this disease. **Methods:** A retrospective analysis of sequencing results for 83 metachronous (defined as specimens collected greater than 28 days apart) EOC specimens was performed. In most instances, comparisons involved two different metastatic sites (n = 50), while the rest involved a comparison of the primary and a subsequent metastatic specimen (n = 33). All specimens had up to 47 genes analyzed using the Illumina MiSeq NGS platform. Tumors were sequenced to a depth of 1500x, enabling the detection of mutations down to 10% variant frequency. **Results:** Metachronous paired specimens were collected from 43 to 2793 days apart (mean = 519). Mutations were detected in 23 different genes (48.9%, 23/47). A majority (56.6%, 47/83) shared just one mutation, with TP53 being the most common (59.0%, 49/83). Only twelve paired specimens had disagreement in gene results and all of these disagreed in only one gene. A change from wild type to mutated status was found in APC (I1307K, I1317K), BRAF (I463T), PIK3CA (E542K), PTPN11 (G503V), SMO (S342F), and TP53 (G245S, R248Q, R282W). Meanwhile, a reversion from mutated status to wild type was detected in APC (E1317Q, A1474T) and NOTCH1 (R1568K). Overall, 85.5% (71/83) of paired samples showed complete agreement. **Conclusions:** This metachronous paired analysis indicates that, at least utilizing this 47-gene panel, a majority of patients with EOC showed no change in their molecular profile, regardless of where the metastatic lesion was located. Utilizing NGS argues for a more comprehensive approach to EOC therapy, and to obtain the most therapeutic options in this disease. These findings, and their clinical impact, should be validated in further studies.

5546 Poster Session (Board #104), Sat, 1:15 PM-4:45 PM

What clinical factors influence advanced *BRCA1/2* mutant ovarian cancer patient (BMOC pt) outcomes to poly(ADP-ribose) polymerase inhibitor (PARPi) treatment? *First Author: Saeed Rafii, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: The PARPi olaparib (Ola) was recently granted FDA accelerated approval in advanced BMOC. Despite impressive clinical activity in BMOC, the impact of baseline pt factors remains unclear. We hypothesized that the platinum chemotherapy (Plt chemo) to PARPi interval (PTPI) can be used to refine the conventional prediction of response to PARPi based on the clinical categorization of pts into Plt sensitive (Plt-S) and Plt resistant (Plt-R). **Methods:** Retrospective study of pt with advanced BMOC treated in relapsed setting with $\geq$ 200 mg bid Ola between 4/2006 – 8/2013 in multiple centers. Pearson Chi^2, odds ratios (OR) and Fisher's exact probability tests were used for statistical analyses. **Results:** 108 advanced BMOC pts were assessed; median age 55y (range 38-79); 83 (77%) pts had high grade serous carcinoma. *BRCA1*:*BRCA2* mutations ratio 71:29. Median prior lines of chemo: 3 (range 1-10). 41 (38%) pts had prior breast cancer (BC). 64% had Plt-S disease and 36% had Plt-R disease prior to Ola. Median PTPI was 53 weeks (w) (range 4-244). Median PTPI was 68.7w for Plt-S pts versus (vs) 25.9w for Plt-R pts ($p < 0.0001$). RECIST complete or partial responses (CR/PR) were observed in 23/65 (35%) Plt-S pts vs 5/38 (13%) Plt-R pts ($p < 0.02$). Pts with $>$ 52w PTPI had higher CR/PR rates than those with $<$ 52w PTPI independent of their Plt status (37% vs 18%, respectively, $p = 0.053$). Pts who had only 1 prior line of chemo had higher CR/PR rates vs pts who had $>$ 1 prior line ($p < 0.005$). No differences in CR/PR rates were noted between pts with *BRCA*1 vs pts with *BRCA2* mutations, pts with prior BC vs pts without, or use of chemo for BC vs none. Median progression-free survival was 70w for pts with PR/CR vs 28w for pts without (log-rank, $p = 0.0004$). Median survival was 161w for pts with CR/PR and 64w for pts without (log-rank, $p = 0.0005$). **Conclusions:** These data suggest that prediction of response to PARPi in advanced BMOC based on conventional Plt-S/Plt-R categorization may be refined by PTPI. Treatment of Plt-R BMOC pts with a non-Plt agent prior to Ola in order to prolong PTPI may be an appropriate clinical strategy. These findings should be validated prospectively in a larger data set.

5547 Poster Session (Board #105), Sat, 1:15 PM-4:45 PM

Development and validation of a prognostic nomogram to predict overall survival (OS) in platinum-resistant ovarian cancer (PROC): An AURELIA substudy. *First Author: Chee Lee, ANZGOG, NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia*

Background: PROC describes a heterogeneous group of patients (pts) with a variable but generally poor prognosis and low response to chemotherapy. Predicting OS in PROC would help stratify pts in trials and guide treatment decisions. We developed a nomogram to predict OS in PROC. **Methods:** Data from two randomized phase III trials evaluating chemotherapy for PROC – CARTAXHY [Lortholary Ann Oncol 2012] and AURELIA [Pujade-Lauraine JCO 2014] (chemotherapy-alone arm) – were combined to form the training cohort (N = 331) for nomogram development. Baseline variables significantly associated with OS were identified using Cox regression analysis. Pts were assigned scores based on the weighted sum of the relative importance of each variable in the multivariate model. The nomogram was then validated in the chemotherapy plus bevacizumab arm of the AURELIA trial (N = 166). Nomogram performance was assessed by calculating the c statistic. A classification based on the nomogram's score was generated to group pts according to prognosis. **Results:** Poor performance status, CA125 $\geq$ 100 U/mL, ascites, platinum-free interval $<$ 3 months, primary platinum resistance, and largest tumor $>$ 5cm were associated with shorter OS. The nomogram predicted OS with a c statistic of 0.69 (training) and 0.67 (validation). In the training cohort, the median OS in good (N = 93), intermediate (N = 162), and poor (N = 76) prognostic groups was 25.3, 15.6, and 6.9 months, respectively ($P < 0.0001$). In the validation cohort, median OS in good (N = 50), intermediate (N = 79), and poor (N = 37) prognostic groups was 26.7, 13.8, and 9.0 months, respectively ($P < 0.0001$). **Conclusions:** This nomogram combining six baseline factors accurately predicts OS in PROC pts treated with chemotherapy either alone or in combination with bevacizumab. It could help to select pts for treatment, counsel pts regarding prognosis, and stratify according to risk in trials. Clinical trial information: NCT00976911.

5548 Poster Session (Board #106), Sat, 1:15 PM-4:45 PM

Exploratory outcome analyses according to stage and residual disease in the ICON7 trial of front-line carboplatin/paclitaxel (CP) ± bevacizumab (BEV) for ovarian cancer (OC). *First Author: Antonio Gonzalez-Martin, GEICO and MD Anderson Cancer Center Spain, Madrid, Spain*

Background: In ICON7, progression-free survival (PFS) was significantly improved in patients (pts) receiving BEV with front-line CP and continued as a single agent [Perren 2011] but no overall survival (OS) difference was detected in the intent-to-treat (ITT) population. Front-line BEV-containing therapy is approved in Europe for pts with stage IIIB–IV OC. **Methods:** In ICON7, pts with advanced (stage IIB–IV) or high-risk early-stage (stage I–IIA and clear cell/grade 3) OC were randomized to receive 6 cycles of CP either alone or with BEV 7.5 mg/kg q3w followed by single-agent BEV for a further 12 cycles (total duration 12 months). The primary endpoint was PFS; OS was a secondary endpoint. A post hoc exploratory analysis of subgroups defined by stage and extent of residual disease at diagnosis within the label population was performed. **Results:** The PFS benefit from BEV observed in the ITT population was seen consistently in all subgroups explored. As in the ITT population, no OS difference was seen in any subgroup except the previously defined 'high-risk' subgroup. Safety results in subgroups were in line with the overall population. **Conclusions:** Adding BEV to CP improves PFS irrespective of stage/residual disease. In pts with stage III >1 cm/IV OC this translates into an OS benefit. No OS difference (benefit or detriment) was seen in other subgroups explored. Clinical trial information: NCT00483782.

	PFS[a]		OS[b]	
	CP	CP + BEV	CP	CP + BEV
'High-risk' subgroup (stage III >1 cm/IV) (N=502)				
No. of events/pts (%)	214/254 (84)	204/248 (82)	174/254 (69)	158/248 (64)
HR (95% CI)	0.71 (0.58–0.86)		0.78 (0.63–0.97)	
Stage IIIB–IV, 0 cm residuum (N=411)				
No. of events/pts (%)	118/203 (58)	110/208 (53)	74/203 (36)	80/208 (38)
HR (95% CI)	0.77 (0.59–0.99)		1.03 (0.75–1.41)	
Stage IIIB–IV, visible residuum (N=749)				
No. of events/pts (%)	295/370 (80)	310/379 (82)	246/370 (66)	242/379 (64)
HR (95% CI)	0.81 (0.69–0.95)		0.87 (0.73–1.04)	
All stage IIIB–IV (N=1160)				
No. of events/pts (%)	413/573 (72)	420/587 (72)	320/573 (56)	322/587 (55)
HR (95% CI)	0.81 (0.70–0.92)		0.92 (0.79–1.08)	

HR = hazard ratio, unstratified [a]Data cutoff 30 Nov 2010 (median follow-up 28 months) [b]Data cutoff 31 Mar 2013 (median follow-up 49 months)

5549 Poster Session (Board #107), Sat, 1:15 PM-4:45 PM

Single agent vanucizumab (RO5520985) for platinum (Pt)-resistant recurrent ovarian cancer (OC): Results from a single arm extension phase of the phase I FIH study. *First Author: Ana Oaknin, Vall d´Hebron University Hospital, Barcelona, Spain*

Background: Vanucizumab is a bi-specific human IgG1 antibody, simultaneously blocking the complementary roles of Ang-2 and VEGF-A induced tumor angiogenesis. Both, VEGF-A and Ang-2 inhibitors are known to be clinically active in ovarian cancer. Hence, co-targeting of both ligands in a bi-specific manner represents an encouraging approach to improve treatment outcomes. **Methods:** Eligiblepatients (pts) had platinum (Pt)- resistant/ refractory epithelial OC (measurable by RECIST 1.1). Pts with history of bowel obstruction, > 2 prior lines of systemic chemotherapy, or previous treatments with agents targeting Ang/Tie2 receptor axis were ineligible. Pts were treated with vanucizumab (RP2D) at 30 mg/kg IV Q2W until disease progression or unacceptable toxicity. Primary endpoint was objective response rate (ORR) per RECIST 1.1, with tumor re-assessments every 8 weeks (wks). **Results:** 41 pts (40 Pt- resistant/ 1 Pt- refractory) with median age of 60 years (range 30-77) were enrolled. 13 (32%) pts were pre-treated with bevacizumab (BEV). All pts had at least 1 tumor re-assessment. At this point in time, twelve (29%) pts achieved partial response (6 confirmed PR/6 unconfirmed PR) including two pre-treated with BEV. Interestingly, a delayed response was observed in 7/12 PRs, following 16 wks (6 pts) or 32 wks (1 pt) of treatment. 22 (54%) pts experienced disease stabilization and 7 (17%) pts progressed. The most frequent adverse events (AE) of any grade (G) were hypertension (53%), asthenia (39%), constipation (34%), abdominal pain (32%), peripheral (24%)/lymphedema (19%), vomiting (24%) and diarrhea (19%). Most common AEs ≥ G3 were hypertension (10/24%), pyelonephritis (3/7%), GI-perforation, peritonitis, intestinal obstruction, pulmonary embolism and dyspnea (2/5%). One AE of peritonitis had a fatal outcome 3 months after onset. **Conclusions:** In this study, vanucizumab Q2W had an acceptable safety profile while demonstrating encouraging anti-tumor activity in pts with Pt-resistant, recurrent OC that seems to exceed reported results for single VEGF-A inhibition in this setting. Clinical trial information: NCT01688206.

5550 Poster Session (Board #108), Sat, 1:15 PM-4:45 PM

Frequency, severity and timing of common adverse events (AEs) with maintenance olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). *First Author: Ursula Matulonis, Dana-Farber Cancer Inst, Boston, MA*

Background: Maintenance monotherapy with the PARP inhibitor olaparib prolongs progression-free survival in PSR SOC pts with no adverse impact on HRQoL. *BRCA*m pts derive greater benefit. Nausea, vomiting, fatigue and anemia are consistently the most common AEs in olaparib trials. **Methods:** In this randomized, double-blind Phase II trial (NCT00753545), pts received olaparib 400 mg twice daily (capsules; n=136) or placebo (n=128). AEs were graded by CTCAE v3.0; the timing and severity of AEs were analyzed. **Results:** Olaparib-treated pts most commonly reported early but transient grade (G)1/2 AEs of nausea, vomiting, fatigue and anemia that resolved with supportive treatment without olaparib regimen changes. G>2 AEs were uncommon and manageable with dose interruptions/reductions and supportive treatment. Anemia was the most common G>2 AE. Common AEs were generally reported later for placebo pts. AEs causing discontinuation were uncommon (olaparib, n=9; placebo, n=2). *BRCA*m pts had a similar AE profile. **Conclusions:** AEs commonly reported with olaparib are of mostly mild to moderate intensity, transient and manageable without olaparib discontinuation. Clinical trial information: NCT00753545.

	Nausea		Vomiting		Fatigue and asthenia		Anemia	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Pts with AE	96 (71)	46 (36)	47 (35)	18 (14)	84 (62)	59 (46)	29 (21)	7 (5)
AE instances*	128	58	82	20	114	72	34	8
G1	101 (79)	46 (79)	58 (71)	12 (60)	66 (58)	58 (81)	5 (15)	4 (50)
G2	24 (19)	12 (21)	21 (26)	7 (35)	36 (32)	10 (14)	21 (62)	3 (38)
G3/4	3 (2)	0	3 (4)	1 (5)	12 (11)	4 (6)	8 (24)	1 (13)
Discontinued†	1 (1)	1 (2)	0	0	0	0	0	0
Dose reduced†	5 (4)	0	4 (5)	1 (5)	9 (8)	1 (1)	6 (18)	1 (13)
Interrupted†	9 (7)	1 (2)	18 (22)	1 (5)	8 (7)	2 (3)	4 (12)	0
Resolved	102 (80)	46 (79)	80 (98)	17 (85)	68 (60)	35 (49)	23 (68)	6 (75)
Treated	57 (45)	10 (17)	19 (23)	3 (15)	5 (4)	3 (4)	24 (71)	2 (25)
Median duration, mo (IQR)‡	2.2 (1, 7)	0.82 (0.1, 2.4)	0.05 (0.03, 0.13)	0.1 (0.03, 0.1)	3.4 (2, 7)	2.8 (1.5, 4.3)	2.4 (1, 6.6)	0.5 (0.3, 1.4)
Time to first occurrence, d (IQR)	3 (1, 15)	12 (4, 29)	49 (10, 112)	64 (25, 106)	24 (7, 57)	28 (7, 48)	28 (14, 59)	91 (49, 133)

Values are n (%) unless stated. *Includes AEs considered unrelated to treatment; †AE related; ‡Includes intermittent events.

5551 Poster Session (Board #109), Sat, 1:15 PM-4:45 PM

Bevacizumab (BEV) with or after chemotherapy (CT) for platinum-resistant recurrent ovarian cancer (PROC): Exploratory analyses of the AURELIA trial. *First Author: Aristotelis Bamias, HECOG, University of Athens, Medical School, Athens, Greece*

Background: In the open-label randomized phase III AURELIA trial, adding BEV to CT for PROC significantly improved progression-free survival (hazard ratio [HR] 0.48; p < 0.001) and response rate (27% vs 12%) vs CT alone, but not overall survival (OS). **Methods:** Eligible patients (pts) had measurable/assessable OC that had progressed < 6 mo after platinum CT. After CT selection, pts were randomized to CT ± BEV until progression (PD), unacceptable toxicity or consent withdrawal. Crossover to BEV at PD was optional in the CT arm but prohibited in the BEV–CT arm. Exploratory post hoc analyses assessed factors potentially affecting the decision to crossover to BEV, and efficacy and safety according to post-PD BEV. **Results:** 179 pts were randomized to BEV–CT and 182 to CT alone. 72 pts (40%) in the CT-alone arm crossed over to BEV after PD and 110 never had BEV. There were no significant differences in pt characteristics between these subgroups at baseline but at the time of PD, 51% vs 35%, respectively, had ECOG performance status (PS) 0 (p = 0.034). 3-month landmark analyses, excluding 28 pts who died or were lost to follow-up before this time, showed significantly longer OS in pts who received BEV either with CT (HR 0.72, 95% CI 0.54–0.97) or after PD (HR 0.69, 95% CI 0.48–0.99) vs those who never received BEV. These differences remained significant after adjusting for identified prognostic factors for OS (chosen CT, platinum-free interval, ECOG PS, baseline ascites, baseline CA-125). When analyzed from the time of PD, the OS HR vs never BEV was 0.84 (95% CI 0.62–1.14) for upfront (pre-PD) BEV–CT and 0.55 (95% CI 0.38–0.79) for BEV after PD. Tolerability was similar with pre- vs post-PD BEV. **Conclusions:** There appears to be no clear difference in OS between upfront vs post-PD BEV therapy. Pts who never received BEV had the worst OS. These analyses of a non-randomized phase of the study with no information on other post-PD therapies do not allow definitive conclusions about upfront vs post-PD BEV efficacy. Nevertheless, as 60% of pts randomized to CT alone never received BEV, upfront treatment with BEV–CT is important, as reserving BEV until after PD may deny some pts the opportunity to benefit from BEV. Clinical trial information: NCT00976911.

5552 Poster Session (Board #110), Sat, 1:15 PM-4:45 PM

Prognostic and predictive value of primary vs secondary platinum resistance for bevacizumab treatment in platinum-resistant ovarian cancer in the AURELIA trial. *First Author: Fabian Trillsch, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: Progression-free survival (PFS) and patient-reported outcomes (PRO) were significantly improved with the addition of bevacizumab (BEV) to standard chemotherapy (CT) for platinum-resistant ovarian cancer (OC) in the randomized phase III AURELIA trial. We examined the relevance of primary (PPR) vs secondary platinum resistance (SPR) on treatment efficacy. **Methods:** Platinum resistance was categorized as PPR if progression was $<$ 6 months after completing first platinum therapy or SPR if not. We performed exploratory Cox and logistic regression analyses to correlate platinum resistance with PFS, overall survival (OS), and PRO from the time of randomization to CT $\pm$ BEV. **Results:** Of the 361 randomized patients (pts), 262 (73%) had PPR and 99 (27%) had SPR. Baseline characteristics were generally similar in the two subgroups, except that FIGO stage IV disease and ascites were more common in PPR pts. In the BEV+CT arm (n = 179), SPR was associated with more favorable PFS (median 10.2 vs 5.6 months [mo] in the PPR subgroup; $P < 0.001$) and OS (median 22.2 vs 13.7 mo, respectively; $P < 0.001$) but not PRO (22.0% vs 21.9% with $\geq$ 15% improvement in abdominal/gastrointestinal symptoms at week 8/9; P = 0.99). In two separate multivariate analyses, SPR remained an independent prognostic factor for better PFS (adjusted hazard ratio [HR] 0.41, 95% CI 0.25–0.67, $P < 0.001$) and OS (HR 0.49, 95% CI 0.30–0.80, P = 0.005) in the BEV+CT arm. In the CT-alone arm, the prognostic effect did not reach statistical significance for PFS or OS. The magnitude of benefit from adding BEV to CT appeared greater in the SPR than the PPR subgroup for PFS (SPR: HR 0.30, 95% CI 0.18–0.48, $P < 0.001$; PPR: HR 0.55, 95% CI 0.42–0.71, $P < 0.001$; interaction P = 0.07) with a similar direction of effect for OS (SPR: HR 0.62, 95% CI 0.37–1.02, P = 0.06; PPR: HR 0.94, 95% CI 0.71–1.24, P = 0.65; interaction P = 0.18). **Conclusions:** Median PFS and OS were more favorable in SPR than PPR pts treated with BEV+CT but BEV effect on PRO was similar. The PFS and OS benefit of BEV+CT over CT alone was more pronounced in the SPR than the PPR subgroup. PPR vs SPR should be a stratification factor in future trials of anti-angiogenic therapy for OC. Clinical trial information: NCT00976911.

5553 Poster Session (Board #111), Sat, 1:15 PM-4:45 PM

Single agent trabectedin in heavily pretreated patients with recurrent ovarian cancer (ROC). *First Author: Feriel Boumedien, Faculty of Medicine, Université de Montreal, Montreal, QC, Canada*

Background: Trabectedin is approved in Canada since 2010 in combination with liposomal doxorubicin for platinum-sensitive ROC in patients who are not expected to benefit, are ineligible or not willing to receive retreatment with platinum-based chemotherapy. In 2012, due to a shortage of liposomal doxorubicin, single agent trabectedin was proposed to patients with ROC. The aim of this study was to evaluate the efficacy and tolerability of trabectedin in this context. **Methods:** This retrospective IRB approved study included all patients who received trabectedin for ROC between January 1st 2012 and June 30th 2014 at the CHUM. This study was not funded.The primary outcome was progression free survival (PFS) based on CA-125 and clinical exam. We also evaluated overall survival (OS), response rate and toxicities (CTCAE v4.0). PFS and OS were estimated by Kaplan-Meier method. **Results:** A total of 25 evaluable patients with a median age of 59 years received trabectedin 1.3 mg/m^2 I.V. in 3 hours every 3 weeks in 3rd or 4th line (36%), 5th or 6th line (36%) and $\geq$ 7 lines (28%). Among the patients, 60% were platinum-sensitive and 40% platinum-resistant. The median number of cycles received was 5 (range 1-16 cycles) for a total of 130 cycles. Complete response (CR), partial response (PR), stable disease (SD) and progression occurred in 16%, 20%, 24% and 40% of patients respectively. The median PFS was 3.7 months (95% CI 1.9-5.6). In patients with a response (CR, PR, SD), the median PFS was 4.9 vs 0.8 months ($p < 0.001$). Death occurred in 15 patients (60%). The median OS was 16.2 months. The Cox model reported that response to treatment is the only variable influencing the PFS and the OS ($p < 0.001$), but not the platinum status or the number of previous lines received. Grade 3 or 4 toxicities include: neutropenia (8%), febrile neutropenia (4%) and muscle weakness (4%). Dose reduction was required in 4 patients for hepatic and hematologic toxicities. No death was attributable to toxicities. **Conclusions:** Our results demonstrate that trabectedin has an interesting efficacy as a single agent in heavily treated ROC patients. At a dose of 1.3 mg/m^2 every 3 weeks, trabectedin is well tolerated with few adverse events.

5554 Poster Session (Board #112), Sat, 1:15 PM-4:45 PM

Early stage ovarian cancer clinical behavior according to FIGO 2014 Staging changes with a focus on IC subtype: data from prospective GEICO registry. *First Author: Ignacio Romero, Instituto Valenciano de Oncología, Valencia, Spain*

Background: Early stage ovarian cancer (ESOC) represents 10-15% of all Ovarian Cancer (OC) cases and most frequent ESOC substage (IC) has undergone major changes in FIGO 2014 staging. **Methods:** A centralized prospective registry of ESOC (I-IIb) patients treated at GEICO (Spanish Group of Ovarian Cancer Research) centers was initiated on January 1998 and updated up to November 2014. We aim at prospectivley explore both the robustness of FIGO in ESOC and the role of ascites in terms of prognosis. We analyze FIGO 2014 stage IA-IB (1), IC1+IC2 (2), IC3 citology positive in washing (3) or in ascites (4) and IIA-B (5). **Results:** A total of 1,178 cases with a median age of 53 yrs. (16-97 yrs) have been included. Histology distribution according to Kurman (Int J Gynecol Pathol 2008) showed type I 65.5% and type II 34.5%, grade 1 23.6%, grade 2 21.4% and grade 3 45%. Distribution of ESOC stages, frequency and Relapse Free Survival (RFS) and Disease Specific Survival (DSS) are summarized in table 1; subclassification in IC stage was unavailable in 80 cases. With a median follow-up of 77 months [0-285 mo], 16.7% relapsed after a median of 27 months [2-221 mo] and 9.1% died after a median of 42 months [4-181 mo]. RFS at 5 and 10 years were 84%, 80% and and DSS 93.5% and 87.2% respectively. RFS was inversely associated with stage ($p<0.001$) (table 1). The presence of positive citology in ascites had worse outcome than in washings. Up to 81% received adjuvant chemotherapy. **Conclusions:** In this large prospective cohort of ESOC, FIGO 2014 staging system for ESOC is prognostic. We propose to further explore the bad prognosis of positive citology in ascites.

Group	FIGO 2014	N	%	RFS 5-yrs (%)	RFS 10-yrs (%)	DSS 5-yrs (%)	DSS 10 yrs (%)
1	IA-IB	428	36.3	96	94	98	97
2	IC1+IC2	398	33.7	93	88	97	96
3	IC3 positive citology in washing	68	5.7	80	74	88	83
4	IC3 positive citology in ascites	33	2.8%	72	72	86	75
5	IIA-IIB	171	14.5	69	63	87	80

5555 Poster Session (Board #113), Sat, 1:15 PM-4:45 PM

Epigenome and genome alterations in platinum resistant ovarian cancer. *First Author: Daniela Matei, Indiana Univ Simon Cancer Ctr, Indianapolis, IN*

Background: Epigenetic changes, particularly DNA methylation aberrations have been implicated in acquired resistance to platinum in ovarian cancer (OC). **Methods**: An ongoing phase I/II multi-institutional clinical trial uses the novel DNA methyl transferase inhibitor (DNMTI) SGI-110 to re-sensitize platinum resistant OC to carboplatin. Patients enrolled in this trial had recurrent, platinum resistant OC and multiple lines of prior therapy. Tumor biopsies were collected at baseline and after two cycles of SGI-110 administered daily for 5 days (30mg/m^2). The objectives of the study were to analyze and integrate global RNA expression and DNA methylation profiles of platinum resistant tumors and to measure genomic and epigenomic changes induced by the DNMTI. RNA and DNA were extracted from 48 and 57 baseline tumors and analyzed using next generation sequencing (RNA-seq) and Infinium HM450 BeadChip array, respectively. Differential gene expression and DNA methylation profiles were generated and used for Ingenuity Pathway Analysis (IPA) to identify significantly altered pathways in response to SGI-110. **Results**: Analysis of a limited number of paired samples before and after treatment (n = 8) revealed significant changes in global gene expression profiles induced by SGI-110, with 960 significantly altered genes representing immunopathway enrichment, including cytokine production in macrophages and T helper cells by IL-17A and IL-17F, granulocyte/agranulocyte adhesion and inflammation, IL-8 signaling, p38 MAPK signaling, cAMP-mediated signaling, and innate immunity. HM450 analysis showed a significantly greater number of hypermethylated genes in baseline tumors compared to primary OC samples in the Cancer Genome Atlas (TCGA) and demethylation (decreased beta-values relative to baseline) of a large number of loci (381 gene promoters) after SGI-110 treatment. IPA analysis of baseline tumor transcriptome and methylome demonstrated significant enrichment in pathways associated with cancer, stem cells, inflammation and the immune system. **Conclusions:** These data suggest that SGI-110 induces reactivation of immune responses in OC. Correlations between methylation changes and expression profiles are being explored. Clinical trial information: NCT01696032.

5556 Poster Session (Board #114), Sat, 1:15 PM-4:45 PM

Validation of a second-generation mia (MIA2G) for triage of adnexal masses. *First Author: Judith Wolf, Vermillion, Inc., Austin, TX*

Background: Many women with ovarian cancer receive non-guideline care. Failure to refer to a gynecologic oncologist is one likely cause. To improve specificity of Multivariate Index Assay (MIA) for ovarian cancer triage, we undertook the re-design and validation of a second-generation test (MIA2G). **Methods:** A panel of MIA-positive malignant and benign case- controls was used to evaluate candidate biomarkers to improve specificity. These, and the 5 MIA biomarkers were then further ranked and developed into the MIA2G using banked samples from a previously published prospective, multi-site FDA registration trial of MIA (N = 585). Upon verification, the algorithm was encoded into diagnostics-grade software to calculate MIA2G in subsequent validation studies. Clinical validity was established under a double-blinded protocol using banked samples from the OVA500 trial, a second prospective MIA multi-site pivotal trial. Samples were assayed at 3 external sites, results were generated at a commercial laboratory and submitted to an independent statistician for decoding and analysis. MIA2G was compared with physician assessment (PA) or MIA. Results were compared for sensitivity, specificity, positive and negative predictive value (PPV and NPV), positive and negative likelihood ratios, concordance and percent overall accuracy. **Results:** Three MIA markers (CA125-II, transferrin and Apo A-1) and 2 new biomarkers (FSH and HE4) were selected for inclusion in MIA2G. MIA2G results range from 0-10, with a single cut-off separating hi- and low- malignancy risk of ^{3}5.0. 493 of 519 OVA500 subjects were evaluable (276 pre and 217 post-menopausal). MIA2G specificity (69.1%) and PPV (40.4%) were significantly improved over MIA (53.6% and 31.4%, respectively). Sensitivity and NPV were not significantly different. Overall accuracy was significantly improved from 60.9% (MIA) to 73.2% (MIA2G). When MIA2G was combined with PA sensitivity was 93.5% and specificity was 64.8% **Conclusions:** The redesigned multivariate index assay, MIA2G, has significantly improved specificity, PPV and accuracy compared with MIA. These changes enable high-sensitivity detection of malignancy while reducing likelihood of over-referral.

5557 Poster Session (Board #115), Sat, 1:15 PM-4:45 PM

The PACOVAR-trial: A multicenter phase I trial of pazopanib (GW786034) and metronomic cyclophosphamide in patients with recurrent platinum-resistant ovarian cancer. *First Author: Michael Hans Robert Eichbaum, St. Marienkrankenhaus Frankfurt, Frankfurt, Germany*

Background: A combined therapy consisting of the investigational anti-VEGFR tyrosine kinase inhibitor pazopanib (GW786034, paz) and metronomic oral cyclophosphamide may offer a well-tolerable treatment option to patients with recurrent platinum-resistant epithelial ovarian cancer (EOC). **Methods:** This study was designed as a multicenter phase I trial evaluating the optimal dose for paz as well as activity and tolerability of a combination regimen consisting of paz and metronomic cyclophosphamide 50mg daily p.o. in monthly cycles. Patients with histologically proven recurrent platinum-resistant EOC were included. Dose escalation of paz followed a phase I design in three dose levels (DL) of 400mg, 600mg and 800mg daily p.o. , respectively. Toxicity and survival data were obtained. **Results:** 16 patients were treated within this trial, mean age was 66 years. In DL I and II one dose limiting toxicity (DLT) was seen in one patient out of six (AST-elevation, hypertonus). Within DL III, two patients out of four showed a DLT (AST-elevation), leading to a maximum tolerated dose (MTD) of 600mg paz daily. Median number of administered cycles was 6 (2-13), with three patients being treated for at least 13 months. Median progression-free survival (PFS) and overall survival (OS) were 6.7 months and 15.2 months, respectively. A total of 254 adverse events (AE) occurred. The most often documented AE were leukopenia in 14.6% of the cases, followed by elevation of ALT (10.2%) and elevation of AST (9.5%). Moreover, 27 AE were probably or very likely related to cyclophosphamide (10.6%) and 55 AE were probably or very likely related to paz (21.7%). A total of five serious adverse events (SAE) occurred in four patients. The events were hypertension as well as sepsis, vomiting, ileus and fatigue. Besides sepsis, which had a fatal outcome, all other SAE were recovered. **Conclusions:** Paz 600mg daily p.o. and metronomic cyclophosphamide 50mg daily p.o. is a feasible regimen for patients with platinum-resistant recurrent, pre-treated EOC. Further evaluation of this palliative regimen in phase II setting is warranted. Clinical trials information: NCT01238770. Clinical trial information: NCT01238770.

5558 Poster Session (Board #116), Sat, 1:15 PM-4:45 PM

Phase 1 study of IMGN853, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC) in patients (Pts) with epithelial ovarian cancer (EOC) and other FRA-positive solid tumors. *First Author: Hossein Borghaei, Fox Chase Cancer Center, Philadelphia, PA*

Background: IMGN853 (mirvetuximab soravtansine) is a FRα-targeting ADC comprising a FRα-binding antibody and potent maytansinoid, DM4. **Methods:** This Phase 1 trial is being conducted to determine safety, pharmacokinetics (PK), pharmacodynamics, maximum tolerated dose, recommended phase 2 dose (RP2D) and evidence of activity of IMGN853 in pts with EOC or other FRa-positive solid tumors. As previously reported, the occurrence of ocular adverse events (AEs) was associated with peak drug exposure and pt weight. Dosing by adjusted ideal body weight (AIBW) instead of total body weight (TBW) was implemented to decrease PK variability. Two dosing schedules are being evaluated; (A) once every 3 weeks and (B) Days 1, 8, and 15, every 4 weeks. **Results:** Fifty nine pts enrolled to dose escalation to date, 44 (30 TBW; 14 AIBW) pts in A, 16 (AIBW) in B. RP2D for A was determined to be 6.0 mg/kg, while dose finding in B continues. Exposure to IMGN853 increased with an increase in dose in a more than dose-proportional manner indicating non-linear PK. AIBW dosing enabled better control of drug exposure, with more pts treated within a clinically relevant therapeutic window. The majority of AEs have been CTCAE grade 1 or 2, generally similar across both schedules: included GI events, ocular events, cough, fatigue, and neuropathy in $>=$ 20% of patients. Nausea, vomiting and headache may be more common on schedule B. Diarrhea may be more common on schedule A. Preliminary evidence of clinical benefit (CB) (partial PR or complete CR response, CA125 response, SD $\geq$ 6 cycles) has been observed with both schedules during escalation. In A, CB was observed in 11/44 pts: 4 PRs; 2 confirmed CA125 responses; 5 SD, 2 for 10 cycles. In B, 5/15 evaluable pts had CB: 1 PR; 4 SD, 3 with confirmed CA125 response; six pts remain on study. Benefit was seen in epithelial and transitional cell ovarian cancer, endometrial cancer and NSCLC. **Conclusions:** With both schedules,IMGN853 demonstrates encouraging clinical activity in heavily pretreated patients during dose escalation with a manageable AE profile. A RP2D has been identified for schedule A, while schedule B continues dose finding. Clinical trial information: NCT01609556.

5559 Poster Session (Board #117), Sat, 1:15 PM-4:45 PM

A phase 1 study optimizing the dosing of olaparib tablet formulation combined with cediranib in recurrent ovarian cancer. *First Author: Joyce Liu, Dana Farber Cancer Inst, Newton, MA*

Background: PARP inhibitors and anti-angiogenics are clinically active in recurrent ovarian cancer (OvCa). Pre-clinical studies suggest these agents can synergize; a phase 2 study demonstrated that combination cediranib/capsule olaparib (C/O) increased progression-free survival (PFS) and response rate (RR) compared to olaparib alone. Olaparib clinical development will proceed using the tablet formulation; we therefore investigated the toxicities and recommended phase 2 dosing (RP2D) of C/O with olaparib tablets. **Methods:** Cediranib (C) once daily and olaparib (O) twice daily were administered orally in cohorts of 3 patients in a standard 3+3 Phase 1 design. Eligibility included pts with recurrent ovarian cancer. Pts had measurable disease by RECIST 1.1 or met GCIG CA125 criteria. No prior anti-angiogenics in the recurrent setting or prior PARP inhibitor were allowed. **Results:** 24 pts have been treated since May 2014 at 6 dose levels (C 20mg QD/O 200mg BID (3 pts); C 20mg QD/O 250mg BID (3); C 20mg QD/O 300mg BID (6); C 30mg QD/O 150mg BID (3); C 30mg QD/O 200mg BID (6); C 30mg QD/O 250mg BID). One DLT (gr 3 rotator cuff injury) occurred at the 30/200 dose level and two DLTs (1 $>$ 7d hold for proteinuria; 1 gr 4 HTN and gr 2 intracranial hemorrhage) at the 30/250 dose level. Other related gr 3/4 adverse events (AEs) included HTN (5), vomiting (1), fatigue (1), myalgia (1), and thromboembolic event (1). Most common AEs included nausea (79%), fatigue (75%), diarrhea (58%), vomiting (42%), and HTN (42%). The RP2D levels are C 30mg QD/O 200mg BID and C 20mg QD/O 300mg BID. Best response in 21 evaluable OvCa pts (13 plat-resistant; 8 plat-sensitive) include 2 CR, 4 PR, 14 SD, 1 PD, including 1 CR, 2 PR and 2 SD in 5 evaluable pts at the 30/200 and 1 CR and 4 SD in 5 pts at the 20/300 dosing levels. **Conclusions:** RP2D for combination C/O tablets is cediranib 30mg/olaparib 200mg BID or cediranib 20mg/olaparib 300mg BID. Observed toxicities are consistent with those seen with combination using olaparib capsules. Preliminary assessment of activity demonstrated a 29% unconfirmed response rate in OvCa pts using a regimen that is safe and tolerable. An expansion cohort will enroll at the cediranib 30mg/olaparib 200mg BID level. Clinical trial information: NCT01116648.

5560 Poster Session (Board #118), Sat, 1:15 PM-4:45 PM

Ovarian carcinosarcoma share similar molecular profile as ovarian serous carcinoma but not endometrial carcinosarcoma. *First Author: Haider Mahdi, Cleveland Clinic, Cleveland, OH*

Background: Ovarian carcinosarcomas (OCS) are rare and aggressive malignancies with limited treatment options. It is unclear if this uncommon type of cancer shares similar molecular changes as endometrial carcinosarcoma (ECS) or serous ovarian carcinoma (SOC). We compared the molecular profile of a cohort of OCS to that of SOC and ECS to explore the potential overlap in treatment paradigms. **Methods:** 110 OCS, 141 ECS and 1587 SOC were evaluated using a commercial multiplatform profiling service (CARIS Life Sciences, Phoenix, AZ). Specific testing performed included a combination of gene sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH or FISH). **Results:** TP53 was the most commonly mutated gene in all three malignancies with 76.4 % of OCS, 68.8 % of ECS and 69% of SOC. Alteration of PI3K/AKT/mTOR and MAPK pathways were noted to be similar in OCS and SOC but was less frequently altered than ECS including mutation in PIK3CA (7.6% and 2.3% vs. 22.2%, $p < 0.001$), FBXW7 (0% and 0.6% vs.12.1%, $p < 0.001$), PTEN (3.7% and 0.8% vs. 12%, $p < 0.001$) and KRAS (5.2% and 5.0% vs. 13.5%, $p < 0.001$). For homologous recombination pathway, SOC and ECS were more likely to have BRCA1 (20% and 18% vs. 9%) and BRCA 2 mutations (18% and 27% vs. 12%) than OCS. However, the differences were not statistically significant. No difference in alteration of RB, NOTCH, angiogenesis and FGFR pathways was noted among the three cohorts. Estrogen (14.6% and 25.1% vs. 53.1%, $p < 0.001$) and androgen receptors (18.8% and 12.2% vs. 32.4%, $p < 0.001$) were expressed less frequently in OCS and ECS than SOC respectively. On the other hand, expression of progesterone receptors was more frequent in in OCS and SOC than ECS (26.5% and 30.5% vs. 20.9%, $p < 0.001$). **Conclusions:** While ovarian carcinosarcoma and uterine carcinosarcoma are histologically similar, we reveal that OCS share molecular changes similar to that of SOC. Both OCS and SOC have significantly lower activity of PI3K/AKT/mTOR, MAPK pathways and higher progesterone receptors expression than ECS. Treatment with regimens that are active in ovarian serous could be considered when treating patients with ovarian carcinosarcoma.

5561 Poster Session (Board #119), Sat, 1:15 PM-4:45 PM

Derivation of a second generation multivariate index assay to improve specificity in pre-surgical evaluation of adnexal masses for risk of ovarian malignancy. *First Author: Zhen Zhang, Johns Hopkins Medicine, Baltimore, MD*

Background: The FDA cleared in vitro diagnostic multivariate index assay OVA1, with its intended utility to assist in referral of high risk patients to gynecologic oncologists, was by design to have a high sensitivity in assessing risk of malignancy in patients diagnosed with an adnexal mass prior to planned surgery. In this study, we developed and evaluated a second generation multivariate index assay (MIAG2) to improve specificity while maintaining a level of sensitivity similar to OVA1. **Methods:** CA 125 II, prealbumin, apolipoprotein A-1 (ApoA1), beta 2-microglobulin, transferrin (TRF), follicle-stimulating hormone (FSH), and Human epididymis protein 4 (HE4) were retrospectively analyzed on serum samples from a prospective multicenter study of patients with a documented pelvic mass planned for surgery. The samples were divided by block randomization into a training set (pre-/post-menopausal: 130/150; benign: 174, malignant: 106 including 35 stage I/II and 16 low malignant potential (LMP) cases) and a preliminary validation set (pre-/post-menopausal: 154/151; benign: 233, malignant: 72 including 19 stage I/II and 13 LMP cases). **Results:** Selected through extensive statistical resampling, the MIAG2 panel consists of CA 125 II, ApoA1, TRF, FSH, and HE4. Its algorithm uses two ensembles of classification models, for pre- and post-menopausal women respectively. However, with the help of FSH, the outputs of the models were integrated into a single-valued index with a cutoff of 5.0 arbitrary units for all patients. The specificity and sensitivity of the MIAG2 for the validation set were 60.1% (140/233) and 88.9% (64/72), respectively, compared to OVA1 which had a specificity of 47.2% (110/233) at a sensitivity of 95.8% (69/72). The improvement in specificity was statistically significant ($p < 0.001$). It is of interest to note that both the MIAG2 and OVA1 had a high sensitivity in detecting non-LMP ovarian cancer at 96.6% (57/59) and 100.0% (59/59), respectively. **Conclusions:** The MIAG2 significantly improved specificity over that of OVA1 while maintaining a comparably high sensitivity in pre-surgical assessment of adnexal masses for risk of malignancy.

5562 Poster Session (Board #120), Sat, 1:15 PM-4:45 PM

Early drug development in advanced gynecologic cancer based on genetic tumor profiling. *First Author: Ana C. Garrido-Castro, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: The broad spectrum of actionable molecular alterations (MA) detected with new techniques has increased interest in matched targeted therapies (MTT) after failure to standard treatment. **Methods:** Advanced gynecologic tumor (GYNT) patients (pts) were analyzed in our Molecular Prescreening Program for MA: mutations (mt) detected with Sequenom (Sq) or VHIO Card Amplicon Seq Panel (VCASP), Notch and PI3K amplifications (amp), PTEN loss (Hscore $\leq$ 50) and PDL1 expression. Pts were allocated to Phase I trials with MTT based on MA. Time to treatment failure (TTF) with MTT (TTF2) was compared to TTF with the previous unmatched therapy (TTF1). **Results:** From Jan 2012 to Dec 2014, 129 GYNT pts (mean age: 52.6 yrs; median no. previous treatments: 3 [0-7]) were screened for MA; 87 ovarian (OC; 23 type I, 64 type II), 27 endometrial (EC; 15 type I, 12 type II) and 15 cervical (CC) cancers. Of 69 pts with MA (53.5%), 33 received MTT (47.8%) including one OC pt treated with 2 consecutive MTT. MA were identified in 15 type I and 27 type II OC pts; mt in *PI3KCA* (9), *KRAS* (7), *BRAF* (2), *TP53* (8), amp in *Notch* (8) and *PI3K* (1), PTEN loss (18) and PDL1+ (3). In 12 type I and 9 type II EC, mt in *PIK3CA* (4), *KRAS* (8), *TP53* (2), *PTEN* (2), *FGFR1* (1), *ESR1* (1) and *ABL1* (1), PTEN loss (13) and PDL1+ (2) were found. *KRAS* (2), *PI3K/AKT*(2) mt and PDL1+ (2) were detected in CC. Two Sq wild-type pts tested with VCASP held TP53 mt. Of 16 *PIK3CA* MA pts, 6 were treated with α-specific PI3Ki, 1 with PI3K/mTORi and 3 with α-PI3Ki combined with IGFR1 or FGFRi. *KRAS* mt pts (17) were matched to MEKi-based combos: 7 MEK/PI3Ki, 2 MEK/AKTi and 1 MEK/IGFR1i. Multiple MA in a type I OC pt (*KRAS/BRAF* mt) were treated with PI3K/MEKi, a type I EC pt (*PIK3CA/KRAS* mt) with mTORi, and a type II EC pt (*TP53/FGFR1/ABL1* mt) with MET/FGFR/AXLi. Of 10 *TP53*mt, 1 PTEN loss pt received PI3Ki. Notch-i was offered to 5 of 8 amp OC and anti-PD1/PDL1 agents to 3 of 6 PDL1+ GYNT. Although no differences were found between TTF1 and TTF2 (17.8 vs 15.0 wks, $p = 0.156$), TTF2/TTF1 was > 1.2 in 11 of 34 MTT (32.4%). **Conclusions:** Albeit statistical significance was not reached, TTF improved in $> 30\%$ of pts meriting further evaluation of MTT in GYNT. More time is needed to elucidate the impact of genetic/proteomic tumor profiling in drug development of GYNT.

5563 Poster Session (Board #121), Sat, 1:15 PM-4:45 PM

Use of neoadjuvant chemotherapy in advanced ovarian cancer. *First Author: Larissa Meyer, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In 2010, a randomized trial demonstrated no difference in survival in advanced ovarian cancer patients treated with neoadjuvant chemotherapy (NAC) or primary debulking surgery (PDS). We examined the use and effectiveness of NAC in clinical practice over time. **Methods:** Prospective cohort study of women with stage IIIC/IV ovarian cancer treated at National Comprehensive Cancer Network (NCCN) institutions between 2003-2012. We examined the use ($N = 961$) and outcomes ($N = 414$) of NAC + interval debulking (IDS) +/- adjuvant chemotherapy versus PDS +/- adjuvant chemotherapy. Propensity score matching was used to balance observed confounders between groups in the outcomes analyses and trial participants excluded. Cox regression, logistic regression, and Fisher's exact test were used to examine overall survival, residual disease, and perioperative morbidity in the matched sample. **Results:** Use of NAC+IDS increased from 0-39% between 2003-2010, and rose to 53% (stage IIIC) and 58% (stage IV) in 2011-2012. Adoption of NAC+IDS varied by institution from 0%-29% (stage IIIC, $P < 0.001$) and 13%-48% (stage IV, $P = 0.04$). After propensity-score adjustment, NAC+IDS was associated with lower survival in stage IIIC disease, compared with PDS (median 31 vs. 50 months, hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.05-2.24), and comparable survival in stage IV disease (median 43 vs. 32 months, HR 0.78, 95% CI 0.50-1.22). NAC+IDS was associated with higher odds of an R0 resection [odds ratio (OR): 2.26, 95% CI 1.28-3.98, stage IIIC; OR 4.03, 95% CI 1.73-9.38, Stage IV), and fewer ostomies (adjusted rates: 3% vs. 9%, $P = 0.11$, stage IIIC and 3% vs. 11%, $P = 0.06$, stage IV). Readmission rates were lower in NAC+IDS, compared with PDS (adjusted rates: 2% vs. 16% for stage IIIC and 2% vs 15% for stage IV, both $P < 0.001$). **Conclusions:** NAC+IDS use increased significantly at NCCN centers between 2003-2012. In this observational study, overall survival was comparable in patients with stage IV disease, and NAC+IDS was associated with lower ostomy rates and perioperative morbidity in stage IIIC and IV disease. NAC+IDS was associated with decreased survival in patients with stage IIIC disease, however additional selection bias may remain after propensity-score matching.

5564 Poster Session (Board #122), Sat, 1:15 PM-4:45 PM

Baseline predictors of early treatment failure in patients with platinum resistant/refractory (PRR) and potentially platinum sensitive (PPS ≥ 3) recurrent ovarian cancer (ROC) receiving ≥ 3 lines of chemotherapy: The Gynaecologic Cancer Intergroup (GCIG) Symptom Benefit Study (SBS). *First Author: Felicia T Roncolato, ANZGOG, NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia*

Background: Women with PRR/PPS ≥ 3 ROC are a heterogeneous group with unpredictable response to palliative chemotherapy (PC). GCIG SBS recently completed recruitment of 949 patients treated with PC. Primary aim is to validate an instrument to measure symptom benefit; secondary aims include identifying factors that predict early progression. 25% of patients with PRR-ROC received < 8 weeks of PC. **Methods:** Physicians recorded baseline characteristics, symptoms (symptomatic ascites, cramping abdominal pain), site/extent of disease and prespecified lab values. Association between baseline characteristics and progression-free survival (PFS) was assessed using time-to-event methods. Median PFS was calculated according to clinically relevant categories and log-rank test applied to assess prognostic value. Cox regression was used to compute hazard ratios and 95% CI to assess the effect of variables on PFS. **Results:** Sufficient follow up for analysis of PFS was available in 791 patients. Median PFS and overall survival were 4.3 (95% CI: 3.9-4.9) and 12.9 months (95% CI: 11.4-14.0) respectively. In univariate analysis factors with statistically significant associations with PFS included: haemoglobin, PRR-ROC, ascites and abdominal cramps, nodal disease, thrombocytosis, CA125 > 1000, LDH > 600, ECOG status, and elevated c reactive protein. Non-significant factors included: visceral metastases, albumin < 25, lymphocytes < 0.5, tumour volume. Significant variables in multivariable analysis included: ECOG ≥ 2 (HR 1.61 95% CI 1.18-2.19 p = 0.003); nodal disease (HR 1.37 95%CI 1.13-1.67 p = 0.002); ascites (HR 1.54 95%CI 1.24-1.92 p = 0.0001); platinum resistant vs. sensitive (HR 1.39 95%CI 1.12-1.72 p = 0.002), CA125 > 1000 (HR 1.35 95%CI 1.09-1.67 p = 0.005); LDH > 600 (HR 1.88 95%CI 1.36-2.60 p = 0.0001). **Conclusions:** Several simple clinical variables help predict patients who progress rapidly and will be used to construct prognostic models to aid clinical decisions and trial stratification for clinical trials in PRR/PPS ≥ 3 ROC Clinical trial information: 12607000603415.

5565 Poster Session (Board #123), Sat, 1:15 PM-4:45 PM

Preliminary phase II results of selinexor, an oral selective inhibitor of nuclear export in patients with heavily pretreated gynecological cancers. *First Author: Ignace Vergote, University Hospital Leuven, Leuven, Belgium*

Background: Multiple tumour suppressor proteins (TSPs) are altered in ovarian (OC), endometrial (EC) & cervical (CC) cancers, including p53, BRCA1/2, CDKN2A & pRB. Selinexor, an oral first in class, inhibitor of XPO1 mediated nuclear export, results in nuclear retention and activation of multiple TSPs. Selinexor has anti-cancer activity in preclinical models of CC & platinum-resistant OC & in a phase I clinical study. This phase II trial explores the efficacy & tolerability of Selinexor in patients (pts) with advanced/metastatic incurable OC, EC & CC. **Methods:** Pts with ≥ 1 line of prior therapy were treated with single agent oral S using Simons two-stage design (NCT02025985). The primary endpoint is disease-control-rate (DCR = PR+SD ≥ 12weeks [wk]). Other endpoints are ORR, PFS, safety, & tolerability. Three treatment schedules (50 mg/m^2 twice-weekly (BIW); 35 mg/m^2 BIW; & 50 mg/m^2 QW in 4-wk cycles) are evaluated. The three cohorts (OC, EC & CC) are evaluated independently for response by RECIST 1.1 after 6 & 12 wks, then every 8 wks. **Results:** All three cohorts have passed efficacy response rates for Simon analysis & proceeded to stage two. 30 OC (Median age [MA] 63, ECOG 0/1: 16/14, median 5.5 (1–11) prior treatment regimens [PTR]), 15 EC (MA 69, ECOG 0/1: 8/7, median 2 (1–5) PTR) & 18 CC (MA 55.5, ECOG 0/1: 13/5, median 3 (1–8) PTR) heavily pre-treated pts have been enrolled. No Grade 4 toxicities have been seen. Grade 3 drug related adverse events (AEs) include: Nausea (13%), Thrombocytopenia (13%), Vomiting (11%), & Fatigue (10%). Commonly reported Grade 1/2 drug related AEs for all three cohorts include: Nausea (54%), Vomiting (5%), Fatigue (32%), & Anorexia (25%). Dose reductions occurred in 30 % of pts. DCR in evaluable pts: OC: 36%; EC: 64%; CC: 28%. ORR in evaluable pts: OC: 9%; EC: 18%; CC 7%. **Conclusions:** The initial phase 2 data demonstrate meaningful single-agent anti-tumor activity of Selinexor in all three heavily pretreated gynaecological malignancies. Some pts required dose reduction of Selinexor due to fatigue & anorexia. The most tolerable dosing regimen will be selected for phase III trials. The trial continues to enrol pts. Updated data will be presented. Clinical trial information: NCT02025985.

5566 Poster Session (Board #124), Sat, 1:15 PM-4:45 PM

Genomic characterization of long-term responders to olaparib. *First Author: Stephanie Lheureux, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: *BRCA1/2* mutations (*BRCA*m) predict benefit from olaparib (*vs* placebo) in platinum sensitive high grade serous ovarian cancer (HGSOC). However not all patients (pts) with *BRCA*m respond and others without *BRCA*m have very durable benefit from PARP inhibitors. This study characterised long (LT ≥ 2 years) and short-term (ST ≤ 3months) responders on olaparib maintenance. **Methods:** Clinical (previous chemo lines, stage, platinum free interval) and molecular variables from archival tumor were assessed from study D0810C000019 – olaparib/placebo after response to platinum in HGSOC. Germline *BRCA1/2* testing, Homologous Recombination Deficiency (HRD) score (positive ≥42) and *BRCA1* methylation were determined by Myriad Genetics. A comprehensive genomic profile with next generation sequencing was performed through Foundation Medicine. Fisher's exact test was used to test the association between presence and absence of any factor comparing ST *vs* LT. **Results:** Of pts who received olaparib maintenance, 32 had LT and 21 ST disease control. In the LT group, 21 pts had *BRCA*m (66%, *BRCA1* 9 pts, *BRCA2* 12 pts), positive HRD scores and deleterious *TP53* mutations. Variants of Unknown Significance were found in 2 LT pts (6%) with positive HRD scores and *TP53* mutations but negative for *BRCA1* methylation. In the overall study population, *BRCA1* methylation was not observed within LT pts: 27/37 LT pts (olaparib/placebo) had *BRCA1* methylation status available and none were methylated. 42/61 ST pts had methylation status available and 8 (19%) had *BRCA1* methylation. Complete response at the time of olaparib maintenance (p=0.026) and HRD deficiency status (p=0.026) were associated with LT on univariate analysis, and did not discriminate ST *vs* LT in the placebo group. LT group showed a trend for the presence of deleterious *TP53* mutation (p=0.051); *TP53* mutation status was available in 28/32 LT and 16/21 ST; deleterious mutations were detected in 27/28 LT *vs* 12/16 ST pts; in contrast with *TP53* wild-type found in 1/28 LT pt and 4/16 ST pts. **Conclusions:** Comparison of LT and ST responders provides a contrasting assessment of the intersection of disease biology on effect of olaparib and may allow identification of predictive patterns of durable benefit that need to be validated.

5567 Poster Session (Board #125), Sat, 1:15 PM-4:45 PM

Phase 2 studies of multiple peptides cocktail vaccine for treatment-resistant cervical and ovarian cancer. *First Author: Satoshi Takeuchi, Iwate Medical University, Morioka Iwate, Japan*

Background: We have conducted phase 2 studies of peptides vaccine (PV) immunotherapy for cervical (CC) and ovarian cancer (OC) using human leukocyte antigen (HLA)-restricted tumor specific epitope peptide and VEGF receptor1 (VEGFR1) and 2. Institutional review board had approved these studies. **Methods:** All patients (pts) with heavily treated and with HLA-A2402 or A0201 within PS2 were enrolled. Written-informed consent had obtained. Enrollment finished on October 20,2014. PV cocktail were as follows: FOXM1, MELK, HJURP,HIG2,VEGFR1 and VEGFR2 for OC, FOXM1, MELK, HJURP,URLC10 and HIG2 for CC. Each peptide (GMP grade) was mixed at a dose of 1mg with 1ml of adjuvant, MONTANIDE,ISA51. Vaccination schedule included 12 subcutaneous weekly injections. Thereafter, additional administrations (adms) were performed. CTL was analyzed by ELISpot assay. Clinical responses were evaluated every three months by RECIST v 1.1 and additional immune-responsive (ir-) RECIST **Results:** Twenty one pts of CC and 46 pts of OC were enrolled. PV was generally well tolerated with no major adverse events, and most of the patients developed specific CTL responses until 8 adms. Two patients showed complete response by RECIST. Median overall survival(mOS) of CC and OV was 15.4 months(m)and 8.8 m,respectively. No significant survival benefits were seen among HLA type and histology subtypes, but c-reactive protein levels (lower than 2.0 mg/dl) at base line in OC and dermatological hypersensitivity (DTH) during adms in CC and OC was strongly related their OS. Lower CRP group showed longer median OS (mOS = 19.0m vs. 3.0m, logrank p = 0.0016) in OC. As for DTH, negative versus positive patients, the mOS was 3.3 m vs. 21.2m, logrank p = 0.065, in CC, and it was 1.4 m vs. 17.7 m, logrank p < 0.0001, in OC. **Conclusions:** These findings suggest that this PV immunotherapy was safe and effective even for incurable patients and they would be applicable for maintenance therapy for cervical and ovarian cancer. Clinical trial information: UMIN000003860,3862,3902,3903.

5568 Poster Session (Board #126), Sat, 1:15 PM-4:45 PM

Propensity-score analysis of neoadjuvant chemotherapy vs. primary surgery in advanced ovarian cancer: Does surgical quality matter? *First Author: Hyo Sook Bae, National Cancer Center, Goyang, South Korea*

Background: Although there are many studies that compared the outcome of neoadjuvant chemotherapy (NAC) and primary surgery in advanced ovarian cancer, most of them showed some limitations such as selection bias and the quality control of surgical procedure. **Methods:** Data of 1124 patients with advanced epithelial ovarian cancer (stage III-IV) were reviewed retrospectively. To mitigate the possible biases from the retrospective nature of the study, we performed a propensity score analysis. Progression-free survival was assessed using a multivariate Cox-proportional hazards regression model with inverse probability weights to adjust for propensity score. **Results:** Among the 1124 patients, 198 patients (17.6%) underwent NAC. The factors associated with the use of NAC were old age, non-serous histology, poor histologic grade, stage IV and higher serum CA 125 levels (P-value 0.211, 0.050, < 0.001, < 0.001 and < 0.001, respectively). After a propensity score adjustment using those factors, the progression-free survival of the NAC group was not significantly different from that of the primary surgery group (HR 1.187, CI 0.932-1.512, *P*-value 0.164). Especially, no significant difference was observed between the two treatment strategies in the subgroup from the hospitals with higher surgical standards with the average rate of optimal cytoreduction was over 50% (HR 1.166, CI 0.885-1.536, *P*-value = 0.275). However, when we did not adjust the confounders, the outcome of primary surgery group was superior to that of NAC group (HR 1.24, CI 1.016-1.515, *P*-value 0.035). **Conclusions:** Progression-free survival of NAC group did not differ significantly from primary surgery in patients with advanced ovarian cancer. Even in the institutions providing a good standard of surgical care, we did not found any evidence suggesting that primary surgery is better than NAC in patients with advanced ovarian cancer.

	All (N = 1124)			High-performance institutions (N = 928)		
Treatment	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Before adjustment NAC	1.24	1.04-1.50	0.020	1.24	1.016-1.515	0.035
After adjustment by the propensity score NAC	1.187	0.932-1.512	0.164	1.166	0.885-1.536	0.275

5569 Poster Session (Board #127), Sat, 1:15 PM-4:45 PM

Feasibility and outcome of interval debulking surgery (IDS) after carboplatin-paclitaxel-bevacizumab (CPB): Results from a subgroup of patient from the MITO-16A-MANGO OV2A phase 4 trial. *First Author: Gennaro Daniele, National Cancer Institute Naples, Castel S Giorgio, Italy*

Background: Few data are available on the outcome of surgery after a bevacizumab-containing regimen. The MITO 16A- MANGO OV2A phase 4 trial evaluates the outcomes of first-line CPB in a clinical-practice-like setting. Here we present the results of the subgroup of patients undergoing IDS after neoadjuvant treatment or suboptimal primary surgery. **Methods:** 400patients aged $\geq$ 18 with untreated AOC, ECOG PS 0-2 were eligible to receive C (AUC 5 d1, q21) plus P (175mg/m^2 d1, q21) and B (15 mg/kg d1 q21) for 6 cycles followed by B maintenance until cycle 22nd within the MITO 16 trial. **Results:** With data available at Dec 31, 2014, 79/400 patients (20%) underwent IDS; bevacizumab was omitted before IDS in 5 patients. In the remaining 74 patients, median age was 61.2, 72% had FIGO IIIC disease, 23% FIGO IV and 5% FIGO IIIB. 60 patients (82.3%) had a suboptimal ($>$ 1cm) primary surgery, while in 14 cases a neoadjuvant therapy was given after a biopsy with no attempt of resection. The median number of cycles before IDS was 3 (Interquartile range, IQR: 3-4) and 3 (IQR: 2-3) for chemotherapy and bevacizumab respectively, with a median interval between the last bevacizumab and the IDS of 38 days (IQR: 34-47). The median duration of the IDS was 3.5 hours (IQR: 2.8-5) and discharge of the patients was after a median of 7.5 days (IQR: 6-10). The outcome of IDS is unknown for 3 patients; 10 patients (12.7%) were suboptimally debulked, while the residual disease was absent or $\leq$ 1 cm in 61 patients (82.4%). After IDS there was no major adverse events. Fever complicated 4% of the interventions and 4% of the patients required blood transfusion after surgery. Surgical wound infection and/or dehiscence, pelvic abscess, intestinal sub-occlusion and fistula were experienced by one patient each. **Conclusions:** In the MITO16A-MANGO OV2A phase 4 trial, combined chemotherapy and bevacizumab did not prevent IDS and the rate of perioperative complications was similar to what expected without bevacizumab. These data support the hypothesis that the opportunity to add bevacizumab to chemotherapy in first line treatment of ovarian cancer might not be denied to patients for whom IDS is planned. Clinical trial information: NCT01706120.

5570 Poster Session (Board #128), Sat, 1:15 PM-4:45 PM

Durable tumor remission in patients with platinum-resistant ovarian cancer receiving nivolumab. *First Author: Junzo Hamanishi, Kyoto University, Kyoto, Japan*

Background: Programmed death-1 (PD-1) is a co-inhibitory receptor expressed on activated T cells which regulates antitumor immunity. Nivolumab is a fully-humanized IgG4 that blocks the engagement of PD-1 by PD-1 ligands. We previously showed nivolumab can mediate tumor regression in a substantial proportion of patients with ovarian cancer in phase II trial (ASCO 2014, UMIN000005714), but the potential of durable anti-tumor response by nivolumab for these patients was unknown. **Methods:** Patients with platinum-resistant ovarian cancer (n=20) enrolled from 2011 to 2014 were treated with nivolumab (1mg/kg, n=10; 3mg/kg, n=10, each) intravenously every two weeks up to one year were followed how long anti-tumor response continued. **Results:** Among 20 patients in whom response could be evaluated, we followed two patients with complete response in 3mg/kg cohort and one patient with partial response of 1mg/kg cohort. At the time of data cut off, a partial responder had responses for 5 months, and two complete responders survived without disease progression for 17 and 14 months, each. The duration of response of these patients after treatment discontinuation was 6months and 3months, each. **Conclusions:** Anti-tumor responses were durable and continued after niolumab-treatment discontinuation. Now we explore the biomarker of these responders and next phase of clinical trials will further assess the significance of nivolumab on survival in patients with ovarian cancer. Clinical trial information: UMIN000005714.

5571 Poster Session (Board #129), Sat, 1:15 PM-4:45 PM

A phase 1b, open-label, non-randomized multicenter study of birinapant in combination with conatumumab in subjects with relapsed epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. *First Author: Erika Paige Hamilton, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: Treating patients (pts) with relapsed ovarian cancer remains challenging. Birinapant is a bivalent SMAC mimetic in clinical development for solid and hematological malignancies. *In vitro* there is synergy with birinapant and Amgen's DR-5 agonist antibody, conatumumab. Birinapant alone was not active in relapsed ovarian cancer, but the combination with conatumumab is thought promising. This study sought to determine the safety and tolerability of birinapant with conatumumab in relapsed ovarian cancer. **Methods**: Pts with relapsed epithelial ovarian, primary peritoneal or fallopian tube cancer were enrolled to 1 of 2 cohorts. Birinapant was dosed intravenously (IV) at 13 mg/m^2 2x weekly, 3 weeks of 4 (Days 1, 4, 8, 11, 15, and 18; Cohort 1); and 13 mg/m^{2}2x weekly, 4 weeks of 4 (Days 1, 4, 8, 11, 15, 18, 22 and 25; Cohort 2), with conatumumab at a fixed dose of 10 mg/kg IV, on Day 1 and Day 15 for each 28-day cycle. Assessments for dose limiting toxicities (DLTs), as well as safety, clinical response, pharmacokinetics (PK) and pharmacodynamics were performed. **Results**: To date 18 pts have been enrolled; 6 to Cohort 1 and 12 to Cohort 2. DLTs were seen in 1 pt in Cohort 1 (Grade 3 amylase and lipase elevation) and 1 pt in Cohort 2 (Grade 3 cranial nerve palsy). The most common ($\geq$ 3 pts) reported adverse events (AE) were fatigue; nausea; vomiting; abdominal pain; headache; hypomagnesemia; pruritis; chills; constipation; depression; diarrhea; dizziness; pyrexia; mucositis; urinary tract infection. The only serious adverse event seen in $>$ 1 pt was bowel obstruction (2 pts). An additional pt in Cohort 2 developed Grade 2 cranial nerve palsy. The PK of birinapant and conatumumab were unchanged from that reported previously for either agent. Pharmacodynamic evaluation is ongoing. Best response was PR seen in 1 pt; an additional 4 pts demonstrated best response of SD. Median time on study is 1.9 months (0.1-5.9 months). **Conclusions**: The combination of birinapant plus conatumumab in relapsed ovarian cancer is tolerable. Dose expansion (Cohort 3) is continuing at a dose of birinapant 11 mg/m^2 2x weekly, 3 weeks of 4. Clinical trial information: NCT01940172.

5572 Poster Session (Board #130), Sat, 1:15 PM-4:45 PM

Carboplatin hypersensitivity reactions (HSR) in carboplatin retreatment for recurrent ovarian cancer. *First Author: Roisin Eilish O'Cearbhaill, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: The reported risk of HSR during carboplatin retreatment is 18-44% and increases with repeated carboplatin exposure. We aimed to prospectively study the effect of an extended incremental infusion of carboplatin on the rate of HSR. **Methods:** Eligible patients (pts) with recurrent ovarian cancer were consented to an IRB-approved phase II randomized study from 01/2011-01/2015. Pts were randomly assigned 1:1 to standard 30-minute or an incremental 3-hour (1% in 1st hour, 9% in 2nd hour and 90% in 3rd hour) carboplatin infusion. Pts were stratified for concomitant taxane. Based on historical estimates the study was powered to detect a reduction in HSR from 20% to 5% with the extended infusion. All pts were prescribed premedication with montelukast 10 mg nocte x 3 days, dexamethasone 20 mg the night before and morning of, as well as famotidine 20 mg (or ranitidine) and diphenhydramine 50 mg (or hydroxyzine) prior to carboplatin. Pts were deemed evaluable for the study endpoint if they completed ≥ 5 cycles of carboplatin-based treatment or had carboplatin HSR. CTCAE criteria were used. **Results:** A total of 143 pts with recurrent ovarian cancer were enrolled. Median age was 62 years (35-82). 104 pts (52 in each arm) were evaluable for the study endpoint. Among these pts, 72 (69%), 27 (26%), 2 (1.9%) and 3 (2.9%) pts had 1, 2, 3 and 4 prior platinum-based regimens, respectively. 27 pts (26%) received carboplatin single agent and the remainder a platinum-doublet (46 liposomal doxorubicin, 24 gemcitabine, 7 paclitaxel). There were 15 HSR (14% of pts); 9 HSR in standard arm (9/52, 17%) and 6 HSR in the extended arm (6/52, 12%). There was 1 grade 3 HSR in the extended arm. No pt required hospitalization or epinephrine for HSR. The other 14 HSR were grade 1 or 2. HSR occurred on cycle #1 (1 pt); #2 (5 pts); #3 (4 pts); #4 (2 pts); #5 (2 pts) and #6 (1 pt). 2/9 HSR pts in standard arm were able to complete therapy with an extended infusion without further HSR. **Conclusions:** We did not demonstrate a statistically significant reduction in carboplatin HSR with use of an extended carboplatin infusion. However, the relatively low frequency of severe HSR in both arms suggests there may be a role for prophylactic premedication prior to carboplatin retreatment. Clinical trial information: NCT01248962.

5573 Poster Session (Board #131), Sat, 1:15 PM-4:45 PM

A phase Ib/II trial with expansion of patients at the MTD trial of olaparib plus weekly (metronomic) carboplatin and paclitaxel in relapsed ovarian cancer patients. *First Author: Saul E. Rivkin, Swedish Cancer Inst, Seattle, WA*

Background: We established the olaparib tablet maximum tolerated dose, dose limiting toxicities (DLT's) and response to therapy of carboplatin, paclitaxel and olaparib tablet given simultaneously, reported at ASCO 2014. This abstract will include data from both the phase 1b and the phase 2 expansion. **Methods:** A total of 54 subjects were evaluated in this trial, 14 in phase 1b and 40 in phase 2. Eligibility required measurable disease, adequate organ function and ECOG performance status of ≤ 2. Subjects had to have failed first line platinum containing chemotherapy. BRCA testing was conducted as available. Subjects received the metronomic therapy of paclitaxel 60mg/m2 IV and carboplatin AUC 2 IV weekly, 3 weeks out of 4, and olaparib tablets at the MTD of 150 mg bid administered orally for 3 consecutive days (D1-D3), every week for each cycle. Subjects were assessed for toxicity and response according to the protocol. Subjects that reached a confirmed complete remission were transitioned to olaparib tablets only, 300 mg bid, until disease progression. **Results:** Median age was 58 and median number of prior regimens was 4. There have been no deaths due to the study regimen. One patient had grade 4 neutropenia and an allergic reaction to carboplatin. The common grade 3 toxicities caused by this regimen were neutropenia, anemia and thrombocytopenia. Two subjects had mild GI toxicities. There was no evidence of cardiac, hepatic, or pulmonary toxicities in any of these subjects. 22.5% of subjects had a complete remission (CR), 30% had PR, 25% had SD and 22.5% had PD. Of the 9 CR's, 6 were gBRCA mutated. PFS median for gBRCA mutated subjects is 19 months vs 4 months for non-mutated gBRCA subjects. OS median for gBRCA mutated subjects is 24 months vs 16 months for gBRCA non-mutated subjects. All of the CR's are alive. **Conclusions:** Olaparib tablets can be safely administered simultaneously with a weekly regimen of carboplatin and paclitaxel in heavily pretreated ovarian cancer subjects. Olaparib appears to be highly effective in gBRCA mutated. This is the first successful combination of olaparib tablets with carboplatin and paclitaxel that has been well tolerated. Clinical trial information: NCT01650376.

5574 Poster Session (Board #132), Sat, 1:15 PM-4:45 PM

BL1 gene expression subtype to predict outcome in serous ovarian cancers. *First Author: Rob Seitz, Insight Genetics Inc, Nashville, TN*

Background: A new 2188-gene model classifies triple-negative breast cancer (TNBC) into six distinct subtypes: two basal-like, two mesenchymal-like, immunomodulatory and luminal androgen receptor subtypes. Among taxane-treated TNBC patients, significantly higher response rates were seen in patients with BL1 compared to BL2 tumors. Recently we showed that a "lean algorithm" of 101 genes could replicate this result in TNBC patients. As TNBC and serous ovarian cancer share many features, similar sub-classification of ovarian cancers may also be clinically important. **Methods:** A cohort of 592 patients with serous ovarian carcinoma (primarily platinum/taxane-treated) was analyzed. Patients were classified using both the original 2188-gene and 101-gene centroid models. Patients who had an insignificant or multiple statistically indistinguishable correlations with the subtype centroids were considered "unclassified." Three-year survival was examined using log-rank test and Cox proportional hazard regression analysis. **Results:** While both models had a higher percentage of unclassified patients in ovarian as compared to TNBC, the 101-gene model classified more patients (60%) than the 2188-gene model (34%). In the subset classified by both models, the models showed 95% agreement. Ovarian cancer patients with BL1 tumors had significantly better 3-year overall survival compared to all other subtypes (hazard ratios of 0.48 and 0.41, p = 0.02 and 0.01, 2188 and 101-gene models respectively). If age and stage—both independent predictors of survival—were included as covariates, only the 101-gene model defined BL1 subtype had a significant association with outcome (HR 0.47, p = 0.02). **Conclusions:** There was excellent agreement between the original 2188-gene TNBC classifier and a streamlined 101-gene classifier when applied to an ovarian cancer cohort. BL1-classified ovarian cancer patients had significantly better 3-year survival outcomes than patients with tumors of other subtypes; however, only the 101-gene classification of the BL1 subtype was independent of age and stage. Studies aimed at the refinement of gene expression-defined serous ovarian carcinoma subtypes that can guide therapeutic management will be presented.

5575 Poster Session (Board #133), Sat, 1:15 PM-4:45 PM

Genomic profile and immune infiltrate in paired ovarian cancer (OC) samples pre- and post-neoadjuvant chemotherapy (NC). *First Author: Alexandra Leary, Royal Marsden Hospital, London, United Kingdom*

Background: Most studies of OC have analysed tumors at diagnosis, little is known about the evolution of the genomic or immune landscape of OC with NC. Profiling after NC may be informative as the residual tumor may be enriched for resistant clones. **Aim**: Compare matched post- vs pre-NC tumors to describe changes in immune infiltrate, genomic stability (GS) and characterize the chemo-resistant sub-populations by identifying SCNAs selectively enriched post-NC. **Methods**: 27 frozen OC samples (13 paired pre/post-NC and 1 subsequent relapse) were subjected to aCGH. GS was evaluated by the % altered genome and the number of altered segments > 15Mbp (*N*). Changes in copy number alterations (CNA) were considered relevant if log(2)ratio difference in matched post- vs pre-NC samples > 0.5. FFPE samples (N = 66; 33 paired) were scored for % stromal tumor infiltrating lymphocytes (sTILs) on whole sections. **Results**: Cellularity of frozen samples was high (70-90%) and included 12 high grade serous OC (HGSOC) and 1 low grade SOC. At baseline, HGSOC were unstable with 10 showing *N*> 10 (range 14-48) and 31%-70% altered genome. LGSOC showed 2% altered genome. GS increased in 8/12 HGSOC resulting in < 2% altered genome post-NC for 3; GS decreased in 2/12 and did not change in 3. CNAs enriched in paired post-vs pre-NC included gains in genes involved in p53 signalling (*MDM4, TP53BP2),* EMT/senescence (*PKD1, ESRP1, RB1CC1*), or epigenetic modification (*CEBBP, SMARCB1, RBBP7*) and changes in DNA repair genes implicated in chemoresponsiveness (*PALB2*, *ERCC4, RAD54B* or *RAD21*). In addition potentially actionable targets were upregulated post NC (*AKT3*, *BRAF, RAS* family or *FGF6*). For the case with 3 samples, the profile at relapse was different from pre-NC but identical to the post-NC. sTILs increased with NC in 48% (16/33) of paired cases, and 6 tumors had ≥ 60% sTILs post-NC. An evaluation of changes in PDL1 with NC is ongoing and will be presented. **Conclusions**: The immune and genomic landscape of OC changes with NC. Surprisingly a proportion showed increasing TILS and GS. Comparative profiling of post- vs pre-NC tumors could be used to select therapies such as immune or targeted therapies to eradicate the residual lethal clones driving relapse.

5576 Poster Session (Board #134), Sat, 1:15 PM-4:45 PM

Homologous recombination (HR) deficiency, tumor *BRCA1/2* mutations (tmBRCA) and association with response and outcome following platinum monotherapy in high grade serous ovarian cancer (HGSOC). *First Author: Robert Brown, Imperial College London, London, United Kingdom*

Background: Response to DNA-damaging agents, including platinum, is associated with defects in BRCA1/2 and other HR pathway genes. The HRD score is a sum of three previously described metrics (Abkevich et al, Birkbak et al, Popova et al), and is significantly associated with both tmBRCA and response to DNA damaging agents. This study examined whether HR deficiency (HRD score ≥ 42 or tmBRCA positivity) was predictive of response or prognostic in a carboplatin monotherapy treated HGSOC cohort from the SCOTROC4 phase 3 trial (Bannerjee et al 2013). **Methods:** DNA from formalin-fixed archival tumor from 165 HGSOC patients treated with first-line single-agent carboplatin was analyzed for HRD scores and tmBRCA. Cox proportional hazards analysis was used to test CA125 response, HR deficiency, and tmBRCA for associations with progression free survival (PFS) and overall survival (OS). HR deficiency and tmBRCA were evaluated as predictors of CA125 complete response using logistic regression. **Results:** BRCA1/2 mutations were detected in 26/165 (16%) of primary HGSOC. HR deficiency was present for 53/151 (35%) tumors analyzed. Patients with CA125 complete response (n = 64) had significantly improved PFS (p = 6.6x10-7) and OS (p = 3.3x10-7) compared to no or partial CA125 response (n = 45). HR deficiency predicted CA125 complete response in all evaluable patients (p = 0.0033, n = 96) and in the *BRCA1/2* wild type subset (p = 0.034, n = 75). TmBRCA trended but was not significantly associated with CA125 response (p = 0.079, n = 107). HR deficiency and tmBRCA were associated with improved PFS (p = 0.00058; 0.012 respectively) and OS (p = 0.0040; 0.026 respectively) in an independent manner from known prognostic clinical factors. **Conclusions:** HR deficiency and tmBRCA were significantly associated with outcome in HGSOC patients treated with platinum monotherapy. HR deficiency was also significantly associated with complete CA125 response in the entire cohort, and importantly, in *BRCA1/2* wild type tumors. Pending validation evaluation of HR deficiency and tumor BRCA status should be considered in the development of platinum combination therapies.

5577 Poster Session (Board #135), Sat, 1:15 PM-4:45 PM

Delayed recurrences and survival after relapse in patients initially treated with intraperitoneal chemotherapy for advanced ovarian cancer: A Gynecologic Oncology Group study. *First Author: Daniel Stuart Kapp, Stanford Univ Medcl Ctr, Stanford, CA*

Background: Randomized trials have shown that intraperitoneal (IP) therapy is superior to intravenous (IV) chemotherapy in advanced ovarian cancer patients with long-term survival outcomes. We proposed to determine the contribution to improved survival in those treated with IP over IV therapy. **Methods:** Data from Gynecologic Oncology Group protocols 114 and 172 were retrospectively analyzed. Kaplan Meier estimates and Cox proportional hazards regression models were used for statistical analyses. **Results:** Of 876 women, the median age was 57 years (range: 49 to 66 years). All patients had stage III disease and 73% had serous, 10% endometrioid, 4% clear cell, 2% mucinous and 12% others. 64% had gross residual and the remaining 36% had no visible disease after surgery. After a median follow-up of 10.7 years, 27% (118/440) of IP vs. 22% (96/436) of IV patients remained free of disease (p = 0.098). Recurrences were delayed for the IP vs. IV patients at a median 24.4 (95%CI: 14.3–60.1 months) vs. 20 months (95%CI: 11.5–43.7 months; p = 0.002). The 10 year progression-free survival was 18% and 16% (p = 0.019), respectively. 201 patients remained on follow-up beyond 5 years with 111 from IP and 90 from IV therapy. We then evaluated the survival after recurrence and found that the median overall survival after relapse for IP vs. IV patients was 25.3 vs. 21.7 months, respectively (HR = 0.84; 95%CI: 0.71–0.99, p = 0.034). Factors associated with survival after recurrence included: younger age (HR = 1.01 95%CI: 1.00–1.02 p = 0.022), clear / mucinous histology (HR = 2.90 95% CI:2.08–4.04 p < 0.001), gross residual disease (HR = 1.25; 95%CI: 1.04–1.50; p < 0.001), and progression-free interval after primary treatment (HR = 0.72; 95%CI: 0.66–0.78 p < 0.001). **Conclusions:** The improvement in long-term survival in patients initially treated with intraperitoneal chemotherapy for advanced ovarian cancer is associated with both delayed recurrence after primary treatment and better survival after relapse. Our findings support the contention that the OS endpoint is attainable even in ovarian cancer patients with long post progression survivals.

5578 Poster Session (Board #136), Sat, 1:15 PM-4:45 PM

Part I of GANNET53: A multicenter phase I/II trial of the Hsp90 inhibitor ganetespib (G) combined with weekly paclitaxel (P) in women with high-grade serous, high-grade endometrioid, or undifferentiated, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. *First Author: Isabelle Ray-Coquard, GINECO and Centre Léon Bérard, Lyon, France*

Background: Stabilized mutant p53 protein (mutp53) is a novel target in epithelial ovarian cancer (EOC). Due to aberrant conformation, mutp53 proteins depend on folding support by the Hsp90 chaperone. Hsp90 blockade induces degradation of mutp53, resulting in tumor cell cytotoxicity and increased sensitivity to chemotherapeutics. Preclinical synergy of the Hsp90 inhibitor G combined with P provided the rationale for testing the combination in relapsed platinum resistant EOC patients (pts) in the GANNET53 trial (EUDRACT 2013-003868-31). **Methods:** Eligiblepts had platinum resistant EOC. Pts with > 4 prior chemotherapy and low grade carcinoma were not eligible. Weekly P (80 mg/m^2) and increasing doses of G (100, 150 mg/m^2) were given i.v. on days 1, 8, 15 in a 28 days cycle until disease progression or unacceptable toxicity. End points were safety and determination of phase II dose. Dose limiting toxicity (DLT) was defined as grade (gr) 4 toxicity (with exceptions) occurring in cycles 1 & 2. **Results:** Ten pts (median age 57 years; range 43-70) were enrolled. No DLT occurred in cohort 1 (4 pts treated with P + G 100 mg/m^2), nor in cohorts 2 and 3 (6 pts treated with P + G 150mg/m^2). The most common adverse events (AEs) related to G were transient gr 1/2 diarrhea (n = 9). The most frequent gr 1/2 AEs were diarrhea (n = 9), nausea (n = 5), anemia (n = 6), fatigue (n = 4), headache (n = 5), and QTc prolongation (n = 6). AEs ≥ gr 3 were anemia (n = 3), neutropenia (n = 2), and acute cardiac failure (n = 1). There was 1 death on study (after DLT period) due to digestive tract hemorrhage from duodenal ulcer. Two pts discontinued due to SAEs (digestive hemorrhage n = 1, cardiac failure n = 1), 4 due to progressive disease, one due to physicians decision. Three pts are still on study at time of abstract submission. **Conclusions:** The combination of ganetespib 150 mg/m^2 with paclitaxel 80 mg/m^2 once weekly for 3 out of 4 weeks was generally well tolerated with no DLTs, and therefore chosen for the planned randomized phase II trial. Clinical trial information: 2013-003868-31.

5579 Poster Session (Board #137), Sat, 1:15 PM-4:45 PM

The use of patient-derived xenograft models for prioritizing therapeutic targets. *First Author: Clare L. Scott, Walter and Eliza Hall Institute of Medical Research, Parkville, Australia*

Background: Treatment options for women with high-grade serous ovarian cancer (HGSC) remain limited. Defective DNA repair capability may underlie response to standard chemotherapy and to PARP inhibitor therapy[1,2]. Thus, molecular characterization of HGSC may indicate likely sensitivity or resistance to therapeutics. However, determining which potential targets actually drive tumor growth and should be prioritized for therapy is challenging. Pre-clinical HGSC cell lines have been shown to poorly reflect human disease[3] and rarely contain DNA repair gene mutations[4]. In contrast, patient-derived xenograft (PDX) models provide relevant, accurate and tractable models for pre-clinical testing, representative of patient outcome[5,6]. **Methods:** A patient derived xenograft (PDX) cohort was generated from consecutive, treatment-naïve human HGSC and stratified according to DNA repair capability including BROCA sequencing[7] and next generation sequencing by Foundation Medicine. *In vivo* response to standard chemotherapy with cisplatin was determined. Resistance to therapy was driven by re-treating relapsed PDX *in vivo*. Potentially "actionable" aberrations were targeted *in vivo* with relevant novel therapeutics. **Results:** To date, of 30 HGSC PDX studied, 11 contained defects in the DNA repair genes, *BRCA1* or *BRCA2* (9 had *BRCA1/2* mutations, 2 had *BRCA1* methylation) and another 3 PDX contained mutations in other DNA repair genes (FANCL, ATM, CHK2). All *BRCA1/2*-mutant PDX responded to platinum therapy. Dominant oncogenes (eg *CCNE1*, *LIN28B*, *MYCN* and *BCL2*) were overexpressed in platinum-refractory PDX. Potentially actionable targets were targeted *in vivo* with novel therapeutic strategies. **Conclusions:** As patient surrogates, PDX models represent a powerful tool for addressing individualized therapy. PDX are reliably generated from HGSC with DNA repair defects, not seen with cell lines. PDX with serial histologic, molecular, therapeutic annotation and clinical outcome data can be useful in assessing response to novel therapies. TCGA Nature 2011 Ledermann Lancet Oncology 2014 Domcke Nat Comms 2013 Stordal Mol Oncol 2013 Topp Molecular Oncology 2014 Weroha Clin Canc Res 2013 Walsh PNAS 2011

5580 Poster Session (Board #138), Sat, 1:15 PM-4:45 PM

Phase II trial of weekly nab-paclitaxel with GM-CSF as an immune modulator in recurrent platinum resistant ovarian, fallopian tube, and primary peritoneal cancer: Clinical and immune responses. *First Author: John Ben Liao, University of Washington, Seattle, WA*

Background: Antitumor immune responses in ovarian cancer have been associated with prolonged survival. In addition to direct cytotoxic activity, chemotherapies can also possess immunomodulatory properties. Paclitaxel may enhance metastasis and drug resistance by signaling via the TLR4 pathway. GM-CSF has been shown to induce the generation of myeloid dendritic cells and enhance antigen presentation. We hypothesized that weekly nab-paclitaxel followed by GM-CSF may enhance overall anti-tumor immunity. **Methods:** Peripheral blood mononuclear cells (PBMC) were evaluated by flow cytometry for circulating monocytes, dendritic cells, natural killer cells, T-lymphocytes, and myeloid derived suppressor cells (MDSC). Elispot assays for interferon gamma were performed on PBMC to identify immunity against ovarian cancer antigens. **Results:** Twenty-one patients with recurrent platinum resistant ovarian, fallopian tube, or primary peritoneal cancer enrolled after receiving an average of 3 prior lines of chemotherapy. 52% had previously received bevacizumab. Median OS was 16.8 months. Mean time to progression was 5.5 months for those patients who achieved a CR and 4.5 months for those who did not. Overall response rate was 71% (29% CR, 43% PR). Interferon gamma Elispot responses at mean follow-up timepoints against insulin-like growth factor 1 receptor (IGF1R) correlated with time to progression ($r = 0.723$, $p = 0.0035$). The fold change achieved above baseline Elispot responses against IGF1R ($r = 0.827$, $p = 0.0003$) also correlated with time to progression. Levels of MDSC at time of study enrollment were associated with achieving a complete response to treatment ($p = 0.0544$). **Conclusions:** Our results show activity of this regimen and immune correlates for response have been identified. Rational combinations of immune modulators with cytotoxic chemotherapies should be investigated further for platinum resistant recurrent ovarian cancer with a focus on identifying immunologic synergies and those patients most likely to respond through immune biomarkers. Clinical trial information: NCT00466960.

5581 Poster Session (Board #139), Sat, 1:15 PM-4:45 PM

Modifiable risk factors for ovarian cancer: A multinational case-control study. *First Author: Mohammed Shaik, Michigan State University, East Lansing, MI*

Background: Prior ovarian cancer (OC) epidemiological studies have investigated the relationship of diet, exercise, and smoking. Evidence of these risk factors for ovarian cancer has been inconsistent. In this multinational case control study we evaluated those potential modifiable risk factors. **Methods:** Data were obtained from the Global Epidemiological Study, a multinational database to assess disease risk factors. A total of 1344 (OC = 672 and controls = 672) matched for age and race, were recruited from Poland, Vietnam, Western Europe and USA. Information regarding risk factors included different diets in number of servings (serv), exercise, and smoking. For categorical and continuous variables chi-square and t-test were used, respectively. Adjusted multivariable logistic regression analysis was used for odds ratios (OR) with 95% confidence intervals (CI) as estimates of the relative risk of OC. **Results:** Median age was 59 yrs and median BMI for cases and controls was 25.7 and 26, respectively. In the multivariate analysis, OC risk was significantly associated with a self-report of dairy [*OR = 1.91; 95% CI (1.4-2.4)*], whole grain *[OR = 0.64; 95% CI (0.51-0.87)*], fish [*OR = 2.7; 95% CI (2.04-3.56)*], exercise [*OR = 1.54; 95% CI (1.19-1.99)*] and tobacco smoking [*OR = 0.43; 95% CI (0.25-0.74)*], respectively. There was no association with fruits, vegetables, and meat consumption on OC risk (see table). **Conclusions:** Consumption of fish (any serv/wk), dairy (> 2 serv/day), whole grains (< 2 serv/day) and exercise (> 120 min/wk) were associated with a decreased risk of OC. Smoking > 40 pack-yr (pyr) showed an increased risk for OC. Further prospective studies are needed to validate our findings.

Modifiable risk factors in ovarian cancer.

Variables	Adjusted OR (CI)	p-value
Fish intake (No *vs.* Yes)	2.7 (2.04-3.56)	< 0.0001
Whole Grain (< 2/day serv *vs.* ≥ 2/day	0.64 (0.51- 0.87)	0.003
Dairy (< 2/day serv *vs.* ≥ 2/day)	1.91 (1.4-2.4)	< 0.0001
Vegetables (< 2/day serv *vs.* ≥ 2/day)	0.78 (0.6-1.02)	0.07
Fruits (< 2/day serv *vs.* ≥ 2/day)	1.16 (0.8-1.5)	0.24
Meat (< 3/wk serv *vs.* ≥ 3/wk)	1.2 (0.95-1.52)	0.10
BMI	1.001 (0.9-1.02)	0.92
Smoking (<40 pyr *vs.* ≥ 40 pyr)	0.43 (0.25-0.74)	0.002
Exercise (< 120 min/wk *vs.* ≥ 120 min/wk)	1.54 (1.19-1.99)	0.0008

5582 Poster Session (Board #140), Sat, 1:15 PM-4:45 PM

EP-100 + paclitaxel to overcome taxane resistance in patients with recurrent LHRH-receptor expressing ovarian cancer. *First Author: Alpa Manchandia Nick, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: EP-100 (E) is a synthetic cytolytic peptide conjugated to Luteinizing Hormone Releasing Hormone (LHRH). It targets cells that overexpress LHRH receptors and kills by membrane disruption. Preclinical studies demonstrate synergy between E and paclitaxel (P). This randomized phase 2 trial explored the efficacy, safety and toxicity of E+P in women with advanced ovarian cancer. **Methods:** "Run-in" dose-escalation specified at least 1 patient would be treated with E per dose level. Patients were randomized 1:1 to receive weekly P (80 mg/m^2 IV) + biweekly E (30 mg/m^2 IV, E+P) vs. weekly P (80 mg/m^2 IV). Unlimited prior regimens were allowed. Central IHC for tumoral LHRH receptors was required. The 1^O endpoint was overall response rate (ORR) per RECIST 1.1. The 2^O endpoint was disease control rate (DCR = CR+PR+SD). For an improvement in ORR and DCR of at least 30% with E+P vs. P, a sample size of 20 patients/arm estimated CIs of 6-47% (P alone) vs. 27-73% (E+P). Patients progressing on P were allowed to receive E (30 mg/m^2 IV) plus continuation of P (80 mg/m^{2}IV). Time to progression (TTP) was assessed. **Results:** The "run-in" consisted of 6 patients and established RP2 dose of E+P: 30 mg/m^2 (E) IV biweekly and 80 mg/m^2 (P) IV weekly. 44 patients were enrolled in the phase 2 study. The ORR 34.8% (E+P: 95% CI: 16-57.3%) vs. 33.3% (P: 95% CI 14.6-57%). The DCR was 73.9% (E+P: 95% CI 51.6-89.8%) vs. 71.4% (P: 95% CI 47.8-88.7%). All 44 patients were assessable for safety; 43.5% (E+P) and 47.6% (P) had grade 3 or 4 events, primarily GI and related to underlying disease. The incidence of infusion-related reactions of all grades was greater with E+P (52%, n = 12) than with P (23.8%, n = 5). 10 patients progressed on P and received E+P. 50% had > 3 months of disease stabilization with TTP of 3-7 months, including 1 PR. 60% of these 5 patients had 3 times > TTP with E+P compared to their respective previous TTP after P alone. The addition of E did not complicate the AE profile of P and was well tolerated. **Conclusions:** EP-100 appears to sensitize paclitaxel-resistant ovarian tumors leading to further shrinkage of target and non-target lesions and prolongation of treatment response. A larger study comprising paclitaxel resistant patients is warranted. Clinical trial information: NCT0145848.

5583 Poster Session (Board #141), Sat, 1:15 PM-4:45 PM

Combination therapy with temsirolimus and trabectedin for recurrent clear cell carcinoma of the ovary: A phase II study with biomarker analysis. *First Author: Masashi Takano, National Defense Medical College, Tokorozawa, Japan*

Background: Recurrent clear cell carcinoma (RCCC) of the ovary showed exceedingly chemo-resistant phenotype, especially in the case with recurrent or refractory to previous therapy. A phase II trial to evaluate the effect of combination therapy with temsirolimus and trabectedin for patients with RCCC was performed. **Methods:** Eligible patients were as follows: (a) ECOG PS = 0~2 (b) histologically confirmed ovarian clear cell adenocarcinoma (c) diagnosed as platinum-resistant ovarian cancer (d) written informed consent. Patients with RCCC were treated with weekly regimen using two drugs: 15mg/m^2 of temsirolimus and 0.15mg/m^2 of trabectedin (3 weeks, one week rest). Treatment was continued until development of progressive disease (PD) or unmanageable adverse effects. There was no significant difference of serum level of VEGF according to the response evaluation. Biomarker analyses including serum VEGF and BNP were also conducted. **Results:** A total of 21 patients were analyzed in the present study. There were no cases that discontinued the therapy due to toxicities. Median age was 59 years (range: 30-69), and median number of previous chemotherapy was 3 (range: 1-6). All cases were assessable by RECIST and CTCAE. One patient (5%) had a complete response (CR), and two cases (10%) achieved a partial response (PR), and 6 patients (29%) had a stable disease (SD) beyond three months, resulting in clinical benefit rate (CBR; CR+PR+SD > 3month) of 43%. Median response duration in CBR case was 3.5 months (range: 3-40+). There were no cases that developed toxicities more than grade2. There was no significant difference of serum level of VEGF according to the response evaluation. **Conclusions:** Combination therapy with temsirolimus and trabectedin was a candidate for salvage therapy for patients with RCCC. These results warrant further study in such clinical settings with biomarker analyses.

5584 Poster Session (Board #142), Sat, 1:15 PM-4:45 PM

Omentin as a biomarker associated with improved overall survival in serous ovarian cancer. *First Author: Michaela Onstad, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Omentin is a protective adipokine secreted by the mesothelial cells of visceral adipose tissue. Its expression is inversely related to obesity and low levels have been found to be associated with disease states, such as diabetes and hypertension. Recently it has been found to have tumor suppressor activity in ovarian cancer, leading to decreased ovarian cancer cell proliferation, motility and invasion potential. We sought to explore whether omentin could be used as a biomarker to predict overall survival among patients with serous ovarian cancer. **Methods:** Serum samples were obtained from 148 women with serous ovarian cancer at the time of initial surgery. Circulating omentin levels were quantified using a commercially available ELISA kit. Clinical and demographic data were obtained from the electronic medical record. Overall survival was measured from the date of omentin collection to the date of last follow-up or death. A multivariate analysis of overall survival was performed to account for potential confounding variables. **Results:** Among women with serous ovarian cancer, a higher omentin level (per 100 units) is significantly associated with a decreased risk of death ($p = 0.0004$). Using a cutoff point of 350ng/mL, a Kaplan-Meier curve demonstrates a significantly improved survival for women with omentin $>$ 350ng/mL at the time of initial surgery ($p < 0.0001$). A multivariate analysis was performed to consider other risk factors that may contribute to risk of death, including stage and grade of cancer, optimal debulking, use of neoadjuvant chemotherapy, BMI, menopausal status, diabetes and metformin use. After adjusting for these factors, the relationship between omentin and overall survival remained statistically significant ($p < 0.0001$). **Conclusions:** Omentin levels $>$ 350ng/mL are predictive of improved overall survival among women with serous ovarian cancer, after adjusting for potential confounders. This may be reflective of the tumor suppressor activity of this adipokine, or may be due to the ability of ovarian cancer cells to down-regulate production of omentin. These findings warrant validation in another large ovarian cancer dataset.

5585 Poster Session (Board #143), Sat, 1:15 PM-4:45 PM

Utility of PET-CT vs CT alone to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer. *First Author: Mostafa Atri, University Health Network, Toronto, ON, Canada*

Background: To assess if PET-CT improves accuracy of CT to detect lymph node (LN) metastasis in advanced cervical cancer. **Methods:** This was a prospective ACRIN/GOG multicenter trial. Patients underwent contrast enhanced PET-CT followed by extra-peritoneal or laparoscopic pelvic and abdominal lymphadenectomy. Seven independent blinded readers reviewed PET-CT and CT only images at least one month apart. Region correlation was performed between pathology and central review results for abdomen (right and left para-aortic, right and left common iliac) and pelvis (right and left external iliac and right and left obturator) regions. Abdomen and pelvic regions were combined, respecting laterality, to calculate accuracy values for these regions at participant level. Reference standard was pathology of resected LNs. Reader average sensitivities/specificities of PET-CT vs CT were compared with generalized linear mixed models. Reader average AUCs were compared with Obuchowski's method. Fleiss' kappa was used to assess reader agreement. **Results:** A total of 153 patients had PET/CT and pathology proof in the abdomen from 169 patients who were enrolled between September 2007 and December 2012. Forty-three of 153 patients had metastasis to abdominal LNs. Forty abdominal positive and 40 randomly selected abdominal negative patients were used for review based on sample size calculation. Reader study cases ranged from 24 to 74 years old (mean;48.9$\pm$10.6). Cancer stages were: IB = 25, II = 44, III = 11; sixty-nine squamous cell carcinomas, 6 adenocarcinoma and 5 others. Mean sensitivities of PET-CT/CT alone in abdomen were 0.50 (CI:0.44,0.56)/0.42 (CI:0.36,0.48) ($p = 0.052$) and in pelvis 0.83 (CI:0.78,0.87)/0.79 (CI:0.73,0.83) ($p = 0.15$). Corresponding specificities were 0.85 (CI:0.80,0.89)/0.89 (CI:0.84,0.92) ($p = 0.21$) and 0.63 (CI:0.54,0.70)/0.62 (CI:0.53,0.69) ($p = 0.83$). Mean AUCs were 0.70 (CI:0.61,0.79)/0.68 (CI:0.59,0.77) ($p = 0.43$) and 0.80 (CI:0.71,0.88)/0.76 (CI:0.67,0.85) ($p = 0.21$). Kappa for PET/CT was 0.65 in pelvis and 0.77 in abdomen. **Conclusions:** Addition of PET to diagnostic CT resulted in statistically borderline increase in sensitivity to detect LN metastasis in abdomen. Clinical trial information: ACRIN6671GOG0233.

5586 Poster Session (Board #144), Sat, 1:15 PM-4:45 PM

Identifying actionable mutations in uterine leiomyosarcoma. *First Author: Tara Soumerai, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Uterine leiomyosarcoma (uLMS) is a rare gynecologic malignancy affecting 2000 women annually in the United States. Little is known about the genomic basis of uLMS and there are no targeted therapies currently approved for this disease. We aimed to describe the genetic alterations present in a cohort of patients with uLMS in order to identify those that are potentially targetable by available or investigational agents. **Methods:** Thirty-one tumor samples were prospectively collected from 2/2014 to 1/2015; all had central pathology review at Memorial Sloan-Kettering. Patients were consented to an IRB-approved biospecimen protocol and samples were analyzed in a CLIA-compliant laboratory with the Memorial Sloan-Kettering Integrated Mutation Profiling for Actionable Cancer Targets (MSK-IMPACT). This NGS, bait-capture platform assesses for mutations, copy number variations, and fusions within 341 genes that are common drivers of oncogenic transformation. Variant calls were made against matched germline DNA. **Results:** All samples were successfully assessed by MSK-IMPACT. The most commonly identified genetic aberrations were deletions/truncating mutations of TP53 in 19 (61%) cases, RB1 in 15 (48%) cases, and ATRX in 10 (32%) cases. MED12 mutations were seen in 3 (10%) cases, 2 of which were hotspot mutations *G44A/C*. Genetic events activating the PI3K signaling pathway were identified in 9 (29%) cases, including PTEN deletions or truncating mutations, PIK3CA activating mutations, or deletions/mutations of PIK3R1 or PIK3CG. One case was hypermutated (epithelioid LMS) with 65 somatic mutations; this tumor was tested for mismatch repair gene deficiency and showed equivocal immunohistochemistry for MSH6. One case had a BRAF *V600E* mutation and this patient was enrolled on a clinical trial of a BRAF inhibitor. In total, three (10%) patients have been enrolled in clinical trials of targeted therapy matched to their mutational status. **Conclusions:** Among 31 patients with uLMS, 10 (32%) were found to have potentially actionable somatic tumor mutations. Genomic characterization of uLMS may offer insights into tumorigenesis and identify potential therapeutic targets in this rare and heterogeneous disease.

5587 Poster Session (Board #145), Sat, 1:15 PM-4:45 PM

Phase II study of concurrent chemoradiotherapy with weekly CDDP/PTX in patients with locally advanced uterine cervical cancer: JACCRO-GY-01 trial. *First Author: Munetaka Takekuma, Department of Gynecologic Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: A multicenter phase II trial was conducted to assess the efficacy and toxicity of concurrent chemoradiotherapy (CCRT) with weekly CDDP/PTX in patients with locally advanced uterine cervical cancer. **Methods:** The patients with FIGO stages III-IVA uterine cervical cancer who had no para-aortic lymphadenopathy ($>$ 10 mm) assessed by CT were enrolled. Patients received definitive radiotherapy (RT) consisting of external beam whole pelvic RT and HDR-ICBT. The cumulative linear quadratic equivalent dose (EQD2) was 62-65 Gy prescribed at point A. Cisplatin 30 mg/m(2) and Paclitaxel 50 mg/m(2) weekly was administered concurrently with RT for 5 courses. **Results:** Of the 70 patients registered, 68 were eligible. The Compete response rate was 76.5% (95%CI, 66.4% to 86.6%). With a median follow-up of 27 months(range: 7.9-33.5), the 2-year progression-free survival rate and pelvic disease progression-free rate were 83.8% (95% CI, 75.1% to 92.6%) and 89.6% (95% CI, 82.3% to 96.9%), respectively. The 2-year overall survival rate was 92.7% (95% CI, 86.4% to 98.9%). The 2-year cumulative late complication rates were 25% for all grades, 13.2% for grade 1, 5.9% for grade 2, 2.9% for grade 3, and 2.9% for grades 4. **Conclusions:** Concurrent chemoradiotherapy with weekly CDDP/PTX for locally advanced cervical cancer demonstrated favorable antitumor activity, and is feasible and safe with respect to the protocol-specified SAEs and AEs. Evaluation of this regimen in phase III trials is warranted. Clinical trial information: UMIN000002937.

5588 Poster Session (Board #146), Sat, 1:15 PM-4:45 PM

Phase II study of the PI3K inhibitor BKM120 monotherapy in patients with advanced or recurrent endometrial carcinoma: ENDOPIK, GINECO Study. *First Author: Pierre-Etienne Heudel, Centre Léon Bérard, Lyon, France*

Background: Patients (pts) with metastatic endometrial carcinoma have a poor prognosis and PIK3CA mutations and amplifications are common in these cancers. This study evaluated the efficacy and safety of a pure PI3K inhibitor BKM120 in advanced or recurrent endometrial carcinoma. **Methods:** This multicenter, single-arm, Phase II, double strata (histological low grade (LG) vs. high grade (HG)) open-label study enrolled pts with histologically confirmed advanced or recurrent endometrial carcinoma, who had received no more than one prior chemotherapy regimen. Primary endpoints were proportion of pts with progression-free survival (PFS) at 2 months (HG strata) or at 3 months (LG strata), objective response rate (ORR), and safety. Initial BKM120 dosage was 100 mg tablets once daily. **Results:** 40 pts were enrolled, of which 16 pts had received BKM120 at 100 mg/d. Due to high rate of grade 3/4 toxicities (cutaneous rash (54%), depressive events (47%), and anxiety (40%)), the IDMC proposed to stop recruitment at 100 mg but to continue the recruitment with a lower dose of 60 mg/d. 24 pts (median age 67 years old) were newly enrolled (14 in the LG strata, 10 in the HG strata). Rate of PFS $>$ 2months in the HG strata was 70% and $>$ 3months was 57% in the LG strata. Median PFS for all pts is 4.5 months (CI 95% 2.8 – 6.1); median PFS for LG strata is 8.3 months compared to 3.8 months for the HG strata. No objective response was reported. At 60 mg/d, 87% of patients experienced grade 3/4 toxicity. The most commonly reported treatment-related grade $\geq$ 3 AEs were cutaneous (13%), increased alanine aminotransferase (13%), HTA (17%), hyperglycemia (17%) and increased aspartate aminotransferase (21%). 5 patients (21%) stopped BKM120 for toxicity. **Conclusions:** BKM120 was associated with an unfavorable safety profile and minimal antitumor activity in monotherapy in advanced or recurrent endometrial carcinoma. The clinical trial was stopped before end of recruitment for toxicity. Clinical trial information: NCT01397877.

5589 Poster Session (Board #147), Sat, 1:15 PM-4:45 PM

Molecular profiling and targeted therapy in advanced endometrial cancer. *First Author: Michelle K. Wilson, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Recurrent endometrial cancer (EC) has a poor prognosis with few effective systemic therapies. We reviewed the outcomes of advanced EC pts in an ongoing institutional molecular profiling program. **Methods**: DNA from blood and tumor (archival FFPE tissue) from EC pts (ECOG $\leq$ 1) was genotyped with a recurrent mutation(s) (mut) assay (Sequenom MassArray, 23 genes, 279 mut) or a NGS assay (Illumina TruSeq Amplicon Cancer Panel, 48 genes) in a CAP/CLIA certified laboratory. Whole exome DNA sequencing (germline and tumor) was performed in pts with exceptional responses. **Results:** From 3/2011 to 8/2014, 77 pts were enrolled: 43% type 1 endometrioid, 57% type 2 non-endometrioid. Median BMI was 29, 11 (14%) had diabetes, 69 (90%) had $\geq$ 1 line of chemotherapy. Somatic mut were seen in 64 pts (83%), 40 pts (52%) had $\geq$ 2 mut. *PIK3CA* (42%), *TP53* (32%), *KRAS* (20%), *PTEN* (16%), and *CTNNB1* (16%) were the most common mut seen. *PIK3CA* mut were seen in 39% of type 1 and 43% of type 2 EC (p = 0.74). *PTEN* mut were more common in type I EC (p = 0.02); *TP53* mut more common in type 2 (p $<$ 0.01). 31 pts (40%) had targeted therapy - 5 genotype-matched. Overall disease control rate (RR + SD at 12 weeks) was 53% with no difference seen with antiangiogenic agents (25 pts; 60%), *PI3K/AKT/MTOR* agents (7; 57%) or matched therapy (5; 40 % p = 0.64)). Time to progression on targeted therapy was not better than prior systemic therapy (HR 1.5 p = 0.09). 15% stopped due to AEs rather than PD. Of 16 pts offered a phase I trial 50% did not start, often due to ECOG decline. Two exceptional responders were identified: (i) clear cell EC (no mut) with PR for 2.6y on ixabepilone; and (ii) recurrent serous EC (3 mut: *PIK3CA*, *KRAS*, *APC*) with CR on sunitinib for 7.2y. Exome sequencing of the 2nd case found $>$ 2400 somatic coding mut (43 point mut/coding Mb) and few copy-number alterations (possible MSI-hypermutated subtype). Preliminary somatic mut of interest include: 5 in genes significantly mutated in EC; 4 in genes encoding known targets of sunitinib; and 13 in kinase domains of other proteins. **Conclusions:** Genotype-matched therapy in EC is complicated by genomic heterogeneity, comorbidities, and tolerance of therapy. Future EC trials should develop algorithms for multiple mutations and account for pt comorbidities in design. Clinical trial information: NCT01505400.

5590 Poster Session (Board #148), Sat, 1:15 PM-4:45 PM

Synergistic effects of cabozantinib to temozolomide and bevacizumab in patients with heavily pretreated relapsed uterine leiomyosarcoma. *First Author: Sayaka Ikeda, Tama-Hokubu Medical Center, Higashimurayama, Japan*

Background: Although uterine leiomyosarcoma (ULMS) has been treated with adriamycin, dacarbazine, ifosfamide, gemcitabine, docetaxel, et al, the effect is not satisfactory. We have reported the effect of temozolomide (T) combined with bevacizumab (B) in heavily pretreated relapsed ULMS (Ref.). In this study, we evaluated the effects of addition of cabozantinib (C) to T and B. **Methods:** From 2009 to 2014, total 20 patients (pts) with heavily pretreated relapsed ULMS were enrolled. Fourteen of 20 pts were treated with T (80mg/body/day, 3 week one week rest) and B (2mg/kg; days 1, 8 and 15, q4 weeks) (TB, n = 14). Since 2013, C (140mg/body/week) was added to TB (TBC, n = 6). Treatment was continued until disease progression and/or unmanageable toxicities. The response and adverse effects were evaluated using the response evaluation criteria in solid tumors (RECIST), and common terminology criteria for adverse events (CTCAE) version 3.0. **Results:** As shown in Table, four (20%) of 20 pts had complete response (CR), four (20%) had partial response (PR) and nine (45%) had stable disease (SD) for at least three months. The response rate (RR; CR+PR) and clinical benefit rate (CBR; CR+PR+SD$>$3mo) were 40% and 85%, respectively. The median progression-free survival was 10.5 (3 - 44) months. Intriguingly, when added C to TB, the effect was significantly reinforced, showing that two (33%) of 6 cases had CR, and the RR and CBR was 50% and 100%, respectively. Toxicity was mild and manageable. **Conclusions:** Addition of C to T and B resulted in synergistic effects with mild toxicity in heavily pretreated relapsed ULMS as shown in Table. These results warrant further prospective and randomized studies.

Response to TB/TBC in heavily pretreated relapsed ULMS.

	n	CR	PR	SD	PD	RR	CBR
TB/TBC	20	4	4	9	3	40%	85%
TB	14	2	3	6	3	35%	78%
TBC	6	2	1	3	0	50%	100%

Reference:Sasaki N, Takano M, Kikuchi Y, et al. Effects of temozolomide and bevacizumab in patients with pretreated relapsed uterine leiomyosarcoma. J Clin Oncol 32:5s, 2014 (suppl; abstr 5603)

5591 Poster Session (Board #149), Sat, 1:15 PM-4:45 PM

Optimal debulking surgery in patients with advanced uterine carcinosarcoma: A multi-institutional retrospective study from the Japanese Gynecologic Oncology Group. *First Author: Kenichi Harano, Department of Medical Oncology, Nippon Medical School Musashikosugi Hospital, Kawasaki Kanagawa, Japan*

Background: The benefit of cytoreductive surgery for uterine carcinosarcoma (CS) is unknown. The objective of this study was to assess the impact of optimal debulking surgery on survival of advanced uterine CS patients. **Methods:** We performed a multi-institutional, retrospective study of women diagnosed with stage III–IV uterine CS between 2007 and 2012. Data were retrospectively obtained from medical records and included demographic, clinicopathologic, treatment, and outcome information. Optimal debulking surgery was defined as surgery resulting in a maximum residual tumor of less than 1 cm. The Kaplan-Meier method was used to calculate disease-free survival (DFS) and overall survival (OS), and the Cox regression model was used to examine the impact of selected factors on survival. **Results:** A total of 225 uterine CS patients (median age, 62 years) were identified including 136 (60%) patients with stage III disease and 89 (40%) patients with stage IV disease. Among them, 185 (82%) patients received the optimal debulking surgery. The median follow-up time was 19 months. The median DFS and OS for the entire cohort were 10.9 months (95% confidence interval [CI], 9.5−12.5) and 29.0 months (95% CI, 21.6−36.2), respectively. The median DFS was 11.5 months (95% CI, 10.6−13.4) for patients who received optimal debulking surgery and 8.1 months (95% CI, 5.1−9.5) for patients who received suboptimal surgery (P $<$ 0.0001). The median OS was 37.9 months (95% CI, 28.3−not reached) for patients who received optimal debulking surgery and 18 months (95% CI, 9.6−21) for patients who received suboptimal surgery (P $<$ 0.0001). In the multivariate analysis, optimal debulking surgery and pelvic lymph node dissection were associated with improved OS. **Conclusions:** Optimal debulking surgery and pelvic lymph node dissection are associated with improved OS in patients with advanced uterine CS.

5592 Poster Session (Board #150), Sat, 1:15 PM-4:45 PM

Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer (EC): An NRG Oncology/Gynecologic Oncology Group study. *First Author: Andrea P. Myers, Novartis Institutes of Biomedical Research, Cambridge, MA*

Background: Rapamycin analogs have reproducible but modest efficacy in EC. Identification of molecular biomarkers that predict benefit from this class of agents could guide their clinical development. **Methods:** Fixed primary tissue and whole blood were collected prospectively from patients (pts) enrolled on GOG 248. DNA was isolated from macro-dissected tumors and blood; next–generation sequence analysis was performed on a panel of cancer related genes. Associations between clinical outcomes [Response rate (RR); 20% overall and progression-free survival (PFS); median 4.9 months] and common mutations (PTEN, PIK3CA, PIK3R1, KRAS, CTNNB1) and other PI3K/mTOR relevant mutations (AKT1, TSC1, TSC2, NF1, FBXW7) were explored. **Results:** Sequencing data was obtained from tumors of 55 of the 73 enrolled pts. Mutation rates were consistent with published reports: mutations in PTEN (45%), PIK3CA (29%), PIK3R1 (24%), K-RAS (16%), CTNNB1 (18%) were common and mutations in AKT1 (4%), TSC1 (2%), TSC2 (2%), NF1 (9%) and FBXW7 (4%) were less common. Increased PFS (HR 0.16; 95% CI 0.01-0.78) and RR (response difference 0.83; 95% CI 0.03-0.99) were noted for AKT1 mutation. An increase in PFS (HR 0.46; 95% CI 0.20-0.97) but not RR (response difference 0.00, 95% CI -0.34-0.34) was identified for CTNNB1 mutation. There were no statistically significant associations between mutations in PIK3CA, PTEN, PIK3R1, or KRAS and PFS or RR. Six patients had PFS > 15 months; of these, two had mutations in CTNNB1, and two had mutations in both CTNNB1 and AKT1. The pt with the longest PFS (on study over 46 cycles) had mutations of NF1, CTNNB1 and PIK3R1 in her tumor. **Conclusions:** Activating mutations in AKT1 are rare in EC, but may predict clinical benefit from temsirolimus. Consistent with a recent report of an association of CTNNB1 mutation with RR in a study of everolimus and letrozole, CTNNB1 mutations were associated with longer PFS on temsirolimus. Studies to elucidate the relationship of the Wnt/β-Catenin and mTOR pathway in EC are needed. Clinical trial information: NCT00729586.

5593 Poster Session (Board #151), Sat, 1:15 PM-4:45 PM

Onapristone (ONA) in progesterone receptor (PR)-expressing tumors: Efficacy and biomarker results of a dose-escalation phase 1 study. *First Author: Paul H. Cottu, Institut Curie, Paris, France*

Background: ONA is a type I PR antagonist, which prevents PR-induced DNA transcription. Immediate release (IR) 100 mg ONA was active in multiple preclinical models and in patients (pts) with breast cancer (BC). We conducted a phase 1 study of extended release (ER) ONA to (i) determine a recommended dose and (ii) explore the role of transcriptionally-activated PR (APR), detected as an aggregated subnuclear distribution pattern, as a predictive immunohistochemical (IHC) biomarker. **Methods:** An open-label, multicenter, randomized, parallel-group, phase 1 study (target n=48; NCT02052128) included female pts ≥18 years with PR^{pos}tumors. APR analysis was performed on archival tumor tissue. Pts were randomized to 5 cohorts of ER ONA tablets 10-50 mg BID, or IR 100 mg QD until progressive disease or intolerability. This abstract reports the APR IHC analysis and clinical benefit (PR/SD≥24 wks). **Results:** Phase 1 is complete (n=52). Tumors (n) were: endometrial carcinoma (EC) 13; breast cancer (BC) 20; ovarian cancer (OC) 13; other 6. Median age was 66 (37-85). No dose limiting toxicity was observed with only transient liver function test elevation, mostly related to liver metastases. PR^{pos}/APR^{pos}tumors (n/n) were: EC 11/6, BC 8/3, OC 5/1, other 2/0 and 8 pts (6 BC) had missing/non evaluable IHC. Median therapy duration was 8 wks (range 2-44), and 8 pts had clinical benefit ≥24 weeks (see Table). **Conclusions:** Clinical benefit was seen in heavily-pretreated pts with EC, OC and BC. Data support ongoing ONA development at 50mg ER BID in APR^{pos} uterine endometrioid cancer with clinical validation of the APR diagnostic. Meanwhile, further development of APR IHC is needed in OC and BC. Clinical trial information: NCT02052128.

Response and stable disease for ≥24 weeks.

Tumor type	PR % retest	APR status	#Prior Rx	Dur-n Prior Rx months	Mets	Dose	Response	% change STL	Dur-n (wks)
Serous OC	0	Neg	3	8	LN	10	PR	-52	40
Serous OC	0	Neg	4	6.5	LN	50	SD	-7	34
Granulosa OC	A: 20 B: 20	Neg	2	5	Liver, peritoneal	40	SD	-24	24
Granulosa OC	A: 80 B: 70	Neg	4	6	Liver, peritoneal spleen	30	SD	+5	32
EC	A: 80 B: 60	Pos	2	3	Lung, bone	30	SD	-13	30+
EC	A: 60 B: 70	Pos	2	6.5	Pelvis, lung	20	SD	+5	32
BC	A: 50 B: 50	Neg	2 +3H	11	Liver, bone	50	SD	-7	32+
BC	A: 60 B: 40	Pos	2 +3H	6.5	Liver, bone	40	SD	-10	24

5594 Poster Session (Board #152), Sat, 1:15 PM-4:45 PM

Does metformin use affect transporter, hormone receptor and mTOR pathway target expression in endometrial cancers of women with Type II diabetes mellitus? *First Author: Dario R. Roque, UNC Durham Division of Gynecologic Oncology, Durham, NC*

Background: Metformin, has been found to decrease proliferation and inhibit downstream targets of the mTOR pathway in a phase 0 trial in endometrial cancer (EC) patients. Given this, we aimed to determine molecular differences between ECs from patients with Type II diabetes (T2DM) taking metformin versus those not on metformin. **Methods:** Patients with T2DM who underwent surgical staging for EC were divided into two cohorts based on whether or not they were on metformin. The use of insulin and other anti-diabetic agents was recorded. Tissue microarrays (triplicate cores) were constructed from formalin-fixed, paraffin-embedded hysterectomy specimens. Expression of the estrogen receptor (ER), progesterone receptor (PR), PTEN, LKB1, phosphorylated (p)-AKT, p-4EBP-1, p-S6, p-insulin growth factor-1 receptor (pIGF1R), p-insulin receptor substrate-1 (P-IRS1), PMAT, MATE1 and MATE2 was measured by immunohistochemistry. **Results:** Of 162 EC patients with T2DM, 102 (63%) were taking metformin and 60 (37%) were not on metformin. There was no significant difference in tumor stage, grade or histology between the two groups. Expression of transporters, hormone receptors, and mTOR pathway targets was similar between the two groups. However, when adjusting for age, BMI, race, tumor grade and stage, there was a trend towards decreased p-AKT expression in metformin users (0.7, 95% CI 0.4-1.1). In addition, BMI > 30 was associated with increased expression of p-S6 (2.8, 95% CI 1.2-6.7) and a trend towards higher p-4EBP-1 expression (2.0, 95% CI 1.0-4.1). **Conclusions:** We did not find a strong relationship between metformin use and transporters, hormone receptors or mTOR pathway targets in EC patients with T2DM. However, metformin use trended towards decreased p-AKT expression, which is consistent with its ability to inhibit the mTOR pathway. Obesity is known to activate the mTOR pathway, and was associated with increased expression of p-S6 and p-4EBP-1 in ECs. Further studies should focus on identifying molecular biomarkers in patients with T2DM that may predict response to metformin as an anti-tumorigenic agent.

5595 Poster Session (Board #153), Sat, 1:15 PM-4:45 PM

Molecular profile comparison of endometrial, renal and ovarian clear cell carcinoma: Is it the same disease at different sites? *First Author: Robert Debernardo, Cleveland Clinic, Cleveland, OH*

Background: Clear cell carcinomas (CCC) are histologically similar, however their clinical course varies widely based on the organ of origin. Clear cell uterine carcinoma (CCUC) accounts for approximately 5% of endometrial carcinomas and exhibit aggressive clinical behavior with poor outcomes. Clear cell ovarian cancers (CCOCs) are a subtype of epithelial ovarian cancers that are chemo-resistant with a poorer prognosis than other subtypes. 70% of renal cell carcinomas are clear cell (CCRCs), and respond to TKIs and mTOR inhibitors. It's unknown if these CCC rely on similar molecular pathways. Tumor profiling was used to identify subsets of CCC that may benefit from different therapies. **Methods:** 139 CCUCs, 409 CCOCs and 94 CCRCs were tested using a commercial multiplatform profiling service (Caris Life Sciences, Phoenix, AZ). Specific tests performed included sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH or FISH). **Results:** CCUCs had more TP53 mutations than CCOCs and CCRCs (40% vs 16% vs 14%). Compared to CCUCs and CCOCs, CCRCs had fewer mutations in the mTOR pathway (PIK3CA – 4% vs 25% vs 40%; PTEN - 1% vs 26% vs 3%) and the MAPK pathway (KRAS – 0% vs 14% vs 11%). VHL mutations were only seen in CCRCs (47% vs 0% vs 0%). ER and PR overexpression was more common in CCUCs than CCOCs and rare in CCRCs (ER – 35% vs 8% vs 0%; PR – 22% vs 13% vs 2%). AR overexpression was more common in CCRCs (26% vs 7% vs 5%). In contrast to CCUC and CCOC, no Her2 alterations measured by IHC, ISH or SEQ were seen in CCRCs.TOP2A, TS and RRM1 were expressed at a higher rate in CCUCs and CCOCs than CCRCs (TOP2A – 81% vs 63% vs 27%; TS - 46% vs 51% vs 16%; RRM1 – 22% vs 19% vs 2%). All CCC types had some immune-positivity for PD-1 (73%,47%, 68%) or PD-L1 (13%, 6%,29%). **Conclusions:** While CCUCs and CCOCs share similarities, the molecular profiling shows significant differences compared with CCRCs. This data suggest blockade of the mTOR and/or MAPK pathways may be important in CCUCs and CCOCs. Further, anti-angiogenic agents are more likely to be of benefit in CCRCs. Immunotherapies warrant further investigation in selected CCC patients. Future studies are needed to correlate these markers with sensitivity to chemotherapy.

5596 Poster Session (Board #154), Sat, 1:15 PM-4:45 PM

Clinical outcomes in advanced cervical cancer (CC) and endometrial cancer (EC) patients (pts) treated in phase I trials of novel molecularly targeted agents (MTAs). *First Author: Angela George, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom*

Background: The prognosis for advanced CC and EC pts is poor, with relapse to approved chemotherapies inevitable. In view of the high rate of putative driver mutations, novel MTAs in phase I trials may benefit such pts. **Methods:** Retrospective study of pt records of CC (01/03-12/14) and EC (11/98-12/14) pts allocated to Phase I trials including efficacy expansion phases of MTAs in the Drug Development Unit at the Royal Marsden. **Results:** 93 CC pts were allocated to 51 trials (186 events); allocation was based on mutational profiles whenever possible. 57 (61%) pts began $\geq$ 1 trials (134 events). 36 (39%) pts did not start; 22 (24%) due to rapid progressive disease (PD), 7 (7.5%) due to other therapy options and 7 (7.5%) due to other reasons. 14 (10%) RECIST responses were seen; chemotherapy/MTA combinations (1 complete response and 7 partial responses [PR]), anti-angiogenics (AA) (2 PR), PI3K/AKT inhibitors (i) (2 PR) and immunotherapy (2 PR) in molecularly selected CC pts. 20 (15%) pts had RECIST stable disease $>$ 4 months (SD $>$ 4m), for a clinical benefit rate (CBR) of 25%. Mean survival was improved in CC pts with CR/PR (662 days) versus (vs) pts who did not start trial (257 days) ($p < 0.001$). Treatments were well tolerated: of 169 toxicities - G1/2: 127 (69%); G3/4: 42 (31%). 78 EC pts were allocated to 39 trials (93 events); 35 (45%) pts began $\geq$ 1 trials (48 events). Of 43 (55%) pts who did not start, 34 (44%) had rapid PD, 5 (6%) had other therapies and 4 (5%) for other reasons. There were 5 (10%) PRs observed in molecularly selected EC pts with mTORC1/2i, IGF-1Ri, AA, RAF/MEKi, and immunotherapy (all n = 1); a further 4 pts (8%) had SD $>$ 4m, for a CBR of 18%. Mean survival was improved in EC pts with PR/SD $>$ 4m (402 days) vs pts with PD (174 days) and pts who did not start trial (178 days) ($p < 0.0001$). Treatments were well tolerated: of 83 toxicities - G1/2: 67 (81%); G3/4: 16 (19%). **Conclusions:** Signs of pt benefit to novel MTAs in phase I trials were observed in molecularly selected pts with advanced EC and CC. A large proportion of pts allocated to such trials did not start treatment due to rapid PD. These data suggest that earlier phase I trial referral and knowledge of mutational profiles may improve pt outcomes.

5597 Poster Session (Board #155), Sat, 1:15 PM-4:45 PM

PET/MRI in cervical cancer: Insights into tumor biology. *First Author: Katja Pinker-Domenig, Medical University Vienna, Vienna, Austria*

Background: To investigate molecular imaging of cervix cancer with combined multiparametric positron emission tomography - magnetic resonance imaging (3T MP PET-MRI) using multiple MRI techniques and PET tracers for an improved understanding of tumor biology and heterogeneity. **Methods:** Ten patients with cervix cancer scheduled for radiation therapy were included in this IRB-approved prospective study. All patients were examined with combined 3T MP PET-MRI. The MRI protocol consisted of a high-resolution T2-weighted, a diffusion-weighted and a T1-weighted sequence with fat-sat before and after the application of contrast agent. All patients underwent ^{18}F-FDG/^{18}F-FMISO PET/CT. Patients were injected with approximately 330 MBq ^{18}F-FDG and ^{18}F-FMISO on different days and scanning was started 45 min after injection of ^{18}F-FDG and 180 min after injection of ^{18}F-FMISO. PET and MR image registrations were performed using Mirada RTx (Mirada Medical, Oxford, UK , ver. 1.4.0.23) software. 3T MP PET-MRI was assessed for tumor size, enhancement (EH)-kinetics, restricted diffusivity and ^{18}F-FDG/^{18}F-FMISO-avidity. **Results:** Molecular imaging with 3T MP PET-MRI was successfully performed in all ten patients. Tumor volumes ranged from 6.2-440.0cc (median 125.5cc). All tumors demonstrated restricted diffusivity (mean 0.75 x 10^{-3} mm^2/sec). All tumors showed a strong initial EH and followed by either a wash-out (n = 6) or a plateau (n = 4). All tumors were highly ^{18}F-FDG-avid (SUV_{max} mean17.3). None of the tumors were highly ^{18}F-FMISO-avid (SUV_{max} mean 3.3). In eight patients, ^{18}F-FMISO PET identified ^{18}F-FMISO-avid spots within the ^{18}F-FDG-avid lesion, indicative of areas of tumor hypoxia. There was a weak correlation for tumor volume and ^{18}F-FDG and ^{18}F-FMISO SUV_{max}, indicating that ^{18}F-FMISO-avidity is independent of tumor volume. **Conclusions:** Molecular imaging with 3T MP PET-MRI in patients with cervix cancer is feasible and provides unique complementary information on tumor biology and heterogeneity. 3T MP PET-MRI can identify areas of tumor hypoxia, which are more resistant to radiation therapy and necessitate dose-escalation, and thus might improve therapy planning and assessment of treatment response.

5598 Poster Session (Board #156), Sat, 1:15 PM-4:45 PM

Feasibility of a physical activity intervention for ethnically diverse endometrial cancer survivors. *First Author: Amerigo Rossi, Long Island University - Brooklyn, Brooklyn, NY*

Background: To determine the feasibility of a 12-week physical activity (PA) intervention guided by social cognitive theory for ethnically diverse endometrial cancer (EC) survivors and to evaluate whether such an intervention might improve PA behavior, physical function, waist circumference, and quality of life. **Methods:** Out of 119 potential participants contacted via telephone, 54 did not respond, 29 declined, and 6 expressed interest but did not complete baseline testing. 30 obese EC survivors (40% non-Hispanic black, 33% Hispanic, 17% non-Hispanic white) were placed into a PA intervention (INT, n = 15) or wait-list control (CON, n = 15). Group classes consisted of 30 min of behavioral counseling and a 60 min exercise program. CON was assigned to usual care. Participants attended classes 1-2x/week and were provided with a 90 min/week at-home exercise program. The intervention data from each group were pooled and the change scores were compared to CON using independent samples t-tests. Data are presented as mean $\pm$ sd. Statistical significance was $p \leq 0.05$. **Results:** Mean age was 64 $\pm$ 8 years and Body Mass Index was 36.5 $\pm$ 6.9 kg$\cdot$m^{-2}. Three control participants did not attend follow-up. For the INT groups (n = 27), 16 attended 75-100% of the weeks, 4 attended 50-67%, 4 never attended, and 3 dropped out due to unrelated illness/injury. Additionally, 13 participants regularly attended twice per week with 85% attendance. Participants reported walking 117 $\pm$ 77 minutes per week at home. There were no reported differences in PA (Yale Physical Activity Survey). However, waist circumference (-5.1 cm vs: 2.6 cm, $p < 0.001$), 6-min walk test (22m vs. 0.3m, $p = 0.007$) and quality of life (FACT-En: 7.9 vs. -0.5, $p = 0.048$) all improved significantly following the intervention compared to the control. **Conclusions:** About 25% of potential participants entered into the study, demonstrating the challenges of working with this population. However, once enrolled, the drop out rate was modest and adherence was high, demonstrating the acceptability and feasibility of this PA intervention in a diverse urban population of EC survivors. Furthermore, the results show promising effects that will need to be confirmed in a larger randomized control trial.

5599 Poster Session (Board #157), Sat, 1:15 PM-4:45 PM

The use of adjuvant treatment in stage I endometrioid endometrial cancer in the National Cancer Database (NCDB). *First Author: Angela Jain, Fox Chase Cancer Ctr, Havertown, PA*

Background: Women with Stage I endometrioid endometrial carcinomas (EEC) tumors have excellant long term survival. Women may be offered adjuvant radiation if high-risk features are present in the resected tumor. Whole pelvic radiation (EBRT) or vaginal brachytherapy (VB) reduce local recurrence, but do not improve survival. GOG249 looked at the use of chemotherapy with VB in high-grade tumors (HGT). This is a retrospective study using the National Cancer Database to understand national trends in using surgery, radiation and chemotherapy in Stage I EEC. **Methods:** We identified women with EEC diagnosed between 1998 and 2012 and treated with surgery and/or chemotherapy and/or radiation using the National Cancer Database, with known grade status. Using Chi-squared tests and multivariate logistic regression, we analyzed pathologic stage of EC by age, grade, histology, facility type, race, payor status, income, location, Charlson score, year of diagnosis and facility location. Due to data availability, survival analysis was restricted to patients diagnosed between 2003 and 2007. We used Kaplan-Meier curves and proportional hazards regression to assess overall survival in patients treated with adjuvant EBRT vs VB. **Results:** Among 241,350 patients identified, patients with HGT had decreased use of EBRT over time from 17% to 5%; the use of VB increased from 7% to 24% ($p = 0.0001$). There were no significant changes for the use of radiation in patients with low-grade tumors. Patients with age $>$ 70 were more likely to receive radiation than patients $<$ 70, but less likely to receive chemotherapy ($p = 0.0001$). The use of chemotherapy in all patients increased from 1% to 14% over time. Multivariate analysis demonstrated that patients with HGT had 84% 5 year survival with VB vs 78% for patients receiving EBRT (HR 0.85 vs 1.16, $p = 0.0001$). In patients with low grade tumors there was no advantage for the use of VB and ERBT decreased survival. The use of chemotherapy did not improve survival. **Conclusions:** The use of VB and chemotherapy has been increasing over time for patients with HGT. However, the use of chemotherapy may not improve survival in this highly curable population, while the use of EBRT is demonstrated to decrease survival.

5600 Poster Session (Board #158), Sat, 1:15 PM-4:45 PM

A limited access phase I trial of paclitaxel, cisplatin and ABT-888 in the treatment of advanced, persistent, or recurrent carcinoma of the cervix: An NRG/GOG study. *First Author: Premal H. Thaker, Washington Univ School of Medicine, St. Louis, MO*

Background: The poly (ADP-ribose) polymerase (PARP) family of proteins is a family of nuclear enzymes required for the repair of single-stranded DNA damage. Preclinical studies demonstrate that PARP inhibition (PARPi) not only augments the apoptotic response in cervical cancer cell lines, but also sensitizes cells to the effects of alkylating agents like cisplatin. Given the use of cisplatin and paclitaxel as primary treatment for advanced, recurrent or metastatic cervical cancer before the findings of the benefit of adding bevacizumab in GOG 240, we aimed to evaluate whether PARPi can enhance the chemotherapy effectiveness in the treatment of cervical cancer. **Methods:** Patient eligibility criteria: Females age ≥ 18 years with persistent or recurrent squamous or adenocarcinoma of the cervix with documented disease progression (disease not amenable to curative therapy). Patients were not required to have measurable disease; have had concurrent chemotherapy and radiation for management of their disease; and have adequate organ function. The trial is a standard 3 + 3 phase I dose escalation with patients receiving paclitaxel 175mg/m2 on day 1, cisplatin 50mg/m2 on day 2, and ABT-888 50mg po bid days 1-7 at dose level 1 and escalating by 50mg every dose level until dose level 8 at 400mg po bid days 1-7. **Results:** Thirty-seven patients were enrolled from 6/1/11-1/8/14, but only 34 are evaluable. Dose limiting toxicities (DLTs) were assessed during cycle on 1 of each dose level of ABT-888 and the three DLTs were as follows: grade 4 dyspnea which was possibly related to the ABT-888 in dose level 2, grade 3 neutropenia > 3 weeks in dose level 4, and febrile neutropenia in dose level 8. Cycles were repeated every 21 days until disease progression. At all dose levels the response rate [complete and partial] (RR) was 34% (95%CI: 20-53%); at the maximum dose level the RR was 60% (95%CI: 23-88%). Translational studies evaluating defects in the Fanconi Anemia pathway are ongoing. **Conclusions:** PARPi plus chemotherapy appears to have significant clinical benefit in cervical cancer therapy and warrants further investigation with bevacizumab in a clinical trial. Clinical trial information: NCT#01281852.

5601 Poster Session (Board #159), Sat, 1:15 PM-4:45 PM

Evaluation of biomarker alterations in small cell cervical cancer identifies therapeutic options. *First Author: Jennifer K. Burzawa, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Small cell cervical cancer (SCCC) is an extremely rare and aggressive form of cervical cancer, accounting for only 1% of all cervical cancer cases, or ~150 cases/yr. 70% of patients will recur, even when diagnosed with early stage disease and there are few therapeutic options in this setting. We evaluated tumor samples obtained from a large repository to determine prevalent targetable molecular aberrations in these rare tumors. **Methods:** Seventy-eight SCCC samples were profiled, 53 of those on a commercial multiplatform, including a combination of gene sequencing (Sanger or NGS, up to 47 genes), amplification (CISH or FISH), and protein expression (IHC). Twenty-five samples were analyzed at a cancer center using a 50 gene NGS platform (CMS50). The profiles were compared to ~800 HPV+ cervical cancers (CC), neuroendocrine tumors (NET, all sites), and small cell lung cancers profiled at the same laboratory. **Results:** TOP2A (85%) and TOPO1 (55%) had high overexpression, while ERCC1 had low expression (11%) in SCCC samples. SCCC tumors had higher protein expression of KIT (26%) than HPV+ non-SCCC (7%, $p < 0.05$), but similar expression of KIT to small cell lung cancers (37%). HER2 amplification was identified in 4.5% of SCCC and 8% of HPV+ CC. EGFR amplification was not seen in SCCC but was identified in 10% of HPV+ CC. Gene sequencing identified higher mutation rates for TP53 (27%) and KRAS (18%) in SCCC compared to HPV+ CC (12% and 7%, respectively) but lower rates of PIK3CA (17% vs. 28%). Comparatively, small cell lung cancers had mutations in TP53 in 34% of cases and in KRAS in 5% of cases. NGS evaluation of 51 cases also identified 3 GNAS and RB1mutations (6%), 2 CTNNB1 and SMAD4 mutations (4%), and single gene mutations in BRCA1, PTEN, MET, SMARCB1, APC, ATM, HNF1A, and FBXW7 (2% each). **Conclusions:** Multiplatform tumor profiling identified high expression of TOP2A and TOPO1 in SCCC, which may explain the sensitivity to etoposide and topotecan, while low levels of ERCC1 raise concern for cisplatinum resistance. Potential druggable mutations include AKT1, KRAS, PIK3CA, and TP53. We have identified one patient with a KRAS mutation treated with a MEK inhibitor who had a complete response and remains in remission at 12 months.

5602 Poster Session (Board #160), Sat, 1:15 PM-4:45 PM

Comprehensive genomic profiling (CGP) of cervical squamous cell carcinoma (cSCC) to identifiy targeted therapy options. *First Author: Julia Andrea Elvin, Foundation Medicine, Inc., Cambridge, MA*

Background: High risk HPV initiates neoplasia in cSCC and progression requires additional genomic alterations (GA). Treatment of localized cSCC is effective but the response to systemic therapy for metastatic disease is inadequate. CGP of 99 advanced stage cSCC was undertaken to identify GA associated with targeted therapeutic options relevant to the systemic treatment of cSCC. **Methods:** DNA was extracted from 99 FFPE cSCC clinical specimens. Hybridization captured libraries of 236 (FoundationOne, n = 66) or 305 (FoundationOne, n = 33) genes, plus select introns frequently rearranged in cancer were sequenced to high (> 450x), uniform coverage. HPV16 and HPV 18 viral sequences were detected, but other hrHPVs were not assayed. All classes of genomic alterations (base subs, small in/dels, rearrangements, and copy number alterations) were evaluated and reported. CRGA were defined as GA associated with on-label targeted therapies and targeted therapies in mechanism-driven clinical trials. **Results:** 99 samples (54% primary,45% metastasis) from women (avg 47.7y) with predominantly advanced stage cSCC were profiled. 368 total GA were identified (3.7 GA per tumor) involving 80 different genes, of which 257 were CRGA (2.57 per tumor). 91% of cSCC cases featured > 1 CRGA, including 67 (67%) cases with CRGA in the *PI3K/Akt/mTOR* pathway. The most common CRGAs observed were: *PIK3CA* (41%), *MLL2* (18%), *PTEN* (16%), *STK11* (14%), *FBXW7 (11%), FGFR3 (4.6%), ERBB2 (4.6%), KRAS (4.6%).* To date, we are aware of one patient with abdominal and thoracic nodal metastases and a CGP-identified inactivating mutation in *FBXW7* who showed a 6-months partial response to everolimus treatment. *FGFR3-TACC3* gene fusions were rarely identified (3%); one late lung recurrence case showed stable disease on a multikinase inhibitor targeting FGFR. **Conclusions:** Most advanced stage cSCC demonstrate CRGAs, most commonly in the *PI3K/Akt/mTOR* pathway, and clinical response to mTOR inhibition can be achieved. Other driver events, including *FGFR3* fusions, present alternatives for targeted therapy. Patients who have exhausted other SOC for metastatic cSCC have achieved clinical benefit from CGP-directed therapeutic decision-making.

5603 Poster Session (Board #161), Sat, 1:15 PM-4:45 PM

Weekly administration of bevacizumab, eribulin, and oxalilplatin in patients with platinum-resistant ovarian carcinomas: A phase II study with biomarker analysis. *First Author: Yuji Ikeda, The University of Tokyo, Tokyo, Japan*

Background: Eribulin, inhibiting a protein component of tubulin, is a candidate for paclitaxel-refractory breast cancers, and Bevacizumab (B) is known to enhance efficacy of anti-cancer agents in ovarian cancers. A phase II study to evaluate weekly administration of B with eribulin and oxaliplatin (EriOX) in patients with platinum-resistant and refractory ovarian carcinomas (PR-ROC) was performed. **Methods:** Eligible patients were as follows: (a) ECOG PS = 0~2 (b) histologically confirmed epithelial ovarian cancer (c) diagnosed as platinum-resistant ovarian cancer (d) written informed consent. Patients were treated with weekly-B-EriOX consisting of B (2mg/kg), eribulin (1mg/m2) and oxaliplatin (30mg/m2), three weeks on and on week off, q4weeks. Response was evaluated with RECIST 1.1, and adverse effects were assessed by CTCAE v4.0. Biomarker analyses including serum VEGF and BNP were also conducted. **Results:** A total of 30 patients were enrolled in the present study. There were no cases that discontinued the therapy due to toxicities. Median age of the patient was 60 years (range: 35-71). Median number of previous regimen was 5 (range: 2-9). Two patients (7%) had a complete response (CR), 5 patients (17%) had a partial remission (PR) and 15 patients (50%) had a stable disease (SD). The response rate and clinical benefit rate (CR+PR+SD) were 23% and 73%, respectively. Median progression-free survival was 3 months (range: 1-10+). Hematological adverse effects (AE) with grade 3/4 were observed in 4 patients (13%). Hypo albuminemia and edema with grade 3 were in 1 patient (3%), respectively. However, all AE were manageable and tolerable. There was no significant difference of serum level of VEGF according to the response evaluation. **Conclusions:** Weekly B and EriOX administration had significant activity with mild AE in patients with PR-ROC. These results warrant further prospective study with biomarker analyses.

5604 Poster Session (Board #162), Sat, 1:15 PM-4:45 PM

Impact of older age on chemotherapy toxicity and quality of life in women with advanced or recurrent cervical cancer: A NRG Oncology-GOG Ancillary Study. *First Author: Emily Meichun Ko, University of Pennsylvania, Philadelphia, PA*

Background: To evaluate chemotoxicity and quality of life (QOL) in older women undergoing treatment for recurrent and advanced cervical cancer within Gynecologic Oncology Group (GOG) phase III chemotherapy trials. **Methods:** 5 trials (GOG 110, 149, 169, 179, 204) were used to characterize chemotoxicity profiles by age. 'Older' was defined as age ≥ 65. Toxicity was based on GOG or CTC scales. Concordant chemotherapy arms between trials were pooled: Cisplatin (C), cisplatin/ifosfamide (CI); cisplatin/topotecan (CT); cisplatin/paclitaxel (CP). Categorical variables were compared using the Pearson chi-square test. The Cox PH model was used to evaluate prognostic factors (at baseline or before a landmark) and to estimate the adjusted effects on survival. Poisson models of toxicity as a function of age were examined. Associations between age and QOL using Fact-G and Fact-Cx (GOG 169,179, 204) were assessed with linear mixed models. **Results:** 1201 women were evaluated (C: 407; CI: 288; CT: 255; CP: 251). Median age was 65 (IQR 58–71) and 107 were age ≥ 65. Being older was associated with improved PFS for C (HR 0.99, 95%CI .98-1.00) and CT (HR 0.98, 95%CI 0.96-0.99); and improved OS in CP (HR0.98, 95CI 0.97-1.00) and CT (HR 0.98, 95%CI0.97-0.99) in adjusted models. The most frequent grade ≥ 3 toxicities in those age ≥ 65 were leukopenia (85% for CP; 80% for CT; 92% for CI), anemia (40% for CT) and thrombocytopenia (40% in CT). Neuropathy and neurologic toxicity did not differ by age for any regimen. Grade ≥ 3 toxicities that differed significantly by age and were most frequent in older women included leukopenia (85%, p = 0.058) for CP; nausea-vomiting (30%, p = 0.03) and metabolic (25%, p = 0.04) for CT. However, age was not associated with overall toxicity for any regimen in the adjusted models. Toxicity did not confound age-dependent outcomes on PFS or OS. QOL did not differ by age group for any regimen. **Conclusions:** Older age was not associated with severe toxicity or poorer quality of life in women who underwent chemotherapy for advanced or recurrent cervical cancer in phase III national consortia trials. Older patients should be encouraged to participate in cervical cancer trials.

TPS5605 Poster Session (Board #163a), Sat, 1:15 PM-4:45 PM

EUTROC PiSARRO: A phase Ib study combining APR-246 with standard chemotherapy in platinum sensitive relapsed high grade serous ovarian carcinoma (HGSOC). *First Author: Charlie Gourley, University of Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom*

Background: p53 mutations are associated with increased chemoresistance. APR-246 is a small molecule that restores mutant p53 to wild type conformation and function (Lambert et al., Cancer Cell. 2009; 15(5):376-88). APR-246 also increases reactive oxygen species levels and ER stress; acts synergistically with DNA damaging drugs *in vitro*; resensitizes ovarian cancer cells to cisplatin and doxorubicin *in vitro* and reduces glutathione levels thereby decreasing cellular drug efflux. APR-246 showed no end-organ toxicity in the non-clinical toxicity studies but C_{max} related reversible CNS effects were identified. In a previous single agent dose finding study recommended phase II dose and safety profile was determined and signs of clinical activity and p53-dependent biological effects were observed in several patients (Lehmann et al., J Clin Oncol. 2012; 30(29):3633-9). As in animals dose limiting toxicity (DLT) was mainly C_{max} related reversible CNS effects. PK was linear and displayed no accumulation. APR-246 was concluded to have a safety and PK profile suitable for further development in combination with chemotherapeutic drugs. The rationale for this study was that p53 mutation occurs in > 97% of HGSOC, thus identifying an appropriate study population for targeted therapy. **Methods:** Patients with relapsed platinum sensitive HGSOC and positive p53 immunostaining were treated with APR-246 in combination with carboplatin AUC 5 and pegylated liposomal doxorubicin 30 mg/m^{2}every 4 weeks for 6 cycles. APR-246 was dosed as a 6h IV infusion on 4 consecutive days; on day 4, chemotherapy was given concomitantly with APR-246. A 3+3 dose escalation design with 3 dose levels (35, 50 and 67.5 mg/kg) was used. Endpoints include determination of the appropriate combination APR-246 dose, safety, PK, progression free survival, response rate, overall survival and multiple translational readouts (transcriptomic and proteomic). Matched pre-treatment and on-treatment radiologically guided biopsies are mandatory. The first two dose cohorts have been recruited with one DLT (GI perforation) in cohort 2. Recruitment to cohort 3 commenced in December 2014. Clinical trial information: NCT02098343.

TPS5606 Poster Session (Board #163b), Sat, 1:15 PM-4:45 PM

A phase III study of trabectedin (T) plus pegylated liposomal doxorubicin (PLD) versus PLD for treatment of advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer. *First Author: Robert L. Coleman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ovarian cancer (OVC) is the eighth most common cancer among women globally, with approximately 60%–70% of cases being diagnosed at an advanced stage (III or IV). Five-year survival rate for advanced stages is under 40%. In a previous pivotal trial, patients with OVC who relapsed after first-line platinum-based chemotherapy (PCT) demonstrated superior progression free survival when treated with the T+PLD combination vs. PLD monotherapy (7.3 vs. 5.8 months; HR = 0.79; p = 0.019). In a subgroup analysis by platinum free interval, T+PLD showed an improved overall survival (OS) for patients with Platinum Free Interval of 6–12 months (HR = 0.64) (J Clin Oncol. 2010 28:3107-14.). Given this demonstrated efficacy, we are conducting a global phase III registration trial to investigate the OS of T+PLD vs. PLD in patients with platinum sensitive epithelial OVC, peritoneal or fallopian tube cancer, in the third-line setting. **Methods:** In this open-label, active-controlled trial, approximately 670 women who have received 2 prior lines of PCT will be enrolled at approximately 135 sites in 9 countries. Key inclusion criteria: all women must be platinum sensitive (defined as no evidence of disease progression for ≥ 6 months after the last dose of first-line PCT), and demonstrated a partial or complete response to second line PCT. Key exclusion criteria: OVC with mucinous histology and > 2 prior lines of chemotherapy. Patients will be stratified by Platinum Free Interval, ECOG performance status, BRCA 1 or 2 mutation status, and prior PLD therapy. Stratified patients will be randomized (1:1) to receive PLD (30 mg/m2, 1.5 h, i.v.) followed by T (1.1 mg/m2, 3 h, i.v.) every 3 weeks or PLD alone (50 mg/m2, 1.5 h, i.v.) every 4 weeks. Primary endpoint is OS. Secondary endpoints include progression free survival, overall response rate (ORR), safety, and pharmacokinetics of T. Planned study duration is 64 months. An interim OS analysis is planned after 308 events. Final OS analysis will be done after ≥ 514 events have been observed. As of 19 January 2015, 145 patients have been randomized (ClinicalTrials.gov #: NCT01846611). Clinical trial information: NCT01846611.

TPS5607 Poster Session (Board #164a), Sat, 1:15 PM-4:45 PM

ENGOT-OV24-NSGO/AVANOVA: Niraparib versus bevacizumab-niraparib combination versus bevacizumab and niraparib as sequential therapy in women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer. *First Author: Mansoor Raza Mirza, NSGO, Copenhagen University Hospital, Copenhagen, Denmark*

Background: Multiple Phase 1 and 2 clinical studies of PARP inhibitors used as monotherapy to treat patients with recurrent ovarian cancer (ROC) suggest that the agents are active in this population and there is level one evidence that bevacizumab is beneficial In the same population. A phase two randomized study demonstrated that the addition of a PARP inhibitor to an anti-angiogenic drug cediranib improves Progression-free survival (PFS). Our aim is to compare tolerability and efficacy of niraparib alone versus niraparib-bevacizumab combination versus sequential bevacizumab and niraparib. **Methods:** The ENGOT-OV24-NSGO/AVANOVA study comprises of two parts. Part 1 is a classic phase 1 trial of niraparib and bevacizumab combination. Part 2 is a three-arm, open-label, phase II, 1:1:1 randomized study of niraparib and/or Niraparib-bevacizumab combination against bevacizumab followed by niraparib in women with platinum-sensitive ROC. BRCAmut and or high-grade serous/endometrioid carcinoma patients with platinum-sensitive ROC are eligible. Patients must have disease that is measurable according to RECIST or assessable according to the GCIG CA-125 criteria. Primary objective of phase 1 part is to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy and determine the Recommended Phase 2 Dose (RP2D) of bevacizumab-niraparib. Primary objective of phase 2 part is to obtain preliminary evidence of efficacy of bevacizumab- niraparib combination or sequential therapy or niraparib single agent treatment. Primary end-point is PFS. Secondary end-points include PFS in each group according to trial stratification factors; PFS comparison of sequential versus concomitant bevacizumab and Niraparib; Objective response rate; Disease control rate (DCR); Patient Reported Outcomes (PROs); Time to subsequent chemotherapy and survival. Study status: The study is activated and sites are invited to participate. ClinicalTrials.gov Identifier: NCT02354131 Clinical trial information: NCT02354131.

TPS5608 Poster Session (Board #164b), Sat, 1:15 PM-4:45 PM

Multicenter randomized Phase II study of AZD1775 plus chemotherapy versus chemotherapy alone in patients with platinum-resistant TP53-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: WEE1 is DNA damage cell-cycle checkpoint protein that inactivates cyclin-dependent kinase 1 (CDC2) and is overexpressed in a variety of malignancies. Pts with deficient p53 expression rely on the WEE1 kinase to arrest cell-cycle progression at the G2 checkpoint for DNA repair. AZD1775, a highly selective, adenosine-triphosphate (ATP) competitive, small-molecule inhibitor of the WEE1 kinase, is being developed for the treatment of advanced solid tumors with TP53-mutated malignancies. Inhibition of WEE1 allows CDC2 phosphorylation and subsequent cell-cycle progression despite DNA damage. This G2 checkpoint abrogation thus sensitizes cells to cytotoxic agents. Preliminary efficacy data have been promising when AZD1775 is used in combination with chemotherapy. In this randomized, phase II trial in pts with platinum-resistant, TP53-mutated cancers, AZD1775 will be added to a standard chemotherapy regimens (paclitaxel, gemcitabine, or carboplatin), with the goal of improving efficacy when compared to chemotherapy alone. The primary endpoints are response rate (Part 1), and progression-free survival (Part 2). **Methods:** In Part 1, up to 69 pts will be randomized to receive AZD1775 plus paclitaxel, gemcitabine or carboplatin (Arm A: AZD1775 175 mg PO BID Days 1, 2, 8,9,15, and 16 plus gemcitabine 1000 mg/m^2 IV Days 1, 8, and 15; Arm B: AZD1775, 5 doses of 225 mg PO BID Days 1-3, 8-10, and 15-17 plus paclitaxel 80 mg/m2 IV Days 1, 8, and 15; Arm C: AZD1775, 5 doses of 225 mg PO BID Days 1-3 plus carboplatin AUC 5 IV Day 1). In Part 2, up to 108 pts will be randomized 1:1 to the most efficacious AZD1775/chemotherapy combination identified in Part 1, or chemotherapy alone. Pts will be restaged every 2 cycles and continue treatment until disease progression or unacceptable toxicity. Key eligibility includes: platinum-resistant TP53-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, measurable disease per RECIST v 1.1, ECOG PS 0 or 1, QTc $<$ 470 msec, and no known CNS disease. Tumor samples will be collected for evaluation of specific biomarkers. Clinical trial information: NCT02272790.

TPS5609 Poster Session (Board #165a), Sat, 1:15 PM-4:45 PM

A phase 2, open-label study of niraparib in women with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer after ≥3 previous chemotherapy regimens. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Niraparib is a potent, orally active PARP-1 and -2 inhibitor in development for the treatment of tumors that exhibit defects in the PARP-mediated homologous recombination DNA repair pathway. In preclinical experiments, niraparib has shown activity against germ line BRCA mutated (gBRCA^{mut}) ovarian cancer cells (OvCa) and other High-Grade Serous OvCa (HGSC) cells. At the recommended dose of 300 mg, 50% of patients with BRCA-mutant ovarian cancer who had received more than 3 lines of prior chemotherapy achieved RECIST responses in the phase 1 study. **Methods**: This is a multicenter (approximately 35 sites), open-label, Phase 2 study of niraparib in up to 225 women with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Eligible pts must have received $\geq$ 3 previous chemotherapy regimens (prior exposure to PARP inhibitors and/or prior anti-angiogenesis inhibitors are not excluded). The primary objective is to evaluate the antitumor activity of niraparib. Secondary objectives are 1) durability of antitumor activity; 2) antitumor activity in Homologous Recombination Deficiency (HRD)-positive pts and in pts with gBRCA^{mut}; 3) disease control rate; 4) progression-free survival; and 5) safety and tolerability. Exploratory objectives are 1) QTc interval in a subset of niraparib-treated OvCa pts; 2) population pharmacokinetics for niraparib and its major metabolite; and 3) potential biomarkers of PARP inhibitor sensitivity and tolerability. Niraparib 300 mg is administered orally once daily on a 28 day cycle until discontinuation.. The overall analysis will use a 1-proportion statistical test that the ORR is $\geq$ 30%. The ORR will be evaluated in the HRD-positive and gBRCA^{mut} subsets. The sample size at 1-sided alpha of 0.025 and $>$ 80% power for the pooled subsets would be N = 200 using a normal approximation with continuity correction. The HRD-positive or gBRCA^{mut} subset represents 100 patients of the total sample population. Clinical trial information: NCT02354586.

TPS5610 Poster Session (Board #165b), Sat, 1:15 PM-4:45 PM

The MILO (MEK inhibitor in low-grade serous ovarian cancer)/ENGOT-ov11 study: A multinational, randomized, open-label phase 3 study of binimetinib (MEK162) versus physician's choice chemotherapy in patients with recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. *First Author: Bradley J. Monk, University of Arizona Cancer Center and Creighton University School of Medicine at Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ*

Background: Low-grade serous (LGS) carcinomas of the ovary, fallopian tube and primary peritoneum are a unique subset of serous carcinomas for which current therapies (chemotherapy, hormonal) have demonstrated limited efficacy. KRAS or BRAF mutations, which activate the RAS/RAF/MEK/ERK signaling pathway, are present in many LGS carcinomas. Binimetinib is a potent inhibitor of MEK1/2, a key component of the RAS/RAF/MEK/ERK pathway, and has demonstrated activity in other disease settings where dysregulation of this pathway is present. **Methods:** This is a 2-arm, open-label, 2:1 randomized Phase 3 study of binimetinib vs physician's choice chemotherapy (pegylated liposomal doxorubicin, paclitaxel or topotecan) in patients with LGS carcinomas. Eligible patients must have LGS carcinoma that is recurrent or persistent following at least 1 prior platinum-based chemotherapy and no more than 3 prior lines of chemotherapy, and must have RECIST v1.1-defined measurable disease confirmed by blinded independent central review (BICR). Prior to randomization, confirmation of LGS diagnosis is required. Patients are eligible regardless of RAS/RAF mutational status; however, tumor tissue will be retrospectively analyzed for mutations in RAS/RAF and other genes. Prior treatment with a MEK inhibitor or BRAF inhibitor is prohibited. Randomization is stratified by last platinum-free interval and number of prior systemic therapy regimens. The primary endpoint is progression-free survival as determined by the BICR; secondary endpoints include overall survival, overall response, duration of response, disease control rate, safety, quality of life and pharmacokinetics of binimetinib. Binimetinib is administered 45 mg BID orally. Patients receive therapy until disease progression or unacceptable toxicity. Crossover is permitted from physician's choice chemotherapy to binimetinib upon BICR-confirmed progression. This study will enroll 300 patients worldwide (NCT01849874). Clinical trial information: NCT01849874.

TPS5611 Poster Session (Board #166a), Sat, 1:15 PM-4:45 PM

A phase I/II study of Enadenotucirev, an oncolytic Ad11/Ad3 chimeric group B adenovirus, administered intraperitoneally (IP): Dose finding and proof of concept in platinum-resistant epithelial ovarian cancer. *First Author: Iain A. McNeish, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland*

Background: Enadenotucirev (EnAd) is a tumor selective Ad11/Ad3 group B adenovirus that has demonstrated preclinical activity in a model of platinum-resistant ovarian cancer. Synergy has also been reported between oncolytic adenoviruses and microtubule manipulating drugs (Ingemarsdotter, Oncogene, 2010, 29(45)). EnAd is suited to IP delivery as it avoids its elimination by the liver and retains it in the peritoneal cavity, where ovarian cancer metastases are principally located. This study aims to establish the maximum-tolerated dose (MTD) of EnAd delivered IP, both as a monotherapy (Phase [Ph.] Ia) and combined with paclitaxel (Ph. Ib) and provide early proof of concept data (Ph. II). **Methods:** Ph. I follows a standard 3+3 dose escalation scheme and Ph. II is a single arm. Patients (pts) with platinum-resistant ovarian cancer receive EnAd as 3 separate weekly IP doses followed by 1 week rest (one cycle) in Ph.Ia and EnAd IP on d1, 8 and 15 ($\pm$1 d) and weekly paclitaxel (80 mg/m2) IV on d9, 16 and 23 ($\pm$1 d) of each 28-day cycle. The starting dose for EnAd in Ph. Ia is 1 x 10^{12} vp. The MTD determined in Ph. Ib is to be tested in 20-23 pts in Phase II. Primary endpoints include determination of MTD for Ph.I (alone and in combination) and progression-free survival (PFS) using RECIST v1.1 for Ph. II. Secondary endpoints include safety and tolerability, blood kinetics, IP distribution, clearance and replication, shedding, blood and IP immune response to EnAd, blood cytokine response as well as response rate, duration of response, clinical benefit rate and PFS using immune-related response criteria (irRC) and GCIG CA-125 criteria. Exploratory endpoints include assessment of IP cytological changes (inflammatory cell infiltrates) in response to EnAd, and EnAd replication in cancer tissues in selected patients. To date, 3 pts have been treated in Ph. Ia and recruitment is ongoing. Clinical trial information: EUDRACT 2013-001276-38. Clinical trial information: NCT02028117.

TPS5612 Poster Session (Board #166b), Sat, 1:15 PM-4:45 PM

Open label phase II clinical trial of orteronel (TAK-700) in metastatic or advanced non-resectable granulosa cell ovarian tumors: The Greko II study—GETHI 2013-01. *First Author: Jf. Rodriguez-Moreno, Centro Integral Oncológico Clara Campal, Madrid, Spain*

Background: Granulosa-cell tumors (GCT) of the ovary are a rare entity characterized by presenting a punctual mutation at the FOXL2 gene 402C→G (C134W) in most cases. Such mutation is responsible for a disregulation and overstimulation of the steroidogenic pathway, that ultimately leads to hormone overproduction. A prior trial by our group (GREKO I trial-GETHI 2011-03; NCT01584297) showed promising activity of ketoconazole, a CYP17 inhibitor used to control steroidogenesis in several conditions. Thus, we aim to assess the activity of Orteronel (TAK700), a selective inhibitor of 17, 20-lyase, in GCT. **Methods:** An open-label phase II single arm clinical trial has been designed for women with metastatic or locally advanced non-resectable granulosa cell ovarian tumor that harbors the somatic mutation FOXL2 402C→G (C134W) and who have not received prior treatment with any CYP17 inhibitor. Treatment will consist on Orteronel 300mg BID, given orally, continuously in a 28-day treatment cycle. The primary objective is clinical benefit rate; secondary objectives are response rate, progression free and overall survival, assessment of the impact of Orteronel in reducing hormonal overproduction and toxicity. Sample size calculation is based on a a two stage Simon´s design that will lead to enroll 12 evaluable participants in stage one and 4 participants in stage two if one or more participants achieved a CR, PR or stable disease longer than 6 months. 16 subjects will allow a 80% power to differentiate between a 5% and a 25% clinical benefit rate. Probability of early termination of the trial is .54. 20% of losses have been assumed thus 20 patients will be enrolled in 9 spanish institutions (members of hte Spanish Group for Research in Orphan and Unfrequent Tumors-GETHI). Key inclusion criteria are histological diagnosis of GCT, advanced disease (meseaurable or evaluable by RECIST), availability of biopsy material for centralized pathologist review and assessment of the FOXL2 mutation. Key exclision criteria is prior therapy with orteronel, ketoconazole, abiraterone, aminoglutethimide or enzalutamide. Two patients have already been included. Clinical trial information: NCT02101684.

TPS5613 Poster Session (Board #167a), Sat, 1:15 PM-4:45 PM

A randomized, placebo-controlled phase II trial comparing gemcitabine monotherapy to gemcitabine in combination with AZD 1775 (MK 1775) in women with recurrent, platinum-resistant epithelial ovarian, primary peritoneal, or Fallopian tube cancers: Trial of Princess Margaret, Mayo, Chicago, and California consortia. *First Author: Stephanie Lheureux, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Platinum resistant ovarian cancer (OC) remains a therapeutic challenge. The majority of high grade serous OC (HGSOC) harbor *TP53* mutations leading to increased dependency on S- and G2-phase checkpoints. Wee1 inhibition with AZD 1775 (MK 1775) induces G2 checkpoint escape. Gemcitabine is an antimetabolite therapy that kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S phase boundary. Preclinical data have shown that the addition of AZD 1775 to gemcitabine increased activity in platinum resistant OC cell lines and xenograft models. We propose to evaluate the combination of gemcitabine/AZD 1775 in patients (pts) with platinum resistant OC. **Methods:** A multicenter 2:1 randomized phase 2 trial was designed to evaluate the progression free survival (PFS) of subjects with recurrent platinum-resistant/refractory OC receiving gemcitabine in combination with AZD 1775 compared to subjects receiving gemcitabine in combination with placebo (NCT02151292). Eligibility requires measurable disease with progression and disease amenable to a paired biopsy for correlative analyses. There is no limitation in the number of prior lines of therapy, but pts with prior gemcitabine are excluded. All histologic subtypes are eligible, but only pts with HGSOC are considered for the statistical analysis. AZD 1775/Placebo is given orally at 175mg on D1-2, D8-9 and D15-16 with gemcitabine 1000mg/m^2 IV D1, D8 and D15 in a 28-day cycle until progression or unacceptable AE. The primary objective is an improvement in median PFS (from 3.5 to 7 months). Integrated biomarkers will evaluate loss-of-function *TP53* mutations by three complementary methodologies: Sanger sequencing, TAm-Seq and IHC as potential predictive factors of benefit to AZD 1775 and gemcitabine. The concordance of *TP53* mutations in tumor specimens is also determined and followed by TAm-Seq in ctDNA. Current status: This trial was activated in Sept 2014. A total of 10 pts with a median age of 66 are enrolled, all HGSOC. Clinical trial information: NCT02151292.

TPS5614 Poster Session (Board #167b), Sat, 1:15 PM-4:45 PM

Targeting VEGFRi resistance through HIF-1á suppression: Phase II clinical trial evaluating CRLX101 as monotherapy and in combination with bevacizumab in recurrent platinum resistant ovarian cancer. *First Author: Carolyn N. Krasner, Massachusetts General Hospital, Boston, MA*

Background: Ovarian cancer (Ov.Ca.) is the leading cause of death among gyn malignancies. Limited treatment options exist for women whose tumors have become platinum resistant. Hypoxia Inducible Factor-1α (HIF-1α) is a master regulator of key cancer cell survival pathways and facilitates resistance to anti-angiogenic therapies. CRLX101, a novel nanoparticle-drug conjugate that differentially delivers camptothecin into cancer cells, durably suppresses HIF-1α and the combination of CRLX101 with anti-angiogenic drugs incl. bevacizumab (Avastin, Genentech/Roche)(BEV) achieves notable drug-drug synergy in pre-clinical models. Phase 2 monotherapy results achieved with CRLX101 and presented at ASCO 2014 exceeded expectations in this setting and established the basis for this follow-on study. **Methods:** This phase 2 open label, two-stage clinical trial evaluates the combination of CRLX101 plus BEV in pts. with epithelial ovarian, tubal or primary peritoneal cancer progressing through prior platinum-containing chemotherapy. Eligible pts. must have platinum-resistant measurable disease and may have received 1 or 2 prior regimens of chemotherapy that includes no prior topo-1 inhibitors or BEV. Pts. receive CRLX101 15 mg/m2 IV plus BEV 10 mg/kg IV on days 1 and 15 of their 28-day cycles. All pts. undergo CT-based tumor evaluations every 2 cycles. The primary endpoint is progression free survival (PFS) at 6 months (PFS6) and secondary objectives include response rate and assessment of toxicity. A 2-stage design is being employed with the study terminated if $\leq$ 2/18 stage 1 pts. achieve the PFS6 endpoint. As this gate has now been met, a 2nd stage will enroll 25 additional pts. and the treatment will be considered worthy of further investigation if $\geq$ 8/43 total pts. achieve PFS6. Enrollment is ongoing and to-date the drug appears well tolerated with no drug-related SAEs, treatment discontinuations, or deaths observed. Clinical trial information: NCT01652079.

TPS5615 Poster Session (Board #168a), Sat, 1:15 PM-4:45 PM

A phase I dose-escalation and pharmacokinetic study of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) carboplatin at the time of primary cytoreductive surgery for advanced ovarian, fallopian tube, and peritoneal carcinomas. *First Author: Leslie M. Randall, UC Irvine, Tustin, CA*

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) administered at the time of cytoreductive surgery (CRS) for ovarian cancer has the potential to permit immediate regional therapy to the lowest achievable disease burden. Though evidence supporting its efficacy in ovarian cancer is lacking, HIPEC is gaining popularity in the clinical setting. Doses and agents administered are chosen empirically without pharmacokinetic (PK) data. Therefore, we are conducting a phase I dose-escalation and pharmacokinetic study of HIPEC carboplatin (NCT02199171) to inform a follow-on randomized phase II study. **Methods:** Women (n = 30) with presumed stage IIC-IVA ovarian, tubal, or peritoneal carcinomas who are planned for primary or interval CRS following neoadjuvant chemotherapy are eligible. Those optimally or completely cytoreduced and stable for continued anesthesia receive a 60-minute, closed-abdomen infusion of carboplatin at 41ºC according to a novel, continual reassessment dose escalation schema that is flexible to interpret adverse events attributable to surgery vs. those of HIPEC. Serum and peritoneal perfusate are collected for PK studies at time 0 and at every 15 minutes for the duration of the infusion. DNA platinum uptake is measured by inductively coupled plasma mass spectroscopy (ICP-MS). Median, range and interquartile range will be reported for the amount of carboplatin absorbed from the perfusate, the rate of drug absorption from the peritoneal cavity into the systemic circulation, the 0-to-60 min AUC's for peritoneal and plasma platinum concentration curves, the total body clearance, and regional advantage. Three small, easily resectable tumors are left in situ during the perfusion for correlative studies which include direct measurement of tissue temperature in tumors and control avascular mesentery, levels of platinated DNA by ICP-MS in tumors exposed to HIPEC, and expression of Hsp90 in tumors before and after HIPEC. Clinical trial information: NCT02199171.

TPS5616 **Poster Session (Board #168b), Sat, 1:15 PM-4:45 PM**

Phase 2 clinical study of onapristone (ONA) in patients (pts) with uterine endometrioid adenocarcinoma (EC) expressing the activated progesterone receptor (APR^{pos}). *First Author: Jacques Bonneterre, Centre Oscar Lambret, Lille, France*

Background: ONA is a type I PR antagonist, which prevents PR-induced DNA transcription. Presence of transcriptionally-activated PR (APR), seen as an aggregated subnuclear PR distribution pattern, is being explored as a predictive biomarker for ONA activity. The proposed IHC companion diagnostic could select pts with uterine EC most likely to respond to ONA. An extended-release (ER) formulation has been developed to provide constant target exposure to the anti-progestin and address previously-observed liver function test abnormalities. ONA anti-cancer activity has been documented in multiple preclinical models. Pts with APR^{pos} EC, breast and ovarian cancers have experienced clinical benefit (PR or SD $\geq$ 6 months) on ONA, with excellent tolerability. The current study was designed to test the hypothesis that the APR companion diagnostic identifies the pts most likely to respond to ONA, with 80% power to detect a response rate of 30%. **Methods:** This is an ongoing multi-center, open-label, randomized, parallel-group, 2-part phase 1-2 study. The randomized phase 1 dose-finding portion is complete (n = 52). Results are presented in separate abstracts. ONA 50 mg ER was selected as the recommended phase 2 dose. The phase 2 portion focuses on post-menopausal female pts $\geq$ 18 years with recurrent or metastatic uterine EC that is APR^{pos}. APR status is determined by IHC on biopsy at study entry; slides are stained at a central lab using a technically-validated procedure, then centrally interpreted by trained pathologists. PR positivity is defined as $\geq$ 10% cells PR^{pos} by IHC and APR positivity as $\geq$ 5% of cells showing the aggregated pattern. Pts are treated with ONA 50 mg ER BID until progressive disease or intolerability. The primary endpoint is objective response rate by RECIST 1.1. Secondary endpoints include relationship between extent of APR expression and ONA activity, safety and tolerability, duration of response, PFS and OS. A Simon 2-stage design includes 10 patients in the first stage. If $\geq$ 2 pts respond, the study will recruit a further 19 pts (stage 2) to confirm anti-tumor activity. As of February 2015 the study is actively recruiting pts with APR^{pos} uterine EC. Clinical trial information: NCT02052128.

TPS5617 **Poster Session (Board #169a), Sat, 1:15 PM-4:45 PM**

Phase II clinical trial of eribulin in advanced or recurrent cervical cancer (CC). *First Author: Jocelyn Garcia, Los Angeles County Hospital/ University of Southern California, Los Angeles, CA*

Background: Eribulin (E), a Halichondrin B analog from the marine sponge H. okadai shows anticancer effects via G2/M cell cycle arrest, mitotic spindle disruption, and apoptosis. E has efficacy in pretreated metastatic breast cancer (BC) patients (pts), and preclinical antitumor activity in squamous cell carcinoma (SCC) tumor models. Microtubules (MT) have a dynamic and critical role in cancer growth and metastasis. Increasing data support their role in endoplasmic reticulum stress (ERS) and the unfolded protein response. The glucose-regulated protein-78 (GRP78), a key regulator of the ERS response, is upregulated by taxane-chemotherapy (CT) and is associated with clinical outcome. Previous reports show that high GRP78 levels predict response to MT inhibitors (paclitaxel) in BC. Given the novel tubulin-specific mechanism of action of E and its activity in SCC, we conducted a 2-stage phase 2 study of E in pts with advanced/recurrent CC to examine the clinical activity and potential predictors of response (e.g., MT-associated proteins, GRP78). We hypothesize that (1) primary CC tumors with higher GRP78 levels may be associated with better response (i.e., longer time to progression) to E; (2) pts with increasing levels of serum GRP78 during E-treatment will show improved clinical responses to E. **Methods:** Pts with recurrent/advanced CC after $\leq$ 1 prior CT regimens, measurable disease and ECOG performance status $\leq$ 2 were treated with E (1.4mg/m^2 IV day 1 and 8 every 21 days) with tumor assessments every 2 cycles. Primary endpoint was 6-month progression free survival (PFS_6); secondary were best overall response (RECISTv1.1), toxicity (CTCAEv4.03), and overall survival; and exploratory were associations of tumor and serum GRP78 as well as tubulin sub-types with clinical activity. This study has 80% power when the true PFS_6= 26% with a 1-sided $\alpha \leq 0.1$ (H_0: PFS_6= 10%). A prespecified futility analysis gating stage 2 was set if 0/15pts showed at least stable disease at 6 months. Archival tumor samples were evaluated by immunohistochemistry for GRP78, τ, and Tubulin-α, -β, -βIII,-βIV. Serum GRP78 levels were quantified by ELISA. The first pt was enrolled in Nov. 2012. Stage 2 began in Dec. 2014. Currently, 16 of the 30 planned pts have been enrolled. Clinical trial information: NCT01676818.

TPS5618 **Poster Session (Board #169b), Sat, 1:15 PM-4:45 PM**

A single arm, single stage phase II trial of trametinib (GSK1120212) and GSK2141795 in persistent or recurrent cervical cancer. *First Author: Ursula Matulonis, Dana-Farber Cancer Inst, Boston, MA*

Background: In the US, invasive cervical cancer (CC) will affect 12,710 women/year with ~4290 deaths; global deaths from CC are ~275,000 women per yr. Though treatment options for recurrent/metastatic (met) CC have improved by adding bevacizumab to chemotherapy, pts with met CC will eventually have cancer progression (Tewari et al ,*NEJM* 2014), and effective therapies are few. Data from our own institution (Wright et al, *Cancer* 2013) found *PIK3CA* mutations in 32% of adenocarcinomas of the cervix (ACC) and in 35% of squamous cell cancers of the cervix (SCC). *KRAS* mutations were present in 17% of AC's and 0% of SCC. Thus, therapies targeting the PIK3CA and RAS-ERK pathways have rationale for treating met CC; this phase II study is testing a MEK and an AKT inhibitor combination. Pre-clinical studies support dual PI3Ki and MEKi given pathway redundancy and negative feedback loops. **Methods:** Trametinib (GSK1120212) is a reversible/selective inhibitor of MEK1/MEK2. GSK2141795 is an AKT1-3 inhibitor. Objectives of this study: RECIST 1.1 activity of trametinib and GSK2141795 in pts with recurrent CC; other objectives include assess PFS and OS duration, toxicities, mutation and co-mutation rates of PI3K and RAS-ERK signaling pathway genes using high throughput mutational analysis on FFPE samples, and mutational status with clinical benefit from trametinib and GSK2141795. Eligibility: recurrent or met CC (any histology eligible), receipt of 1 prior chemotherapy, and up to 1 add'l regimen, no prior use of PI3K or RAS-ERK pathway inhibitor, ECOG PS 0-2, normal organ function, and availability of FFPE tissue. The treatment regimen is as follows: trametinib 1.5 mg and GSK2141795 50 mg, both given PO and daily. Cycle length is 28 days and pts are assessed for RR every 2 cycles. The study opened in 10/2013, and as of 2/2015, 12 pts have been enrolled. Target accrual is 35 pts; there is a 91% power to detect an improvement in RR from 0.07 to 0.22 using a one-sided 0.09-level exact binomial test. The null hypothesis will be rejected if 5 or more pts respond to trametinib and GSK2141795; the null hypothesis of 0.07 is based on a weighted average of the observed RR from the 11 cohorts enrolled to GOG 127 and 227 series. Clinical trial information: NCT01958112.

TPS5619 **Poster Session (Board #170a), Sat, 1:15 PM-4:45 PM**

Phase I trial of nelfinavir added to cisplatin chemotherapy with concurrent pelvic radiation for locally advanced cervical cancer. *First Author: Arlene Esther Garcia-Soto, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Despite platinum based chemoradiation (C-XRT), 40-50% of women with locally advanced cervical cancer will die from their disease. Nelfinavir (NFV), a protease inhibitor, has been shown to target the Akt pathway sensitizing cancer cells to chemoradiation. The objective of this Phase I trial was to determine dose-limiting toxicities (DLT) and genomic and proteomic effects of NFV in combination with standard concurrent C-XRT in locally advance cervical cancer. **Methods:** After obtaining IRB approval, previously untreated patients with clinical stage IIA to IVA cervical cancer were identified. Patients with HIV were excluded from the trial. Cohort dose level 1 (Dose Level (DL) 1) has been completed. NFV 875 mg PO BID with a 7 day run-in prior to initiating C-XRT. NFV was continued with weekly cisplatin 40 mg/m^2 and pelvic radiation. Patients received a total dose of approximately 80 Gy to the pelvis. Toxicity was evaluated during treatment and every 3 months for 1 year. Pathologic and clinical responses by RECIST 1.1 were also assessed at 3 months intervals for a period of one year. Tumor biopsies were obtained at baseline, after one week of NFV, after 4 and 6 weeks of NFV plus C-XRT and at 3 month follow up for IHC, gene expression analysis and RPPA analysis. Clinical trial information: NCT01485731.

6000 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Phase III randomized trial of standard fractionation radiotherapy (SFX) with concurrent cisplatin (CIS) versus accelerated fractionation radiotherapy (AFX) with panitumumab (PMab) in patients (pts) with locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): NCIC Clinical Trials Group HN.6 trial. *First Author: Lillian L. Siu, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Concurrent administration of anti-EGFR monoclonal antibody with radiotherapy (RT) increases survival compared to RT alone in pts with LA-SCCHN. No prospective data are available comparing bioradiotherapy to standard chemoradiotherapy. **Methods:** Pts with TanyN+M0 or T3-4N0M0 LA-SCCHN were randomized 1:1 to receive SFX (70Gy/35 over 7 weeks) plus CIS at 100 mg/m^2 intravenous (IV) for 3 doses on weeks 1, 4 and 7 (Arm A) versus AFX (70Gy/35 over 6 weeks) plus the anti-EGFR monoclonal antibody PMab at 9 mg/kg IV for 3 doses on weeks -1, 3 and 6 (Arm B). Primary endpoint was progression-free survival (PFS). A total of 320 patients were accrued from 12/2008 to 11/2011 with a median follow-up of 46.4 months (range: 0.1-64.3). Due to an observed declining event rate, the protocol was amended to analyze data with a clinical cut-off date of October 31, 2014. **Results:** Of 320 pts randomized, 5 did not receive protocol treatment, 156 received Arm A and 159 Arm B. Demographics: median age = 56 (range 35-80); male = 84%; ECOG 0:1 (%) = 71:29; primary site: oropharynx (81%), larynx (11%), hypopharynx (6%), oral cavity (2%); smoking history > 10 pack-years (58%). Of 259 oropharynx pts p16 status was known in 217 (84%), with 176 (81%) positive and 41 (19%) negative. A total of 93 PFS events occurred. By intention-to-treat, 2-year PFS was 73% (95% CI: 65-79%) in Arm A and 76% (95% CI: 68-82%) in Arm B, hazard ratio (HR) = 0.95; 95% CI: 0.6-1.5; p = 0.83. Upper bound of HR's 95% CI exceeded the pre-specified non-inferiority margin. Two-year OS was 85% (95% CI: 78-90%) in Arm A and 88% (95% CI: 82-92%) in Arm B, HR = 0.89; 95% CI: 0.54-1.48; p = 0.66. By multivariable analysis, anatomic location, ECOG PS, p16 status, and T category were significant predictors of PFS ($p < 0.05$). Incidence of any > grade 3 non-hematologic adverse event (AE) was 88% in Arm A and 91% in Arm B (p = 0.25). QOL is reported separately. **Conclusions:** With a median follow-up of 46.4 months, PFS of PMab+AFX was not superior to CIS+SFX in LA-SCCHN and non-inferiority was not proven. Clinical trial information: NCT00820248.

6001 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Weekly paclitaxel, carboplatin, cetuximab (PCC), and cetuximab, docetaxel, cisplatin, and fluorouracil (C-TPF), followed by risk-based local therapy in previously untreated, locally advanced head and neck squamous cell carcinoma (LAHNSCC). *First Author: Erminia Massarelli, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We designed a randomized phase II trial to determine the efficacy of two induction chemotherapy (ICT) cetuximab (C) containing regimens with demonstrated efficacy and acceptable toxicity in previously untreated LAHNSCC. ICT was followed by risk-based definitive local therapy, where risk was defined by Human Papillomavirus (HPV) status and stage and stratification by smoking status (low vs intermediate/high). Primary endpoint was 2-year progression free survival (2yr PFS). **Methods**: 136 patients (pts) median age 58 years, 84% males, 89% caucasian, 66% ECOG PS 0, 40% never smokers, with stage IV (40% T3-4, 98% N2b-c/N3), 77% HPV-positive, HNSCC (oropharynx 79%, others 21%) were randomized 1:1 to receive PCC [paclitaxel 135 mg/m2, carboplatin AUC 2 weekly (wy) and C 400 mg/m2 week (w) 1 then 250 mg/m2 wy] for 6 weeks or C-TPF [docetaxel 75 mg/m2, cisplatin 100 mg/m2 day (d) 1, fluorouracil 700 mg/m2 24-hr infusion d 1-4 every 3 w and C 400 mg/m2 w 1 then 250 mg/m2 wy] for 9 weeks. **Results**: As of January 2015 with a median follow-up of 18.4 months and 128 evaluable pts, 14 pts recurred (5 in PCC, 9 in C-TPF) and 4 died (2 per arm). Median PFS has not been reached yet. Sites of recurrence were: primary site (3 in PCC, 6 in C-TPF), cervical lymph nodes (1 in PCC, 3 in C-TPF) and lung metastasis (1 in PCC). Overall grade 3-4 toxicities were seen in 90% PCC pts vs 88% C-TPF pts. C-TPF pts were more likely to experience dehydration (31% vs 12% p = 0.006), nausea (25% vs 9% p = 0.01), hypokalemia (21% vs 2% p = 0.0005), but less likely rash (3% vs 35% $p < 0.0001$), compared to PCC pts. **Conclusions**: Overall ICT with C, a platinum and a taxane combination, followed by risk-based local therapy has promising results with a manageable toxicity profile. Survival results are excellent and distant failure is very uncommon. Formal comparison with historical data within risk groups and predictive biomarker analysis are ongoing. Clinical trial information: NCT01154920.

		PCC (%)	C-TPF (%)
Response Rate (RR) post ICT		78	82
Overall RR (post local therapy)		94	85
Estimated 2yr PFS rate	All pts	89	80
	HPV-positive	94	78
	HPV-negative	76	83
	Low risk	95	82
	Intermediate/high risk	72	75

6002 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Long-term results of GORTEC 2000-01: A multicentric randomized phase III trial of induction chemotherapy with cisplatin plus 5-fluorouracil, with or without docetaxel, for larynx preservation. *First Author: Guillaume Janoray, Centre Hospitalier et Régional Universitaire, Henry S. Kaplan Center, Clinique d'Oncologie et de Radiothérapie, Tours, France*

Background: To compare the long-term efficacy and safety of induction chemotherapy with cisplatin (P) and 5-fluorouracil (F) with or without docetaxel (T) for larynx preservation. **Methods:** Operable patients with untreated stage-III or -IV larynx or hypopharynx invasive squamous-cell carcinoma and who required a total laryngectomy were randomly assigned to receive three cycles of induction chemotherapy with either TPF or PF, followed by radiation therapy for responders. The primary endpoint was 3-year larynx-preservation rate. Secondary endpoints included larynx dysfunction-free survival (LDFFS), overall survival, disease-free survival, locoregional control rate, cause of death, and later toxicity rates. **Results:** Two hundred and thirteen patients were treated with a median follow-up for surviving patients of 105 months. The 5- and 10-year larynx preservation rates were, 74.0% (95%CI, 0.64–0.82) vs. 58.1% (95%CI, 0.47–0.68) and 70.3% (95%CI, 0.58–0.8) vs. 46.5% (95%CI, 0.31–0.63, $p = 0.01$) in TPF versus PF arm, respectively. The 5- and 10-year LDFFS rates were 67.2% (95%CI, 0.57–0.76) vs. 46.5% (95%CI, 0.36–0.57) and 63.7% (95%CI, 0.52–0.74) vs. 37.2% (95%CI, 0.24–0.52, $p = 0.001$), respectively. Overall survival, disease-free survival, and locoregional control rates were not statistically improved in the TPF vs. the PF arm. Significantly fewer grade 3–4 late toxicities of the larynx occurred with the TPF regimen compared to the PF arm (9.3% vs. 17.1%, g-test, $p = 0.038$). **Conclusions:** Long-term follow-up confirms that induction chemotherapy with TPF increased larynx-preservation and larynx dysfunction-free survival. In this larynx preservation approach using induction chemotherapy, TPF should be recommended, followed by radiation therapy. Clinical trial information: NCT00169182.

6003 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

The effect of age on outcome in prospective, phase III NRG Oncology/RTOG trials of radiotherapy (XRT) +/- chemotherapy in locally advanced (LA) head and neck cancer (HNC). *First Author: Julie Ann Kish, Moffitt Cancer Center, Tampa, FL*

Background: The effect of advanced age on outcome for single agent XRT and combined modality therapy in LA-HNC is not well defined. **Methods:** The effect of age (< 70 vs ≥ 70 years) on survival and toxicity was examined in LA-HNC patients (pts) on RTOG 9003 testing 3 altered fractionation (fx) XRT schedules versus standard daily XRT (SFX); RTOG 0129 comparing concurrent SFX + cisplatin (DDP) to accelerated fx with concomitant boost XRT (AFX-C) + DDP; and RTOG 0522, testing AFX-C + concurrent DDP +/- cetuximab. **Results:** Secondary analysis included 2,688 pts. Median followup for surviving pts was 5.2 years (range 0.01 to 20.3) overall, 14.1 yrs in RTOG 9003, 7.9 years in RTOG 0129, and 4.6 years in RTOG 0522. Pts age ≥ 70 were more likely to be female with poorer PS, heavier smoking history and p16 (-) status ($p < 0.001$ each). Adjusting for covariates, patients age ≥ 70 had worse survival regardless of smoking or p16 status. Adverse effect of patients age ≥ 70 may have been worse in p16 (+) pts (HR 2.07 vs. 1.30; interaction p = 0.09), (n = 34). Maximum grade stomatitis and other toxicities were similar by age cohort and tx arms on RTOG 9003. In the DDP-based studies, the elderly experienced more grade 3-5 thrombocytopenia (p = 0.02), anemia (p = 0.03), nephrotoxcity (p = 0.01) and possibly ototoxicity (p = 0.06) but less mucositis (p = 0.04). **Conclusions:** Pts age ≥ 70 were under-represented in RTOG trials evaluating tx for LA-HNC relative to their population overall. Their survival was inferior compared to pts age < 70; this was more apparent in combined modality, DDP-based trials, which featured heightened nephrotoxicity, myelosuppression, and ototoxicity. Delineation of causes of death and tx compliance will provide insight into future trial design. NCI grants U10CA21661, U10CA180868, U10CA180822, U10CA37422 and UG1CA189867. Funded in part under grant with PA Dept of Health which disclaims responsibility for any analyses, interpretations or conclusions and BMS.

Trial	Total accrual	N(%) ≥ 70 yrs	Hazard Ratio(HR) for death(95% CI)	P Value
9003	1076	207(19.2)	1.34(1.15-1.57)	< 0.001
0129	721	48(6.7)	2.34(1.68-3.26)	< 0.001
0522	891	54(6.1)	2.45(1.69-3.53)	< 0.001
Combined	2688	309(11.5)	1.55(1.35-1.77)	< 0.001

6004 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

A prospective phase II trail of de-intensified chemoradiotherapy for low-risk HPV-associated oropharyngeal squamous cell carcinoma. *First Author: Bhishamjit S. Chera, UNC Chapel Hill, Chapel Hill, NC*

Background: This is a prospective multi-institutional phase II study of a substantial decrease in chemoradiotherapy (CRT) intensity as concurrent primary treatment for favorable risk oropharyngeal squamous cell carcinoma. **Methods:** The major inclusion criteria were: 1) T0-T3, N0-N2c, M0, 2) HPV or p16 positive, and 3) ≤ 10 pack-years smoking history. Treatment was limited to 60 Gy Intensity Modulated Radiotherapy with concurrent weekly intravenous cisplatin (30 mg/m^2). The primary study endpoint was pathologic complete response rate (pCR) based on required biopsy of the primary site and dissection of pretreatment positive lymph node regions, regardless of radiographic response. Power computations were performed for the null hypothesis that the pCR rate is 87% and N = 40 (type I error = 14.2%). Secondary endpoint measures included physician reported toxicity (CTCAE), patient reported symptoms (PRO-CTCAE), quality of life (EORTC QLQ-C30 & H&N35), and penetration aspiration scale (PAS) scores for modified barium swallow studies. **Results:** The study population is 43 patients. The pCR rate was 86% (37/43). Median time to biopsy/neck dissection was 9 weeks (7 - 14 weeks). All 6 non-pCR cases were limited to microscopic foci of residual cancer: 1 primary site, 5 nodal. All patients are alive with no evidence of disease (median follow-up 15 months, 4 - 31 months). Incidence of CTCAE acute Grade 3/4 toxicity and PRO-CTCAE severe/very severe symptoms were: mucositis 34%/45%, pain 5%/48%, nausea 18%/52%, vomiting 5%/34%, dysphagia 39%/55%, and xerostomia 2%/75%. Grade 3/4 hematological toxicities were 11%. 39% required a feeding tube, for a median of 15 weeks (5 - 22 weeks). Mean pre- and post-CRT EORTC QOL scores were: Global 80/69 (lower worse, $p < 0.01$), Pain 15/20 (higher worse, p = NS), Swallowing 11/18 (p = 0.04), Coughing 17/22 (p = NS), Dry Mouth 16/64 ($p < 0.001$), and Sticky Saliva 6/49 ($p < 0.001$). There were no significant differences in PAS scores before and after CRT. **Conclusions:** Cancer control following 60 Gy of IMRT with weekly cisplatin 30 mg/m^{2}is likely to be very high in favorable risk oropharyngeal squamous cell carcinoma. (ClinicalTrials.gov, NCT01530997). Clinical trial information: NCT01530997.

6005 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Prognostic implication of persistent HPV16 DNA detection in oral rinses for HPV-positive oropharyngeal carcinoma. *First Author: Eleni Marie Rettig, Johns Hopkins School of Medicine, Department of Otolaryngology-Head and Neck Surgery, Baltimore, MD*

Background: Human papillomavirus-positive oropharyngeal carcinoma (HPV-OPC) has a favorable prognosis; however, 10-25% of HPV-OPC cases recur. Oral HPV DNA detection is associated with HPV-OPC, but its value as a prognostic biomarker is unclear. **Methods:** Patients with incident HPV-OPC treated with curative intent were enrolled from October 2009-May 2013 at four centers. Oral rinses were collected at baseline (diagnosis) and post-therapy at 9, 12, 18 and 24 months after diagnosis. Oral rinses were evaluated for 36 types of HPV DNA. Survival analyses were performed using Kaplan Meier method and Cox regression models. Disease free survival (DFS) and overall survival (OS) were estimated. **Results:** 151 patients were included and 124 (79%) had one or more post-treatment oral rinse (median three). Oral HPV16 DNA was common at baseline (N = 85, 56%). In contrast, oral HPV16 DNA was detected in only six patients in follow up (5%), including five who had HPV16 DNA at baseline (persistent oral HPV16 DNA) and one who did not. Two-year DFS and OS were 92.2% and 97.5%, respectively for all 151 cases. Persistent oral HPV16 DNA was associated with significantly worse DFS (adjusted HR 34.0, 95%CI 7.9-146) and OS (adjusted HR 16.9, 95%CI = 3.1-93). Among patients who recurred (n = 15, 10%), median time to recurrence was 15 months from diagnosis. All five patients with persistent oral HPV16 DNA recurred. Three of these cases included local recurrence. Median time from earliest post-treatment oral HPV16 DNA detection to recurrence was seven months (range 3-11). Among 108 patients with a post-treatment oral rinse collected 9-12 months after diagnosis, detection of persistent oral HPV16 DNA had 100% positive predictive value (3/3), 96% negative predictive value (4/108), 43% sensitivity (3/7) and 100% specificity (104/104) for predicting recurrence between 12-24 months. **Conclusions:** Oral HPV16 DNA detection in oral rinses is common at baseline but rare after treatment for HPV-OPC. Our data suggest that persistent oral HPV16 DNA in post-treatment rinses is strongly associated with poor prognosis, may have high positive and negative predictive value for recurrence, and is a potential tool for long-term tumor surveillance.

6006 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Mutational patterns of HPV+ and HPV- squamous cell carcinomas of the head and neck (SCCHN) and their interference with outcome after adjuvant chemoradiation: A multicenter biomarker study of the German Cancer Consortium Radiation Oncology Group. *First Author: Inge Tinhofer, Dpts. for Radiation Oncology, Comprehensive Cancer Center, Charite University Medicine Berlin, Berlin, Germany*

Background: The genetic landscape of SCCHN is currently being unravelled, but the role of distinct mutations for treatment outcome remains largely unknown. We compared mutational patterns of HPV+ and HPV- tumors with outcome after uniform chemoradiation. **Methods:** Archival tumor specimens from 208 patients with carcinomas of the hypopharynx, oropharynx or oral cavity, all uniformly treated with surgery and adjuvant cisplatin-based radiochemotherapy, were included in this study. An in-house gene panel for semiconductor-based next-generation ultra-deep sequencing, covering 211 exons from 45 genes frequently altered in SCCHN was used for mutational analysis. Genetic alterations were correlated with HPV status and patient outcome. **Results:** Mutational profiles were successfully established for 185 SCCHN cases. Interestingly, HPV+ carcinomas were significantly enriched for activating mutations in driver genes (*PIK3CA* 27%, *KRAS* 8%, *NRAS* 4%, *HRAS* 2%) compared to HPV- cases ($P = 0.002$). Conversely, HPV- tumors showed an increased frequency of loss-of-function alterations in tumor suppressor genes (*TP53* 67%, *CDKN2A* 30%, *PTEN* 4%, *SMAD4* 3%) compared to HPV+ cases ($P < 0.001$). After a median follow-up of 55 months, alterations in tumor suppressor genes significantly increased the risk of death (HR 2.9, 95% CI 1.5-5.8, $P = 0.001$), locoregional recurrence (HR 5.4, 95% CI 1.6-18.1, $P = 0.006$) and distant metastasis (HR 2.3, 95% CI 1.0-5.1, $P = 0.04$). The occurrence of activating driver gene mutations did not influence outcome in the total cohort of patients; however, they were associated per trend with increased risk of locoregional recurrence and death (HR 3.7, 95% CI 0.7-20.6, $P = 0.12$) in HPV+ oropharyngeal carcinomas. **Conclusions:** Overall, loss-of-function tumor suppressor gene mutations negatively interfere with efficacy of adjuvant cisplatin-based chemoradiation, whereas activating driver gene mutations define poor risk specifically in HPV-driven SCCHN. These genes and their signalling pathways might represent therapeutic targets for improving cure rates of SCCHN.

6007 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Serial early post-IMRT undetectable plasma EBV DNA to predict outcomes in non-metastatic nasopharyngeal cancer. *First Author: Victor HF Lee, Department of Clinical Oncology, Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong*

Background: The relationship between early undetectable plasma EBV DNA after intensity-modulated radiation therapy (IMRT) for NPC and long-term survival remains unclear. Early post-IMRT undetectable plasma EBV DNA is a proposed efficacy endpoint which warrants investigation as a predictor of long-term survival. We prospectively explored the predictive power of post-IMRT 8th week and 6th month undetectable plasma EBV DNA for 3-year survival outcomes in patients with non-metastatic NPC. **Methods:** Two hundred and sixty patients with non-metastatic NPC were treated with IMRT +/- concurrent /induction/adjuvant platinum-based chemotherapy. Plasma EBV DNA was taken at diagnosis and then 8 weeks and 6 months after IMRT. Time-dependent Receiver-Operating Characteristics (TD-ROC) were used to obtain C_τ indices. Cox regression models identified interaction between undetectable post-IMRT 8th week and 6th month plasma EBV DNA and outcomes including progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS). **Results:** A strong relationship was shown between post-IMRT 8th week and 6th month undetectable plasma EBV DNA with PFS, CSS and OS (TD-ROC revealing higher C_τ indices for stage IVA–B compared to stage I–III). Cox regression showed that post-IMRT 8th week and 6th month undetectable plasma EBV DNA were prognostic of PFS ($p < 0.001$ and $p < 0.001$, respectively), CSS (p = 0.006 and p = 0.004, respectively) and OS (p = 0.039 and p = 0.012, respectively). Baseline plasma EBV DNA was not prognostic of any survival outcome. **Conclusions:** Our study showed a strong relationship between post-IMRT 8th week and 6th month undetectable plasma EBV DNA and 3-year survival outcomes. This suggested the use of early plasma EBV DNA as a predictor of survival in this setting.

	Post-IMRT 8th week plasma EBV DNA		Post-IMRT 6th month plasma EBV DNA	
	C_τ	95% CI	C_τ	95% CI
PFS				
stage I–III	0.651	0.504 – 0.799	0.601	0.463 – 0.738
stage IVA–B	0.670	0.531 – 0.810	0.826	0.715 – 0.937
p value		< 0.001		< 0.001
CSS				
stage I–III	0.679	0.471 – 0.886	0.517	0.502 – 0.532
stage IVA–B	0.694	0.447 – 0.940	0.771	0.498 – 1.044
p value		0.0048		< 0.001
OS				
stage I–III	0.584	0.462 – 0.707	0.517	0.502 – 0.533
stage IVA–B	0.694	0.447 – 0.940	0.771	0.498 – 1.044
p value		< 0.001		< 0.001

LBA6008 **Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): Preliminary results from KEYNOTE-012 expansion cohort. *First Author: Tanguy Y. Seiwert, The University of Chicago, Chicago, IL*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 29, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

6009 **Clinical Science Symposium, Mon, 8:00 AM-9:30 AM**

PET-NECK: A multi-centre, randomized, phase III, controlled trial (RCT) comparing PETCT guided active surveillance with planned neck dissection (ND) for locally advanced (N2/N3) nodal metastases (LANM) in patients with head and neck squamous cell cancer (HNSCC) treated with primary radical chemoradiotherapy (CRT). *First Author: Hisham Mohamed Mehanna, InHANSE, School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom*

Background: Planned ND after radical CRT for LANM remains controversial. 30% of ND specimens show histological evidence of tumour, albeit tumour viability cannot be confirmed. Consequently, many clinicians still practice planned ND. In mainly retrospective single-institution studies, FDG-PETCT demonstrated high negative predictive values for persistent nodal disease, providing a possible alternative paradigm to ND. This study aimed to determine the efficacy and cost-effectiveness of PETCT guided surveillance, compared to planned ND, in a multicentre randomised setting. **Methods:** *Eligibility:* Patients with LANM of oro-, hypo-pharynx, larynx, oral or occult HNSCC receiving CRT and fit for ND. *Randomisation (1:1)*: to planned ND before or after CRT (control), or CRT followed by FDG-PETCT 10-12 weeks post CRT with ND only if PETCT showed incomplete or equivocal response of nodal disease (intervention). Balanced by centre, planned ND timing, CRT schedule, disease site, T / N stage. *Primary outcome:* Overall Survival (OS), minimum follow-up 2 years. *Analysis:*560 patients needed to detect non-inferior OS in the intervention arm with 80% power, Type I error 5%, defining non-inferiority as having a hazard ratio (HR) no higher than 1.50. Intention to treat analysis was performed by Cox proportional hazards model. **Results**: 564 patients recruited (282 ND arm, 282 surveillance arm; 17% N2a, 61% N2b, 18% N2c, 3% N3). 84% had oropharyngeal cancer. 75% of tested cases were p16+ve. Median follow-up 36 months. The HR for OS was 0.92 (95% CI: 0.65, 1.32) indicating non-inferiority. HR margin of 1.50 lies at the 99.6 percentile of this estimate, $p = 0.004$. There were no differences by p16 status. There were 54 NDs performed in the surveillance arm with 22 surgical complications; 221 NDs in the ND arm with 85 complications. **Conclusions:** PETCT guided active surveillance showed similar survival outcomes to ND arm, but resulted in considerably fewer NDs, and fewer complications, supporting its use in routine practice. Clinical trial information: 13735240.

6010 **Clinical Science Symposium, Mon, 8:00 AM-9:30 AM**

Is PET-CT guided management for patients with locally advanced head and neck squamous cell cancer (HNSCC) cost-effective? Results from a UK non-inferiority phase III randomized trial. *First Author: Alison Florence Smith, University of Leeds, Leeds, United Kingdom*

Title: Despite ongoing controversy, planned node dissection (ND) remains a common treatment strategy after radical chemoradiotherapy (CRT) for locally advanced nodal metastases in patients with HNSCC. Accurate detection of persistent disease using combined Positron Emission and Computerised Tomography (PET-CT) could reduce unnecessary and expensive node dissections (ND) in low-risk patients and potentially improve overall outcomes. **Methods:** 564 patients with N2/N3 oropharyngeal, laryngeal, oral, hypopharyngeal or occult HNSCC were randomized (1:1) to receive either planned ND (before or after CRT), or PET-CT surveillance (CRT followed by PET-CT, with ND administered if incomplete response in the neck nodes). To accurately inform reimbursement decisions, individual patient data from the trial was used to assess within-trial (2-year) cost-effectiveness of PET-CT surveillance versus planned ND from an NHS secondary care perspective. Health benefit was measured using quality-adjusted life-years (QALYs) and costs are reported in 2015 GBP. Probabilistic analysis was conducted using bootstrap methods. **Results:** PET-CT surveillance was cost-effective over the trial period, producing an average per-person cost saving of £1,415 (95% CI: -607 to -2,218) and a health gain of 0.07 QALYs (95% CI: -0.04 to 0.19) compared to planned ND. The average cost was £12,127 (95% CI: 11,601 to 12,686) for PET-CT surveillance vs. £13,542 (95% CI: 12,968 to 14,131) for planned ND; the average QALYs were 1.26 (95% CI: 1.18 to 1.34) vs. 1.19 (95% CI: 1.10 to 1.27). At a £20,000 per QALY threshold, the probability that PET-CT was the cheapest, most effective and most cost-effective strategy was 99%, 91%, and 98%, respectively. Expanding the analysis to include additional NHS, personal social services and societal costs increased the expected costs for each arm but did not alter the overall cost-effectiveness of PET-CT surveillance. **Conclusions:** Results of the economic evaluation indicate that PET-CT surveillance is cost-effective over a short time horizon. Clinical trial information: NCT00720070.

6011 **Clinical Science Symposium, Mon, 8:00 AM-9:30 AM**

Establishing quality indicators for neck dissection: Correlating the number of lymph nodes with oncologic outcomes, NRG Oncology/RTOG 9501-0234. *First Author: Vasu Divi, Stanford University, Palo Alto, CA*

Background: Quality of head and neck surgery has thus far focused on adherence to clinical national guidelines and margin status. For other solid tumors, an association has been found between lymph node counts from regional nodal dissection and overall survival; as such, lymph node counts have been proposed as measure of quality. Yet, for neck dissection, no prospective metrics for surgical quality have been established for mucosal squamous cell carcinoma. The purpose of this study is to investigate the association between lymph node counts from primary neck dissection, local-regional recurrence, and overall survival (OS). **Methods:** Secondary analysis of patients in RTOG trials 9501 and 0234 was performed. The number of lymph nodes counted from regional nodal dissection was evaluated for its prognostic impact on overall survival using a multivariate Cox model adjusted for demographic, tumor, and lymph node data, and stratified by postoperative treatment group: (1) radiation or (2) chemoradiation on RTOG 9501 or (3) chemoradiation and cetuximab on RTOG 0234. Models were compared by Akaike Information Criterion (AIC). **Results:** Five hundred and seventy-two patients were analyzed. Median follow-up for surviving patients was eight years. Median number of lymph nodes recorded on the left and right sides were 24 and 25. Fewer than 18 nodes was associated with significantly worse OS relative to $\geq$ 18 nodes (hazard ratio 1.38, 95%CI 1.09-1.74, $p = 0.007$). The model with this cut point had minimum AIC of all possible models. The difference appears to be driven by local-regional failure (HR 1.46, 95%CI 1.02-2.08, $p = 0.04$) but not distant metastasis (HR 1.08, 95%CI 0.77-1.53, $p = 0.65$). Limited to RTOG 0234, adding p16 status to the model does not affect the hazard ratio for sampled nodes and the effect of nodes is not different by p16 status (p-value for interaction 0.99). **Conclusions:** Identifying 18 or more lymph nodes was associated with improved overall survival and lower rates of local-regional failure. The benefit is seen in both p16-positive and p16-negative patients. The removal and identification of at least 18 lymph nodes should be considered as a measure of quality in neck dissections for mucosal squamous cell carcinoma.

6012 Poster Discussion Session; Displayed in Poster Session (Board #335), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Final overall survival analysis of EXAM, an international, double-blind, randomized, placebo-controlled phase III trial of cabozantinib (Cabo) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline. *First Author: Martin Schlumberger, Institut Gustave Roussy, Villejuif, France*

Background: Cabo inhibits tyrosine kinases including MET, VEGFR2, and RET. EXAM, a randomized double-blind placebo (P)-controlled study in patients (pts) with progressive, locally advanced, or metastatic MTC (NCT00704730), met its primary end point with a statistically significant improvement in progression-free survival (PFS) (hazard ratio [HR] = 0.28, $p < 0.001$) (Elisei et al, JCO, 2013). This report contains the final analysis of the secondary endpoint, Overall Survival (OS). **Methods:** Eligible pts were required to have documented RECIST progression within 14 months (mo) of screening, and were randomized 2:1 to receive Cabo (140 mg qd) or P. Crossover between treatment arms was not allowed. The primary endpoint was PFS assessed by RECIST via independent review. The study was designed with 80% power to detect a HR of 0.667 for the secondary endpoint of OS. **Results:** At the final analysis, median follow up time was 52.4 mo. 218 events were recorded in the intent-to-treat (ITT) population (N = 330). The estimated median OS was 26.6 mo for Cabo vs 21.1 mo for P (stratified HR = 0.85; 95% CI 0.64-1.12; p = 0.241). For 126 pts with known RET M918T mutations, median OS was 44.3 mo for Cabo vs 18.9 mo for P (HR = 0.60, p = 0.026). 32% of Cabo-treated pts received subsequent systemic anticancer therapy vs 50% for P-treated pts. The median duration of treatment was 10.8 mo for Cabo and 3.5 mo for P. 46% and 26% of Cabo-treated pts remained on study treatment for over 1 year and 2 years, and 10% and 1.8% for P, respectively. The most common serious adverse events ($\geq$ 2%) on the Cabo arm were pneumonia (4.2%), pulmonary embolism (3.3%), mucosal inflammation (2.8%), hypocalcemia (2.8%), hypertension, dysphagia, dehydration and lung abscess (2.3% each). **Conclusions:** The secondary endpoint of improved OS was not met, with a median OS 5.5 mo longer with Cabo compared to P that did not reach significance in the ITT population. OS improvement with Cabo was greatest in patients with RET M918T mutations, with a 25.4-month increase in median OS compared to P. The safety profile of Cabo remained consistent with longer term exposure. Clinical trial information: NCT00704730.

6013 Poster Discussion Session; Displayed in Poster Session (Board #336), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Efficacy and safety of lenvatinib for the treatment of patients with ^{131}I-refractory differentiated thyroid cancer with and without prior VEGF-targeted therapy. *First Author: Kate Newbold, Royal Marsden Hospital National Health Service Trust, London, United Kingdom*

Background: Lenvatinib (LEN), an oral multikinase inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT, significantly prolonged progression-free survival (PFS) vs placebo in the phase 3 SELECT trial of patients (pts) with ^{131}I-refractory differentiated thyroid cancer (RR-DTC). Here we report the prespecified analysis of LEN-treated pts based on prior VEGF-targeted therapy exposure. **Methods**: Pts with measurable RR-DTC and independent radiologic documentation of disease progression within 13 months were randomized 2:1 to LEN (24 mg/d; 28-d cycle) or placebo. Pts were stratified by age, region, and prior VEGF-targeted therapy (0 [VEGF-naive] or 1 [prior-VEGF]). **Results**: 195/261 (75%) LEN-treated and 104/131 (79%) placebo-treated pts were naive to VEGF-targeted therapy. 93 Pts had received prior-VEGF therapy: sorafenib, 77%; sunitinib, 9%; pazopanib, 5%; other, 9%. LEN prolonged PFS vs placebo in both groups (Table; VEGF-naive: HR 0.20; 95% CI 0.14–0.27; P<0.0001; prior-VEGF: HR 0.22; 95% CI 0.12–0.41; P<0.0001). Objective response rates (ORR) were similar between both groups (Table). VEGF-naive pts received more cycles of LEN than prior-VEGF pts (medians of 16 and 12.5 cycles, respectively), but had lower overall daily dose intensity (16.1 and 20.1 mg/d, respectively). The proportion of LEN-treated pts with at least 1 dose reduction was similar (VEGF naive: 87%; prior-VEGF: 82%), but VEGF-naive pts had an earlier median time to first dose reduction than pts with prior-VEGF (8.9 and 14.8 weeks, respectively). Most common LEN-emergent adverse events for VEGF-naive and prior-VEGF pts were, respectively: hypertension (72% and 62%), diarrhea (70% and 61%), decreased appetite (54% and 55%), decreased weight (52% and 49%), and nausea (45% and 52%). **Conclusions**: In SELECT, LEN conferred comparable efficacy in pts with and without prior exposure to VEGF-targeted therapy, with similar safety profiles. Clinical trial information: NCT01321554.

	Lenvatinib		Placebo	
	VEGF-naive n=195	Prior-VEGF n=66	VEGF-naive n=104	Prior-VEGF n=27
Median PFS, months (95% CI)	18.7 (16.4–NE)	15.1 (8.8–NE)	3.6 (2.1–5.3)	3.6 (1.9–3.7)
ORR, n (%)	128 (65.6)	41 (62.1)	1 (1.0)	1 (3.7)

NE, not evaluable.

6014 Poster Discussion Session; Displayed in Poster Session (Board #337), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Pharmacodynamic biomarkers of outcomes in the phase III study of lenvatinib in ^{131}I-refractory differentiated thyroid cancer (SELECT). *First Author: Makoto Tahara, Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Lenvatinib (LEN)–an oral multikinase inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT—significantly prolonged progression-free survival (PFS) vs placebo (PBO) in the SELECT study. Baseline (BL) Ang2 levels were previously identified as prognostic and predictive of LEN response, and increase in FGF23 levels is a surrogate pharmacodynamic biomarker of FGFR1 inhibition. Here we investigated serum circulating cytokine/angiogenic factors (CAFs) as potential pharmacodynamic biomarkers of LEN efficacy and disease progression in SELECT. **Methods:** Blood samples from 387/392 (99%) randomized patients (pts) were collected at baseline, cycle 1 day 15 (C1D15), day 1 of subsequent cycles, and treatment end. TG and CAF levels (Ang2, VEGF, sTie2, and FGF23) were measured by ELISA. **Results:** From cycle 1,VEGF levels were consistently elevated for pts on LEN, whereas Ang2 and sTie2 levels were consistently decreased compared with PBO. FGF23 levels increased by 20.8% (C1D15) and 28.6% (C2D1). Although TG decreases in LEN pts were correlated with tumor shrinkage (TS; $P < 0.0001$) and objective response rate (ORR; $P < 0.05$, through C9D1), TG decreases also occurred in pts with stable or progressive disease. Increased VEGF ($P < 0.0001$) and decreased Ang2 ($P < 0.0001$) and sTie2 ($P < 0.0001$) levels also correlated with TS, but not with ORR. Amongst LEN-treated pts with disease progression, decreased levels of TG (31/34 pts, $P < 0.0001$), Ang2 (32/38 pts, $P < 0.0001$), and sTie2 (39/42 pts, $P < 0.0001$) at C2D1 compared to BL were observed. However, at treatment end, increased levels of TG, Ang2, and sTie2 from C2D1 were observed in 79.4%, 78.9%, and 81.0% of these pts, respectively. In some cases, these increases occurred prior to disease progression. **Conclusions:** TG changes were correlated with TS and ORR in the LEN arm of SELECT; CAF analyses may provide additional information.Increased levels of VEGF and FGF23 may indicate that LEN is targeting these signaling networks in pts with RR-DTC in SELECT. Preliminary analyses of pts who progressed on LEN indicated elevated levels of Ang2 and sTie2. Further analyses of the Ang2/Tie2 axis using serum biomarkers are warranted. Clinical trial information: NCT01321554.

6015 Poster Discussion Session; Displayed in Poster Session (Board #338), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Analysis of tumor growth rate for radioiodine (RAI)-refractory differentiated thyroid cancer patients receiving placebo and/or sorafenib in the phase III DECISION study. *First Author: Christian Kappeler, Bayer Pharma AG, Berlin, Germany*

Background: In the phase III DECISION trial, patients were randomized to receive double-blind (DB) sorafenib (SOR) or placebo (PLC) until tumor progression, at which time PLC patients were allowed to switch to open-label (OL) SOR and SOR patients to continue OL. We conducted an exploratory analysis of target lesion size over time to gain insight into tumor growth rate during treatment. **Methods:** Target lesions were assessed by central radiologic review every 8 weeks based on RECIST criteria. Changes in target lesions over time were approximated by a parabola-like 3-parametric model and tumor growth rates (TGR) derived for DB and OL treatment periods. TGR was defined as % change per month of sum of target lesion diameters. **Results:** Patients receiving SOR DB and then OL totaled 207 and 55, and patients receiving PLC DB and then SOR OL totaled 210 and 150, respectively; patients evaluable for TGR were 176, 38, 189 and 123, respectively. For SOR patients, TGR was typically negative early reflecting target lesion shrinkage from baseline [-3.9 (-4.7, -3.1), mean % change/mo (95% CI)] and then positive from nadir to progression [2.6 (1.9, 3.3)] reflecting tumor growth, as was TGR for the subgroup of SOR patients continuing OL treatment from 2nd baseline [1.7 (-0.9, 4.3)]. For PLC patients, TGR was typically positive [5.0 (2.2, 7.8)], as was TGR for the subgroup prior to switching to SOR at progression [6.1 (1.9, 10.3)]. The TGR pattern of PLC patients on OL SOR was similar to the DB SOR pattern, i.e. negative post second baseline [-4.4 (-5.6, -3.2)] and positive from nadir to progression [1.8 (0.5, 3.1)]. **Conclusions:** SOR reversed tumor growth (negative TGR) during the DB period and for PLC patients switching to SOR. TGR from nadir to progression for patients receiving SOR or post-progression for patients continuing on SOR was less than for patients on PLC, suggesting that despite evidence of tumor growth or prior RECIST progression, SOR continued to slow tumor growth relative to growth in its absence. The clinical relevance of these findings for treatment decisions needs to be further investigated. TGR may be an additional efficacy parameter to consider when monitoring SOR treatment. Clinical trial information: NCT 00895674.

6016 Poster Discussion Session; Displayed in Poster Session (Board #339), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Enriched expression of PD-L1 and other immune targets after epithelial-mesenchymal transition (EMT) in squamous head and neck and lung cancers. *First Author: Milena Perez Mak, Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil*

Background: Epithelial-to-mesenchymal transition (EMT) is associated with poor prognosis and resistance to EGFR inhibitors. To determine molecular alterations and novel targets associated with EMT in head and neck squamous cell cancers (HNSCC), we conducted a comprehensive analysis of molecular alterations associated with EMT, using our previously established EMT gene signature. **Methods:** 504 HNSCCs from two independent patient cohorts and 178 lung squamous (LUSC) tumors were scored using the EMT gene signature. EMT score was correlated with mRNA, miRNA, and protein (reverse phase protein array, RPPA) levels (Spearman correlation) and with mutations and HPV status (t-test). Ingenuity Pathway Analysis (PA) software was used for PA. **Results:** Mesenchymal (M) HNSCCs had higher expression of known EMT markers, such as vimentin and fibronectin, lower levels of E-cadherin and miR-200 family members ($p < 0.001$ for all), and a higher frequency of TP53 mutations ($p = 0.016$). In contrast, epithelial (E) tumors were more commonly HPV positive ($p = 0.019$) and were associated with better survival ($p = 0.054$). At the protein level, the receptor tyrosine kinase (RTK) Axl was overexpressed in M tumors ($p < 0.001$), whereas other RTKs, such as pHer2 ($p = 0.005$) and pEGFR ($p = 0.02$) were higher in E tumors. PA revealed a striking enrichment in genes involved with immune trafficking and inflammatory response in M tumors from HNSCC and LUSC. In a supervised analysis, of 20 targetable immune checkpoints, 18 were overexpressed in M tumors, including PD-L1, ADORA2, CCL2, CD276 ($r > 0.44$, $p < 0.001$ for all). PD-L1 overexpression was confirmed by RPPA ($p < 0.001$). Consistent with these results, EMT was positively correlated with scores from ESTIMATE, which assesses stromal and immune infiltrates in tumor samples ($r = 0.63$, $p < 0.001$). **Conclusions:** Among several molecular alterations associated with EMT, we found a strong enrichment in targetable immune checkpoints (mRNA and protein) and immune cell infiltrates in HNSCC and LUSC cohorts. Given our recent findings that EMT promotes immune escape in lung cancer, our data suggests that EMT status could improve patient selection for immune targeting.

6017 Poster Discussion Session; Displayed in Poster Session (Board #340), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancer patients. *First Author: Tanguy Y. Seiwert, The University of Chicago, Chicago, IL*

Background: Immunotherapy with anti-PD-1 checkpoint blockade shows encouraging activity in head and neck squamous cell carcinoma (HNSCC). We tested 4 multi-gene expression signatures previously derived in melanoma patients (pts) in PD-L1$^+$HNSCC pts from the KEYNOTE-012 (NCT01848834) study as candidate predictive biomarkers. **Methods:** 43 of 61 pembrolizumab-treated patients had RNA expression profiling and survival data; 40 were evaluable for objective response. FFPE-extracted RNA was analyzed on the NanoString nCounter system. Four previously established gene signatures (1) "interferon-γ," (2) "TCR signaling," (3) "expanded-immune," and (4) "de novo" were examined as possible predictors for formal hypothesis testing prior to unblinding clinical outcome data. **Results:** Overall response (OR) rate was 9/40 = 23%. Three signatures showed significant ($P < 0.05$) association with OR; all 4 signatures showed strong associations ($P < 0.005$) with PFS. Signature scores and PFS readily segregated into 2 groups (>5 versus <5 months PFS). Using an optimal cutoff for the top-performing interferon-γ signature, positive predictive value (PPV) for response was 40.0%, and negative predictive value (NPV) was 95.0%; AUC = 0.80 [95% CI, 0.61-0.95]. When evaluating the individual signature genes, T-cell–mediated interferon-γ inducible MHC-II expression appeared to be the immune biological connection. Interferon-γ signature correlated strongly with the previously independently discovered inflamed/mesenchymal HNSCC intrinsic subtype (Keck/Seiwert CCR 2015) (R = 0.9). **Conclusions:** "Inflamed phenotype" signatures are strong predictors of clinical benefit from anti-PD-1 treatment for HNSCC even among a group of patients already considered to be PD-L1$^+$. Clinical trial information: NCT01848834.

	Nominal 1-sided *P* value[a]	
Signature	OR N = 40	PFS N = 43
IFN-γ (6-gene)	0.005	< 0.001
TCR signaling (13-gene)	0.071	0.002
Expanded-immune (18-gene)	0.015	< 0.001
De novo (33-gene)	0.018	< 0.001

[a]From logistic or Cox regression for overall response and progression-free survival, respectively.

6018 Poster Discussion Session; Displayed in Poster Session (Board #341), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

PDL1-expressing circulating tumor cells (CTCs) in head and neck squamous cell carcinoma (HNSCC). *First Author: George Koutsodontis, Attikon Hospital, National Kapodistrian, University of Athens, Athens, Greece*

Background: Blockade of PD-1/PD-L1 immune checkpoint pathway emerged as promising novel therapeutic strategy for cancer. Predictive biomarkers for response to anti-PD1 therapy are lacking. Because therapy with checkpoint inhibitors is cost intensive, noninvasive tools for early prediction of responders are of major interest. We assessed gene expression of *PDL1* in CTCs at baseline and posttreatment in HNSCC patients (pts). **Methods:** 70 pts with locally advanced (n = 58) or recurrent/metastatic (n = 12) HNSCC were included in this analysis. Patients with locally advanced disease were treated with cisplatin chemoradiotherapy +/- TPF induction chemotherapy (IC). We assessed *PDL1* expression at baseline, after completion of induction chemotherapy, at end of chemoradiotherapy and at relapse. We quantified PDL1 gene transcripts in immunomagnetically positively selected CTCs and 20 healthy individuals. A quantitative real time RT-qPCR assay for *PDL1* was developed based on de novo in-silico design of primers and Taqman probes. The specificity was first tested by homology searches in the nucleotide database (NCBI, nucleotide BLAST). To assess univariate differences of study parameters according to *PDL1* expression chi-square test was used for the categorical clinicopathological variables, while patients' survival curves according to *PDL1*expression were generated by Kaplan-Meier analysis and tested for significance using the Mantel-Cox log-rank test. **Results:** From 88 total evaluable CTC samples, 26 of 46 were PDL1+ at baseline, 6 of 17 post-IC, 11 of 23 at end of treatment and 1 of 2 at relapse. The assay sensitivity was evaluated using external quantification calibrators ranging from 105 copies/μL to 10 copies/μL. There was trend ($p = 0.07$) for adverse association between PDL1 expression at baseline and progression-free survival. **Conclusions:** We report for the first time a highly sensitive, specific and reproducible quantitative real-time RT-qPCR assay for the assessment of *PDL1* expression in CTCs. The assay is currently validated in CTCs isolated from a large number of HNSCC pts. Serial *PDL1* expression assessment has potential to select and monitor pts for PD-1 targeted therapies.

6019 Poster Discussion Session; Displayed in Poster Session (Board #342), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Utilization and outcomes of low dose versus high dose cisplatin in head and neck cancer patients receiving concurrent radiation. *First Author: Stuart J. Wong, Medcl Coll of Wisconsin, Milwaukee, WI*

Background: Although level I evidence supports the use of high dose (HD) intermittent cisplatin with concurrent RT for locally advanced head and neck squamous cell carcinoma (LA-HNSCC), low dose (LD) weekly cisplatin has been adopted, including in recently activated national clinical trials. We sought to examine patterns of care and outcomes of cisplatin in this setting using a US prospective observational registry. **Methods**: We utilized Longitudinal Oncology Registry of Head And Neck Carcinoma (LORHAN). Patients (pts) included in the analysis had newly diagnosed, stage III or IV, non-metastatic HNSCC, received RT and chemotherapy, were ≥ 18 years and had provided written informed consent. Pts were enrolled to the LORHAN Registry from 2005 to 2010, with data available through 2011. Propensity score weighting was applied to adjust for confounding in comparisons between dose groups. **Results**: 1,091 pts received cisplatin plus concurrent RT and were categorized by initial cisplatin dose received: LD (≤ 40 mg/m2) cisplatin (N = 334) or HD (≥ 75 mg/m2) cisplatin (N = 757). The total cumulative dose of cisplatin was 322.5 mg (standard deviation SD = 108.6) for the LD group and 475.8 (SD = 160.5) for the HD group. This difference was statistically significant for both the unadjusted and the propensity-score adjusted analysis between cohorts ($p < 0.001$). The cumulative dose was also significantly different, for the subset of pts with oropharyngeal cancers (n = 806): 328.6 mg (SD =114.6) for those in the LD group versus 486.6 mg (SD = 156.6) for the HD cisplatin, $p<0.001$. A significant difference in overall survival favoring the HD group (log rank test, $p<0.001$) was observed, although this analysis was limited by incomplete follow-up data (> 75% censored in both cohorts). **Conclusions**: In contrast to anticipated results, a higher cumulative dose of cisplatin was observed in LA-HNSCC pts treated with RT who initiated therapy with HD compared to LD cisplatin. No definitive conclusions can be made regarding the impact of cisplatin dose and schedule upon survival; however our hypothesis generating observations suggest further study of this question is warranted. Clinical trial information: NCT01080313.

6020 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Differential impact of cisplatin dose intensity on human papillomavirus (HPV)-related (+) and HPV-unrelated (−) locoregionally advanced head and neck squamous cell carcinoma (LAHNSCC). *First Author: Anna Spreafico, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Definitive radiotherapy with concurrent cisplatin (CDDP) is a standard treatment for patients (pts) with LAHNSCC. We evaluated the impact of CDDP dose intensity (mg/m^2) on overall survival (OS) of HPV+ and HPV- LAHNSCC pts. **Methods:** Princess Margaret Cancer Centre (PM) and Istituto Nazionale dei Tumori (INT) LAHNSCC cohorts treated from 2000 to 2012 were reviewed. Kaplan-Meier method was used to estimate the 5-year (yr) OS in HPV+ vs HPV− pts. HPV status was determined by p16 staining or in situ hybridization HPV DNA for all oropharyngeal (OPC), unknown primary (UNK), and ≤ 10 pack-year (PY) smoking laryngo-hypopharyngeal cancer (LHC). Untested p16, >10 PY LHC pts were assumed HPV−. Multivariable analysis (MVA) with Cox regression identified OS predictors for HPV+ and HPV− pts. **Results:** A total of 659 pts (584 PM; 75 INT) were evaluated. Pts characteristics included: median age 58 (range: 27-81); primary site: OPC 73%, LHC 24%, UNK 3%; non-smokers 27%; stage: T4 25%, N2c-N3 60%; HPV+ 404 (61%), HPV− 255 (39%) pts. Median CDDP dose was 200 mg/m^2 for both HPV+ and HPV− cohorts. Median follow-up was 4.3 yrs. Five year OS was inferior for HPV− CDDP ≤ 200 vs > 200 mg/m^2 (44 vs 62%, p < 0.01), while no difference was detected in HPV+ CDDP ≤ 200 vs > 200 mg/m^2 (83 vs 87%, p = 0.30), confirmed by MVA (Table). In N3 or T4 HPV+ pts, a trend on OS in CDDP >200 mg/m^2(HR = 0.62, 95% CI: 0.30-1.31) was observed. **Conclusions:** In this large multicenter cohort study, CDDP dose intensity ≤ 200 mg/m^{2}had a detrimental impact on OS in HPV− LAHNSCC pts. The impact of CDDP dose intensity on HPV+ pts was not significant. These results warrant prospective validation.

MVA for OS in HPV+ and HPV– pts.

HR (95% CI) & p value

	CDDP (mg/m^2) > 200 vs ≤ 200	Age 1 yr increment	Smoking 10 PY increment	T HPV+: T4 vs T0-3 HPV−: T3-4 vs T1-2	N HPV+: N2c-3 vs N0-2b HPV−: N2b-3 vs N0-2a	Disease Site Non-OPC vs OPC
HPV+	0.8 (0.4-1.4) p = 0.46	0.98 (0.95-1.01) p = 0.25	1.2 (1.02-1.3) p = 0.03	2.5 (1.3-4.5) p < 0.01	2.4 (1.3-4.4) p < 0.01	NA
HPV–	0.5 (0.3-0.8) p < 0.01	1.00 (0.98-1.02) p = 0.93	1.1 (0.98-1.2) p = 0.12	1.4 (0.9-2.1) p = 0.13	2.4 (1.5-3.9) p < 0.01	1.2 (0.8-1.8) p = 0.38

6021 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Symptom reduction from IMRT dose deintensification: Results from ECOG 1308 using the Vanderbilt Head and Neck Symptom Survey version 2 (VHNSS V2). *First Author: Anthony Cmelak, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: The prevalence, severity, and functional implications of high-dose radiation for locally advanced head and neck cancer (HNC) are substantial. E1308 allowed dose reduction of IMRT (54Gy) in HPV+ patients if a complete clinical response were obtained to induction chemotherapy (IC). The VHNSS V2 instrument was used to quantify symptom burden following treatment. **Methods:** The VHNSS V2 is a 50-item survey, scored 0 (none) to 10 (severe) arranged into symptom clusters. The tool was utilized pre-treatment, and at 6 and 12 months to pts with resectable stage III/IVa,b HPV+ oropharyngeal HNC who received IC q3 weeks x 3 with paclitaxel 90mg/m2 days (D) 1,8, 15, cisplatin 75mg/m2 D1, and standard weekly cetuximab (C). IC response determined IMRT dose independently at primary site and involved nodes: C-IMRT 54Gy/27 if cCR and 69.3Gy/33 if < cCR. Only pts who completed ≥ 50% of the items in a given symptom cluster were considered evaluable for that cluster **Results:** 80 pts were enrolled (3 did not receive IMRT) with 44 pts classified as NED at 12 months post-treatment (35 received ≤ 54Gy and 9 received > 54Gy). Moderate to severe average symptom cluster scores (scores ≥ 2) appeared numerically reduced with lower IMRT dose: mouth pain 6% vs. 25%, general pain 27% vs. 50%, nutrition 6% vs. 40%, taste/smell changes 37% vs. 50%, voice 13% vs. 25%, teeth 17% vs. 33%. Difference in difficulty swallowing solids 35% vs. 100% reached statistical significance (p = 0.01). A composite analysis evaluating moderate to severe symptoms at 12 months for any of these 3 clusters (difficulty swallowing solids, dry mouth, taste/smell changes) was 70% vs. 100%. Difficulty swallowing liquids 6% vs. 0%, and mucous 27% vs. 25% did not appear to be reduced by the lower IMRT dose. **Conclusions:** The VHNSS V2 instrument provides granular analysis of specific symptoms experienced by HNC patients. Reduction of IMRT dose from 69.3Gy to 54Gy appeared to ameliorate late toxicities in locally advanced HPV+ HNC. This dose reduction in pts with cCR to IC was associated with favorable long-term DFS. VHNSS V2 will be used in subsequent ECOG-ACRIN studies to evaluate treatment effects prospectively. Clinical trial information: NCT01084083.

6022 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Safety analysis of a phase III randomized trial of chemotherapy with or without bevacizumab (B) in recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). *First Author: Athanassios Argiris, The University of Texas Health Science Center at San Antonio, San Antonio, TX*

Background: The addition of B, an anti-VEGF monoclonal antibody, to chemotherapy has improved outcomes in several solid tumors. Pemetrexed plus B in R/M SCCHN showed promising efficacy but significant incidence (15%) of grade 3-5 bleeding (Argiris et al. JCO 2011). **Methods:** Patients (pts) with performance status (PS) 0-1, adequate laboratory parameters, no history of bleeding, not receiving anticoagulation or having blood vessel invasion were randomized to: A) one of 4 regimens (investigator's choice): A1, cisplatin (C) 100 mg/m^2, 5-FU 1000 mg/m^2/day x 4 days; A2, carboplatin (Cb) AUC 6, 5-FU 1000 mg/m^2/day x 4 days; A3, C 75 mg/m^2, docetaxel (D) 75 mg/m^2; A4, Cb AUC 6, D 75 mg/m^2, every 3 weeks, or B) the same regimen (B1, B2, B3, B4) plus B 15 mg/Kg IV, every 3 weeks, until progression. All pts received prophylactic antibiotics. Chemotherapy could be stopped after 6 cycles after maximum response. The primary endpoint was overall survival with a planned sample size of 400. **Results:** We report safety results from a total of 357 pts, 183 in Arm A (A1 = 15; A2 = 10; A3 = 88; A4 = 68) and 174 in Arm B (B1 = 12; B2 = 8; B3 = 85; B4 = 66). PS 1, 55%; female, 14%; age ≥ 65, 25%. Grade (G) 5 treatment-related adverse events (AEs), 5% in arm A vs 8% in arm B (p = 0.23), causes (%): febrile neutropenia, 1 vs 0; cardiac arrest, 0 vs 1; gastric hemorrhage, 0 vs 1; tracheal/tracheostomy hemorrhage, 0 vs 2; laryngeal/pharyngeal/bronchial hemorrhage, 0 vs 3; lung infection 1 vs 0; sepsis, 0 vs 1; nervous system/other 0 vs 2. G 5 bleeding AEs, all reported, 1% vs 4% (p = 0.06); treatment-related, 0 vs 3.6 (p = 0.007); G 3-5 bleeding AEs, all reported, 3.6 vs 7.8 (p = 0.08); treatment-related, 0.5 vs 7.3 (p = 0.0004). G 3/4 treatment-related AEs in arm A vs B (%): febrile neutropenia, 7/2 vs 9/6; fatigue, 9/0 vs 17/0; diarrhea, 1/0 vs 5/0; mucositis, 4/0 vs 15/1; vomiting 4/0 vs 6/1; neutropenia, 1/25 vs 7/32; thrombocytopenia, 1/5 vs 5/3; hypertension, 0/0 vs 5/0; thromboembolic, 0/0 vs 4/1. Female gender, age ≥ 65 and PS 1 were risk factors for G 3-5 bleeding with B. **Conclusions:** The incidence of G 5 toxicities was similar to previous phase III ECOG trials. B increased grade 3-5 bleeding but not overall G 5 AEs. Clinical trial information: NCT00588770.

6023 Poster Discussion Session; Displayed in Poster Session (Board #346), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Biomarker analysis in recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) patients (pts) treated with second-line afatinib versus methotrexate (MTX): LUX-Head & Neck 1 (LUX-H&N1). *First Author: Ezra E. W. Cohen, UC San Diego Moores Cancer Center, La Jolla, CA*

Background: In the Phase III LUX-H&N1 trial, afatinib improved PFS (median 2.6 vs 1.7 months; HR 0.80; p = 0.03) vs MTX in second-line R/M HNSCC pts. As there are no accepted predictive biomarkers in this setting, the association of pre-specified biomarkers with clinical outcomes was explored. **Methods:** Pts were randomized 2:1 to 40 mg/d afatinib or 40 mg/m^2/wk MTX. The primary endpoint was PFS. Tumor biomarker analyses included human papillomavirus status assessed by p16 immunohistochemistry (IHC), EGFR amplification (FISH), HER3 (IHC) and PTEN (IHC) on archival tissue, and the VeriStrat proteomic signature (classifying pts likely to have good or poor outcomes with EGFR inhibitors) on plasma samples. **Results:** Of 483 ptsenrolled, 301 (62%) provided plasma and 234 (48%) provided tissue for biomarker analyses. A more pronounced PFS benefit with afatinib vs MTX was observed in p16-negative vs p16-positive, PTEN-high vs PTEN-low, and HER3-low vs HER3-high disease (Table). A trend towards prolonged PFS was observed with afatinib vs MTX in EGFR-amplified tumors. PFS was similar with afatinib and MTX in VeriStrat good and poor groups. Further tumor samples are being analyzed and updated results of PFS and OS will be presented. **Conclusions:** Subgroups of R/M HNSCC pts who may achieve increased benefit from afatinib vs MTX were preliminarily identified based on biomarkers. PFS benefit with afatinib was more pronounced in pts with p16-negative, PTEN-high, HER3-low, and EGFR-amplified disease. Clinical trial information: NCT01345682.

Subgroup	No. of pts (Afatinib vs MTX)	Median PFS, mos (Afatinib vs MTX)	HR (95% CI) (Afatinib vs MTX)	p-value
p16-neg	135 vs 64	2.7 vs 1.6	0.70 (0.50, 0.97)	0.029
p16-pos	23 vs 12	2.0 vs 2.3	0.81 (0.39, 1.69)	0.564
EGFR-amplified	48 vs 17	2.8 vs 2.2	0.64 (0.34, 1.20)	0.162
EGFR not amplified	47 vs 19	1.6 vs 2.1	1.25 (0.70, 2.23)	0.455
HER3-low	49 vs 17	2.9 vs 2.0	0.47 (0.25, 0.86)	0.014
HER3-high	64 vs 26	1.7 vs 2.4	1.33 (0.79, 2.24)	0.289
PTEN-high	30 vs 12	2.9 vs 1.4	0.36 (0.16, 0.81)	0.014
PTEN-low	82 vs 33	2.6 vs 2.7	1.01 (0.65, 1.58)	0.965
VeriStrat: good	127 vs 69	2.7 vs 2.0	0.79 (0.57, 1.09)	0.145
VeriStrat: poor	70 vs 35	1.5 vs 1.5	0.91 (0.58, 1.43)	0.678

6024 Poster Session (Board #347), Sat, 1:15 PM-4:45 PM

Ultra-deep targeted sequencing to identify *HRAS*, *TP53*, and *CDKN2A* somatic mutations as molecular prognostic markers in patients with advanced oral squamous cell carcinoma. *First Author: Tzu-Chen Yen, Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital, Taoyuan, Taoyuan, Taiwan*

Background: Ultra-deep targeted sequencing (UDT-Seq) was used to identify somatic mutations predicting disease-specific survival (DSS) in patients with advanced oral squamous cell carcinoma (OSCC). **Methods:** Formalin-fixed paraffin-embedded primary tumor specimens were collected from 249 node-positive OSCC patients, including 147 patients with (ECS+) and 102 without (ECS-) extracapsular spread. Mutational hotspots of 45 cancer-related genes were examined with UDT-Seq at an average depth of 1000×. Kaplan-Meier plots and Cox regression analyses were used to investigate the association between the mutation status and DSS. **Results:** Non-synonymous variants were identified in 179 (71.9%) specimens. *TP53*, *CDKN2A*, *HRAS* and *PI3KCA* were the most frequently mutated genes. The presence of ECS did not statistically significantly influence the mutation spectrum. *HRAS* mutations were strongly associated with poor DSS independent of ECS. Mutations in *TP53* (especially located in the DNA-binding domain) and *CDKN2A* predicted poor DSS in ECS- and ECS+ patients, respectively. No association between *PI3KCA* mutations and prognosis was detected. **Conclusions:** Our findings demonstrate that *HRAS, TP53* and *CDKN2A* mutations identified by UDT-Seq predict DSS in advanced OSCC, potentially serving as molecular markers for individualized patient care through risk-adapted therapy.

6025 Poster Session (Board #348), Sat, 1:15 PM-4:45 PM

New aspects regarding the induction chemotherapy with TPF and radio chemotherapy in head and neck cancer. *First Author: Edwin Boelke, University of Duesseldorf, Duesseldorf, Germany*

Background: Induction chemotherapy with docetaxel, cisplatin, and 5 FU (TPF) before radiotherapy (RT) or radio-chemotherapy (RT-CHX) improves the overall survival rate compared to induction chemotherapy with cisplatin and 5 FU in locally advanced squamous cell carcinoma of the head and neck (SCCHN). If TPF induction before RT-CHX improves clinical outcome in comparison to RT-CHX alone is still uncertain. Recently, the results of 5 randomized trials addressing this question have become available. **Methods:** 1060 patients with locally advanced SCCHN were randomly assigned to receive either TPF induction CHX followed by concurrent RT-CHX or concurrent RT-CHX alone. Platin or taxane based CHX was used during RT. 53,4% of patients had oropharyngeal, 17,3% hypopharyngeal, 6,4% laryngeal, 18,5% oral cavity and 4,4% other SCCHN. Published hazard ratios and hazard ratios extracted from available survival curves for overall survival (OS) and progression free survival (PFS) were basis of the meta-analysis. Meta-analysis of the effect sizes on OS and PFS was performed using a random effects model based on parameter estimates of log hazard ratios in Cox models and their standard errors. **Results:** Additional induction CHXwith TPF before RT-CHX did not result in a significant improvement of overall survival (Hazard Ratio: 0.950, 95% confidence limits (CL) 0.791-1.140 p = 0.579). **Conclusions:** Additional induction CHX with TPF before RT-CHX does not improve overall survival in SCCHN.

6026 Poster Session (Board #349), Sat, 1:15 PM-4:45 PM

Phase I trial of intravenous attenuated vaccinia virus (GL-ONC1) with concurrent chemoradiotherapy (CRT) for locoregionally advanced head and neck carcinoma. *First Author: Loren K. Mell, UC San Diego Moores Cancer Center, La Jolla, CA*

Background: We aimed to test the safety of GL-ONC1, an attenuated vaccinia virus, delivered intravenously (IV) with concurrent CRT for locoregionally advanced head and neck carcinoma (LA-HNC). Secondary objectives were to test for tumor susceptibility to viral infection in baseline specimens and for tumor infection on mid-treatment biopsies. **Methods:** This was a 3+3 phase I dose escalation trial for unresected LA-HNC, excluding HPV-positive oropharyngeal cancer (NCT01584284). CRT was given in 33-35 fractions of 2.00-2.12 Gy over 6.5-7 weeks using IMRT with concurrent cisplatin 100 mg/m^2 given on days 1, 22, and 43. Escalating doses of GL-ONC1 were given as follows: cohort 1, 3×10^8 pfu on day 3; cohort 2, 1×10^9 pfu on day 3; cohort 3, 3×10^9 pfu on day 3; cohort 4, 3×10^9 pfu on days 3 and 8; and cohort 5, 3×10^9pfu on days 3, 8, 15, and 22. Dose-limiting toxicity (DLT) was defined as grade $\geq$ 4 toxicity or grade $\geq$ 3 mucositis or skin reaction persisting $>$ 6 weeks after CRT attributed to GL-ONC1. **Results:** From May 2012 to Dec 2014, 24 patients consented (19 enrolled, 5 screen failures). 18 patients completed CRT, with 1 currently on treatment. Mean age was 56 years. 74% had stage IVA and 26% had stage IVB disease. 26% were HPV-positive. One DLT occurred in cohort 4. Maximum tolerated dose was not reached. Adverse events included grade $\geq$ 2 rigors (47%), grade $\geq$ 2 thrombocytopenia (32%), grade $\geq$ 2 fever (26%) and grade $\geq$ 1 rash (21%). The rash was confirmed to be viral in origin in 2 patients. Viral tumor infection was confirmed by qPCR for A21L gene in 4 patients. No viral shedding was detected on urine or oral swab 1-2 days post infusion of GL-ONC1. Serious adverse events considered unrelated to GL-ONC1 were myocardial infarction (1), pulmonary embolism (1), syncope (1), grade 3 emesis (1), and grade 3 neutropenia (1). Of 18 patients completing CRT, 78% had 3 cycles of cisplatin and 22% had 2 cycles. With median 17 month follow-up, Kaplan-Meier estimates of 1-year (2-year) PFS and OS were 82% (75%) and 87% (75%) respectively. **Conclusions:** This is the first trial to establish the safety of IV GL-ONC1 for LA-HNC patients undergoing concurrent CRT. A phase II trial in this population is warranted. Clinical trial information: NCT01584284.

6027 Poster Session (Board #350), Sat, 1:15 PM-4:45 PM

Can somatic copy number alterations detected by ultradeep targeted sequencing predict prognosis in oral squamous cell carcinoma? *First Author: Tzu-Chen Yen, Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital, Taoyuan, Taoyuan, Taiwan*

Background: Targeted sequencing technologies have greatly advanced our knowledge of the incidence and functional significance of somatic genomic copy number alterations (CNA) in various malignancies. To understand the underlying genetic alterations in oral squamous cell carcinoma (OSCC) and aid in molecular classification of OSCC and patient prognosis, CNA were analyzed using ultradeep-targeted sequencing (UDT-Seq) with DNA from formalin-fixed paraffin-embedded (FFPE) OSCC specimens. **Methods:** First, a linear model was developed to overcome uneven coverage across target regions. We then designed 189 primer pairs to selectively amplify mutational hotspots targeting 46 cancer-relevant genes. Samples were obtained from 310 FFPE tissue specimens from OSCC resections and 14 control samples. The 5-year rates of local recurrence, distant metastases, and overall survival served as the main outcome measures. We finally confirmed the prognostic signatures by profiling an additional 105 primary OSCC samples. **Results:** We found that CNA burden across 16 targeted genes was associated with clinical outcomes in the two cohorts. *FGFR1* and *PIK3CA* amplifications were significant predictors of prognosis independent of traditional risk factors. Moreover, we identified CNA in genes involved in proteoglycan metabolism as well as *FOXO* and *PI3K-AKT* signaling pathways, for which targeted drugs are already available or under development. **Conclusions:** We observed that CNA detected by UDT-Seq may predict prognosis in OSCC patients, complementing the clinicopathological information. Prognostically detrimental CNA can provide added value in the combined molecular and clinical prognostication of OSCC.

6028 Poster Session (Board #351), Sat, 1:15 PM-4:45 PM

Adjuvant chemo-radiotherapy (CRT) versus radiotherapy (RT) alone for locally advanced salivary gland carcinoma among older population: SEER-Medicare analysis. *First Author: Tawee Tanvetyanon, H Lee Moffitt Cancer Ctr and Rsrch Inst, Tampa, FL*

Background: Salivary gland carcinoma is an uncommon malignancy. For locally advanced or high risk disease, current standard of care consists of surgery followed by adjuvant RT. Limited data on the efficacy of adjuvant CRT exists. We sought to compare the effectiveness of adjuvant CRT vs. RT alone among older patients in real world setting. **Methods:** SEER-Medicare database (1992-2009) was searched for beneficiaries 66 years of age or older with Medicare coverage ≥ 1 year following a diagnosis of locally advanced (T3-4 and/or N1-3, M0) major or minor salivary gland carcinoma. Patients must have had definitive surgery within 4 months from diagnosis and adjuvant RT or CRT within 6 months from diagnosis. **Results:** Analyses included 741 patients: 100 received CRT and 641 received RT. The most common concurrent chemotherapy agents used were Cisplatin or Carboplatin (37%), Carboplatin plus Taxane (19%) and Cetuximab (18%). Patients in CRT group were younger (median age 74.2 vs. 76.8 years, $p = 0.01$), with greater node positive disease (73% vs. 64%, $p = 0.05$) than RT group. The median overall survival was 24.0 months with CRT vs. 41.0 months with RT, $p = 0.012$. Multivariable analysis adjusting for patient-, tumor- and treatment-related factors still showed that CRT increased mortality over RT alone: HR 1.40 (95% CI: 1.08, 1.81). Hospitalization with treatment-related toxicity was more frequent in the CRT group, 27.0% vs. 11.5%, $p < 0.01$. An effect modification (*p-interaction* = 0.02) between histology and CRT was present such that an increase in mortality from CRT was observed only among adenoidcystic, mucoepidermoid or acinic cell carcinoma, but not adenocarcinoma or squamous cell carcinoma. Sensitivity analysis performed by changing the adjuvant definition to within 4 months from diagnosis or restricting analytic cohort to those receiving RT within 2 months post-surgery showed results robust. **Conclusions:** In this older, population-base cohort, there existed a wide variation in the practice of adjuvant CRT. Adjuvant CRT, when compared with adjuvant RT alone, was associated with an increased risk of mortality and hospitalization with treatment-related toxicity.

6029 Poster Session (Board #352), Sat, 1:15 PM-4:45 PM

Application of a robust and novel ex vivo platform mimicking patient heterogenous tumor microenvironment for personalized cancer treatment. *First Author: Kanaka Govind Babu, Kidwai Memorial Institute of Oncology, Bangalore, India*

Background: Predicting clinical response to anticancer drugs remains a major challenge in the management of cancer. Recent advances show that Tumor Micro Environment (TME) and heterogeneity impact therapy outcomes; indicating the limitations of biomarker-guided strategies for personalizing therapy. There is a need for platforms that can predict treatment outcome with high fidelity by contextually integrating tumor heterogeneity and phenocopying the TME. **Methods:** Tumor and grade-matched matrix support along with autologous sera from individual patients were used to engineer personalized Tumor Ecosystems (TE) in head and neck, breast and colorectal cancers. We evaluated functional outcomes as a measure of response to a panel of anticancer drugs in this platform. In the training data set obtained from a cohort of 109 patients, TE read-outs were integrated with their corresponding clinical outcomes for generation of a machine learning (M-score) algorithm to predict clinical response to these drugs. This algorithm was further validated in a test group of 55 new patients. **Results:** Histopathological and molecular characterization of the tumor slices cultured in TEs revealed a close approximation to the parental tumor at baseline as confirmed by Ki-67 index, critical phosphoproteomic status, global transcriptomic profiles and balance in active components of tumor and stromal phenotypes. The M-score algorithm when applied to the test cohort of more than 100 patient tumors assessed in the functional TE achieved 100% sensitivity while keeping specificity in a desired high range for predicting short term clinical outcome. **Conclusions:** The high specificity and sensitivity observed in predicting clinical outcomes using the TE supports the use of this novel platform for personalized cancer treatment. (Part of the data is accepted in Nature Communication).

6030 Poster Session (Board #353), Sat, 1:15 PM-4:45 PM

Response rates, toxicity, and quality of life for locally regionally advanced head and neck squamous cell carcinoma after induction chemotherapy with weekly *nab*-paclitaxel, carboplatin, and cetuximab. *First Author: Jared Weiss, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC*

Background: Although induction studies of TPF have been negative, phase II studies of weekly carboplatin (CbP), paclitaxel and cetuximab (C225) have shown positive results. *Nab*-paclitaxel-based chemotherapy has demonstrated a higher response rate (RR) than solvent-based paclitaxel in SCC of the lung with favorable toxicity. **Methods:** Patients with treatment naïve SCCHN of any site with ≥ N2b disease or that was unresectable by strict criteria were eligible. Subjects were screened for risk of anaphylaxis to C225 with ELISA for IgE antibodies against galactose-α-1,3-galactose (alphagal); negativity was required for subjects residing in the SE of the US. Patients were treated with *nab*-paclitaxel 100mg/m^2, CbP AUC 2 and C225 400mg/m^2 week 1 then 250mg/m^{2}for six weeks, followed by standard of care (SOC) chemoradiotherapy (CRT). Herein we report the results of induction, including the primary endpoint of RR. **Results:** 62 subjects were screened; 20 were excluded due to positivity for alphagal, 1 withdrew consent and 5 were excluded due to other reasons; 36 were eligible and 35 have completed induction chemotherapy. Primary sites were: oropharynx (OPX) (23), larynx (3) and oral cavity (OC) (9). Grade 3/4 toxicity included rash (8), decreased neutrophil count (4), decreased white blood cells (2), fatigue (1), palmar-plantar erythrodysesthesia syndrome (1), and febrile neutropenia (1); there was no anaphylaxis to C225. All patients proceeded to SOC CRT. RRs to induction were: primary site 66%, nodal 79%, ORR 74%, CRR 26%, OPX 78%, p16+ OPX (17/19 with known status) 77%, larynx 100%, OC 56%. FACT-HN scores were (mean improvement in points, p): overall (5.3, NS) head/neck subscale (4.7, .046), swallow naturally and easily (1.6, 0.002) and voice quality and strength (0.9, .06). 24 patients are alive and NED, 3 are alive with PD, and 8 have died; median follow up of survivors is .7 years. **Conclusions:** The combination of *nab*-paclitaxel, CbP and C225 is very active against locally advanced SCCHN and toxicity is low. SCCHN-specific quality of life improved, particularly in speech and swallowing. Clinical trial information: NCT01412229.

	N1	N2b/c	N3
T1	0	3	1
T2	0	5	2
T3	1	5	1
T4	1	13	3

6031 Poster Session (Board #354), Sat, 1:15 PM-4:45 PM

A phase II study of axitinib in patients with recurrent or metastatic nasopharyngeal carcinoma (NPC). *First Author: Edwin Pun Hui, Partner State Key Laboratory of Oncology in South China, Sir Y K Pao Centre for Cancer, Department of Clinical Oncology, Hong Kong Cancer Institute and Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong*

Background: Axitinib has demonstrated potent in vitro and in vivo activity in preclinical models of NPC [*Cancer Res 2012;72(8 Suppl):Abstract 1373*]. We aimed to validate the findings in NPC patients (pts). **Methods:** This is an open label, single arm, phase II study of axitinib monotherapy in recurrent or metastatic NPC pts who failed at least one line of platinum based chemotherapy. Pts with Eastern Cooperative Group (ECOG) 0-1, adequate organ functions, and without local recurrence or tumor close to major vessels, received a starting dose of axitinib at 5 mg twice daily in continuous 4-weeks cycles until progression or unacceptable toxicity. Primary endpoint was clinical benefit rate (CBR), defined as % of pts achieving complete response (CR), partial response (PR) or stable disease (SD) by RECIST for > 12 weeks. Secondary endpoints included time to progression (TTP), overall survival (OS), safety and plasma axitinib pharmacokinetics (PK). Simon's Minimax two-stage phase II design (P0 = 0.50, P1 = 0.70, type I error 0.05, power 80%) was used to calculate the sample size (n = 37). **Results:** 37 pts were accrued. Median age was 53 (22-74). M:F = 32:5. Pts received a median of 3 lines of prior chemotherapy (range 1-6). 36 pts (97%) had prior radiotherapy and 2 pts (5%) had prior surgery for NPC. Axitinib treatment was delivered for a median of 4 cycles (range 1-21, 3 pts were still on treatment), with 15 pts (41%) received ≥ 6 cycles, 6 pts ≥ 10 cycles and 2 pts ≥ 18 cycles. 10 pts had dose reductions and 8 pts had dose escalations. Of 34 pts evaluable for response, CBR = 73.5% (95% CI: 60.7%-86.3%; 1 confirmed PR, 4 unconfirmed PR, 20 SD >12 weeks). Median TTP 5.4 months (95% CI: 3.9-5.9). Median OS 10.4 months (6.5-19.0). 1-year survival rate 43.6%. Treatment-related adverse events (AEs) by CTCAE v3, all grades (Gr) in ≥ 25% of pts: hypothyroidism 46% (Gr 3: 3%), fatigue 43% (Gr 3: 3%), hand-foot 43% (Gr 3: 3%), hypertension 32% (Gr 3: 5%), diarrhea 27% (Gr 3: 3%), mucositis 27% (Gr 3: 0%). Gr 3 AEs were uncommon (≤ 5%) and there was no Gr 4 or above treatment-related AE. All hemorrhages (16%) were Gr 1. PK data will be presented. **Conclusions:** Single agent axitinib achieved prolonged disease control with a good safety profile in this cohort of heavily pretreated NPC pts. Clinical trial information: NCT01249547.

6032 Poster Session (Board #355), Sat, 1:15 PM-4:45 PM

A gene expression profile to predict recurrence of advanced tongue squamous cell carcinoma (TSCC): Discovery and external validation. *First Author: Tomohiro Enokida, Division of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Extracapsular spread and positive microscopic surgical margins are known high risk factors of recurrence in head and neck cancer patients. However, molecular biological markers to predict recurrence have not been identified. Here, we aimed to identify markers of recurrence using DNA microarray profiling in patients with squamous cell carcinoma of the tongue (TSCC). **Methods:** We conducted exploratory Affymetrix gene expression profiling using 26 primary tumor tissue samples from patients meeting the following criteria: 1) histologically confirmed TSCC, 2) surgical resection of the primary tumor and lymph node dissection, and 3) follow-up for longer than one year after surgery. Median age and pathological stage were 60 years (37-85) and pStageIII/IV = 8%/92% (pT: 2/3/4a = 3/1/22, pN: 0/1/2a/2b/2c = 5/5/0/8/8), respectively. The relationship between gene expression pattern and relapse-free survival (RFS) was examined. Predictive candidate genes were independently validated using published survival and gene expression data similarly derived from 23 patients with oral SCC (http://www.ncbi.nlm.nih.gov/geo, GSE31056). **Results:** Cases were classified into clusters A (n = 10) and B (n = 16) by unsupervised hierarchical clustering analysis. RFS of cluster B was longer than that of cluster A (median RFS: not reached vs. 111days, p= 0.025) with a median follow-up period of 253 days (58-1341). The number of genes highly expressed by more than two-fold their expression in the opposite cluster was 175 in cluster A and 400 in cluster B. We then identified 27 genes with the most predictive value for recurrence, 5 genes highly expressed in the low-risk group (e.g. ALDH3A1) and 22 highly expressed in the high-risk group (e.g. MMP-10). Clustering into high- and low-risk groups based on this 27-gene expression in a validation study also showed a significant association with recurrence (median RFS: low-risk not reached vs. high-risk 25.1 months, p = 0.046) with a median follow-up of 13.27 months (1.43-59.67). **Conclusions:** We identified27 genes which could predict recurrence, indicating a promising candidate factor for high-risk relapse. A larger prospective study is warranted.

6033 Poster Session (Board #356), Sat, 1:15 PM-4:45 PM

Genomic landscape of anaplastic thyroid cancer. *First Author: Jaume Capdevila, Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain*

Background: Anaplastic thyroid cancer (ATC) is a rare and highly lethal malignancy. Chemotherapeutic agents and surgery have had no impact on local control or prognosis and novel actionable therapeutic targets are needed. Genetic instability of ATC has been often reported but comprehensive genomic landscape is unclear. **Methods:** We have performed Exome-seq on 13 cases of ATC (matched tumor-normal tissue/ peripheral blood), including two cases of concomitant papillary thyroid cancer (PTC) and ATC in the same patient (PTC, ATC, normal). **Results:** We identified several mutations in genes previously related with ATC, including TP53 (30%), RAS (29%), PIK3CA (23%), STAT (23%), BRAF (15%), and mutations in genes involved in SWI/SNF (15%), CDK (15%), and hedgehog (15%) pathways. The analysis of the two cases of concomitant PTC and ATC present in the same thyroid gland showed a significantly different genomic background with few common root mutations between both tumor entities (3 and 9 mutations respectively were present with a similar allelic frequency in both tumors). Clonal oncogenic BRAF and NRAS mutations were enriched in PTC but decreased in ATC, while other well-known driver mutations were only detectable in the ATC samples, including TP53, PI3KCA, STAT and PDGFR. Globally, our results suggest an early clonal divergence of PTC and ATC during tumor evolution. **Conclusions:** To our knowledge this is the first time where an early divergence on genomic evolution from PTC to ATC is suggested challenging the hypothesis of a multistep mutational model that leads from follicular thyroid cell to PTC and ATC. Candidate therapeutically actionable alterations have been identified.

6034 Poster Session (Board #357), Sat, 1:15 PM-4:45 PM

The SMART strategy: Subdividing M1 stage and aiming remission for target nasopharyngeal carcinoma patients with metachronous metastasis. *First Author: Lujun Shen, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Metastatic nasopharyngeal carcinoma (mNPC) varied greatly from potentially curable to incurable. This study set out to identify the target patients with chance of cure through extensive M1 stage subdivision and treatment response assessment. **Methods:** 1172 NPC patients with metachronous metastasis from three medical centers in Southern China were retrospectively analyzed (916 pts in derivation dataset; 256 pts in validation dataset). Various metastatic features were assessed, including involvement of specific locations, n of metastatic locations and n of metastatic lesions. A new nomenclature system for precise M staging was designed based on the independent prognostic factors. The best treatment response was assessed based on RECIST 1.1 or the modified RECIST criteria. **Results:** Multivariate analysis in derivation cohort showed that n of metastatic lesions, n of metastatic locations, liver involvement, bone involvement, together with age, UICC N stage, local recurrence, were independent prognostic factors for overall survival (OS). Subdividing the population by n of metastatic lesions and n of metastatic locations could result in subgroups with highly significant differences in OS. The external validation by two independent datasets showed congruent results. A new nomenclature system (M [n of locations]-Location [n of lesions in location]; B, bone; L, lung, H, liver, N, node) was designed, our data showed that mNPC patients with isolate metastatic lesion (M1-B_1, M1-L_1, M1-H_1, M1-N_1), and those with two lesions in liver only (M1-H_2) had high rates of complete remission (CR) or complete surgical resection (cSR), and 3-year OS after treatment (CR+cSR, > 30%; 3-yr OS, > 50%); for patients with more than three metastatic lesions in specific location (M1-B_m, M1-H_m) or multiple-location metastasis, the treatment response was generally poor, and the rates of cSR and 3-yr OS were low (CR, < 4%; cSR, 0%; 3-yr OS, < 30%). **Conclusions:** The SMART strategy could serve as a powerful tool in identifying the mNPC patients with chance of cure. More trials are needed to evaluate the feasibility and significance of achieving complete remission among the target patients.

6035 Poster Session (Board #358), Sat, 1:15 PM-4:45 PM

A meta-analysis of weekly cisplatin versus three weekly cisplatin chemotherapy plus current radiotherapy for advanced head and neck cancer. *First Author: Yue Zhang, Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China*

Background: Cisplatin based chemoradiotherapy (CRT) is the standard treatment for advanced head and neck cancer (HNC), currently the recommended doses are 30-40 mg/m^2 every week or 80-100mg/m^2 every three weeks. However, there has no meta-analysis to evaluate the adverse effects and survival events of the two schedules for HNC patients **Methods:** We conducted a systematic review and meta-analysis by searching PubMed, MEDLINE, ScineceDirect, Cochrane Library and China National Knowledge Infrastructure (CNKI) databases (1982-2015). Study endpoints included overall survival (OS), locoregional recurrence-free survival (LRFS), and grade ≥ 3 adverse events. Hazard ratios with 95% confidence intervals (95%CIs) were calculated for OS and LRFS, and risk ratios were for adverse events. Kaplan-Meier curves were read by Engauge-Digitizer, and RevMan 5.2 software was used to perform this meta-analysis. **Results:** 779 patients of 10 studies were eligible. There was no significant difference on OS (2-year: HR 1.05, 95%CI 0.61-1.81; 3-year: HR 1.12, 95%CI 0.68-1.85; 5-year: HR 1.79, 95%C 0.97-3.31) and LRFS (1-year: HR 1.26, 95%CI 0.46-3.46; 2-year: HR 1.14, 95%CI 0.51-2.56) between the patients treated with weekly and three weekly cisplatin CRT. Risk ratios of neutropenia, dermatitis and anemia were similar in the two groups. There was a trend that patients treated with weekly cisplatin had less gastrointestinal reactions than those of three weekly (RR = 0.59, p = 0.06). In subgroup analysis, patients in weekly group had more grade ≥ 3 mucositis when the primary disease located in oral cavity, oropharynx, hypopharynx or larynx (RR = 1.72, p = 0.01). In addition, the occurrence of therapy related delay or interrupt was obviously higher in weekly cisplatin compared to three weekly (RR = 2.37, P = 0.01). **Conclusions:** Three weekly cisplatin CRT didn't differ with weekly in OS and LRFS. Weekly cisplatin had higher risk in dermatitis, therapy delay and interrupt, but lower in gastrointestinal reactions. In subgroup analysis, threeweekly cisplatin had less grade ≥ 3 mucositis in non-nasopharynx of HNC patients, it might be more easily accepted by patients in terms of comfort or financial burden.

6036 Poster Session (Board #359), Sat, 1:15 PM-4:45 PM

A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). *First Author: Qinyang Li, Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China*

Background: The cisplatin (CDDP)-based CT is considered as the standard regimen for the treatment of moderate to advanced SCCHN. Recently, an alteration is made to carboplatin (CBDCA) because of its similar mode of action. We conducted a meta-analysis to compare the efficacies and toxicities of these two treatments. **Methods:** The search strategy included Pubmed, Science Direct, the Cochrane Library, China National Knowledge Internet Web. Statistical analyses were performed using RevMan 5.2. The primary endpoint was overall survival (OS) with secondary endpoints of locoregional control (LRC) and severe toxicity (grade $\geq$ 3). Hazard ratio (HR) and risk ratio (RR) were calculated using random- or fixed-effect models. Kaplan-Meier curves were read by Engauge-Digitizer. **Results:** Overall 12 studies and 1165 patients were included. CDDP-based CT significantly improved 5-year OS (HR = 0.67,95%CI 0.49-0.91;P = 0.01) compared to the CBDCA group. No difference in 3-year OS/LRC was observed (P = 0.08;P = 0.64), but a subgroup analysis showed a better 3-year OS in the CDDP arm for non-nasopharynx carcinoma (non-NPC) SCCHN (HR = 0.66,95%CI 0.48-0.91;P = 0.01). The CDDP-based CT was associated with more gastrointestinal toxicities (RR = 4.58,95%CI 1.57-13.37;P = 0.005) and nephrotoxicity (4/110 = 3.6%) compared to the CBDCA group, but less hematologic toxicities (anemia, leukopenia and thrombocytopenia) with RRs of 0.27 (95%CI 0.12-0.63),0.71 (95%CI 0.52-0.96),0.28 (95%CI 0.15-0.54). Risk of skin toxicity was identical. Moreover, we found that for non-NPC SCCHN, mucositis occurred more frequently and severely in CDDP-based treatment (RR = 3.55,95%CI 1.42-8.88;P = 0.007), whereas less for NPC (RR = 0.20,95%CI 0.09-0.45;P $<$ 0.0001). **Conclusions:** Patients with CDDP-based CT can achieve a higher OS, but there is no significant difference in LRC. The CDDP-based CT is associated with less hematologic toxicities but more gastrointestinal toxicities and nephrotoxicity compared to the CBDCA arm. Risk of mucositis in the CDDP group is higher for non-NPC SCCHN, but lower for NPC. The precise roles of CDDP and CBDCA in the management of SCCHN remain to be determined.

6037 Poster Session (Board #360), Sat, 1:15 PM-4:45 PM

Phase II study with conventional radiotherapy (RT) + cetuximab in patients with advanced larynx cancer who responded to induction chemotherapy (IC): An organ preservation TTCC study. *First Author: Ricard Mesia, Institut Catala d'Oncologia, Barcelona, Spain*

Background: IC with docetaxel/cisplatin/fluorouracil (TPF) is superior to PF in organ preservation. Bioradiotherapy (BRT) is superior to RT alone in the loco-regional control of locally-advanced head and neck tumors. The aim of our study was to evaluate the efficacy and safety of IC followed by BRT for functional larynx preservation. **Methods:** Phase II, open-label, multicenter study in patients with stage III-IVA laryngeal carcinoma candidates to total laryngectomy (TL). Study was designed to evaluate the laryngo-esophageal dysfunction–free survival (LEDFS) rate at 3 years. Using the one arm survival sample size program (SWOG), calculated recruitment: 94 patients (α .05; ß .1). Critical value $>$ 59%. Patients received 3 cycles of IC with TPF (75/75/750 mg/m^2): those who responded received conventional BRT (70 Gy/7 weeks) with cetuximab. Patients without response underwent TL + RT. Neck dissection was planned in patients with residual nodal disease at 2 months after BRT. **Results:** A total of 93 patients started TPF from October/2008 to February/2011: median age 59.4; 92% male; all PS: 0-1; 35% glottis / 65% supraglottis; 51% stage III / 49% IVA. Response to IC on larynx target lesion: 37 (40%) CR, 34 (37 %) PR, 8 (9 %) SD, 2 (2%) PROG and 12 (13%) not evaluated (2 death, 6 AEs, 3 missing, 1 lost follow-up). Overall response 72 (86 %). 73 (78%) patients followed by BRT: 68 as per protocol, but 2 with only SD and 3 without any response evaluation. Median follow-up: 48 months. 3-year actuarial rates: LEDFS: 69.5% (95%CI: 60-79%); laryngectomy-free survival: 71.2% (95% CI: 61-81%); overall survival: 77.2% (95%CI: 69-86%); disease-free survival: 47.9% (95%CI: 38-58%). TL was performed in 18 patients: 9 (9.7 %) after preservative treatment failure and 9 (9.7 %) in the follow-up (recurrences). The toxicity observed during both IC and BRT were as expected, with only 1 toxic related death (local bleeding during BRT). **Conclusions:** LEDFS rate was clearly higher than the critical value and with an acceptable toxicity with this protocol, so it is warranted to move to a phase III trial. Clinical trial information: 2008-000332-40.

6038 Poster Session (Board #361), Sat, 1:15 PM-4:45 PM

Bioradiotherapy for head and neck cutaneous squamous cell carcinoma. *First Author: Joshua David Palmer, Kimmel Cancer Ctr Thomas Jefferson Univ Hosp, Philadelphia, PA*

Background: Locally advanced, high-risk head and neck cutaneous squamous cell carcinomas (CSCC) are typically aggressive. We sought to compare treatment tolerability, disease control and survival between radiotherapy alone and radiotherapy plus cetuximab in CSCC patients. **Methods:** Patients diagnosed with high-risk CSCC based on NCCN criteria between 2006-2013 were included. Patients were divided into two groups: radiotherapy alone versus radiotherapy plus cetuximab. Primary analysis examined disease-free and overall survival, freedom from local and distant recurrence in the propensity score matched cohort. Propensity score analysis was performed with weighted factors including: Charlson Comorbidity Index score (age-adjusted), age. KPS, primary location, T and N stage, recurrent status, margin status, LVSI, PNI and grade. Toxicity was assessed using the CTCAE v4.0. **Results:** Among 68 patients meeting study criteria, we identified 29 treated with cetuximab plus RT and 39 with RT alone. Median follow-up for living patients was 30 months. Patients in the cetuximab group were more likely to have advanced N stage, positive margins and recurrent disease. After propensity score matching the groups were well balanced. OS and DFS were not statistically significant between the two groups but there were 37% more survivors free of disease in the cetuximab group. Loco-regional control was 77% and 54% in the cetuximab and radiation alone groups, respectively. The rate of distant metastases was lower in the cetuximab group 6.8% versus 17%. The incidence of grade 2-3 toxicity was 41% in the cetuximab group. There was one grade 3 cetuximab acneiform rash, one grade 4 dysphagia and no grade 5 toxicity. **Conclusions:** Although limited by small numbers; this therapy was well tolerated and there were more long-term survivors as well as less distant metastasis in the cetuximab group. This is the largest known report of CSCC patients treated with radiotherapy and cetuximab. These promising findings warrant further studies to establish the benefit of combined cetuximab and radiation in head and neck CSCC.

Disease-free survival by year in propensity score adjusted cohorts.

Years:		1	2	3	4	5
Weighted	Cetuximab	86%	72%	72%	66%	66%
	No Cetuximab	77%	53%	43%	39%	29%

6039 Poster Session (Board #362), Sat, 1:15 PM-4:45 PM

Alliance A091104: A phase II trial of MK-2206 in patients (pts) with progressive, recurrent/metastatic adenoid cystic carcinoma. *First Author: Alan Loh Ho, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recurrent/metastatic adenoid cystic carcinoma (ACC) is a rare, incurable disease with no standard treatments. MYB is an oncogenic driver in ACC that is often overexpressed via a t(6;9) translocation. Based on preclinical data that Akt inhibition with the allosteric inhibitor MK-2206 (Merck) can decrease MYB expression, we conducted this NCI/CTEP, Alliance cooperative group trial of MK-2206 in ACC pts. **Methods:** Pts with incurable ACC were enrolled. Radiographic or symptomatic progression documented within 6 months (mo) of enrollment was required. MK-2206 150 mg weekly was given; escalation to 200 mg was allowed. Primary endpoint was response (RR); secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. A Simon-Optimal two-stage design was used to detect a 20% RR (vs. 5%) (alpha = 10%; beta = 90%). $>$ 1 response(s) in the first 12 would trigger accrual to 37; $>$ 4 responses would be considered promising. Archival tissues were analyzed for MYB expression and rearrangement. Pre-/post-MK-2206 biopsies were obtained in 5 pts. **Results:** 16 pts were enrolled (10 F, 6 M). 12 of 16 were escalated to 200 mg. 9 of 16 pts (56%) had a grade 3/4 treatment-related adverse event (rash (38%), fatigue (19%) hyperglycemia (13%)). 14 pts were evaluable for efficacy. Best response included 13 stable disease and one disease progression. PFS at 12 mo was 9.2% (95% CI: 0.6-33.3%); median PFS (mPFS) was 9.2 mo (95% CI: 3.8-11.0). With a median follow-up of 17.1 mo, OS at 12 mo was 77.4% (95% CI: 44.9-92.1%). 12 of 14 tumors had detectable MYB by IHC; 8 of 14 had *MYB* gene rearrangement by FISH. Analysis of serial biopsies revealed Akt inhibition and MYB downregulation with MK-2206 therapy in 4 of 5 cases. **Conclusions:** The study was stopped after no PR was observed in the first stage. In this limited sample, the 9.2 mo mPFS may reflect disease stabilization in progressive pts that compares favorably to other ACC trials (axitinib phII: 3 PRs, mPFS 5.7 mo). Correlative tissue analyses provide the first *in vivo* evidence that clinical Akt inhibition can diminish MYB levels. Future studies should focus on PFS and further elucidate the therapeutic relevance of MYB suppression. (NCI-supported) Clinical trial information: NCT01604772.

6040 Poster Session (Board #363), Sat, 1:15 PM-4:45 PM

Comprehensive genomic profiling of salivary gland adenocarcinomas to reveal frequency of druggable targets. *First Author: Matthew J. Hawryluk, Foundation Medicine Inc., Cambridge, MA*

Background: Salivary gland adenocarcinomas (SAC) are a distinct group of frequently aggressive epithelial tumors. We queried whether the genomic alterations (GA) identified by comprehensive genomic profiling (CGP) in refractory and metastatic SAC could lead to potential targeted therapy selection. **Methods:** DNA was extracted from 40 microns of FFPE sections from 92 clinically advanced SAC. Comprehensive genomic profiling was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 682X for 3,230 exons of 236 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. The results were evaluated from each sample for all classes of genomic alterations. **Results:** There were 2 grade 1, 27 grade 2 and 63 grade 3 relapsed/refractory SAC in 30 (33%) female and 62 (67%) male patients with a median age of 59.6 years (range 25 to 84 years). There were 27 Stage III and 65 Stage IV cases. The majority (88%) of SAC harbored at least 1 clinically relevant alteration (mean 1.9 per patient) with a mean of 3.7 GA per tumor. GA occurred in 49 different genes including: *PIK3CA* (25%); *HRAS* (20%); *CDKN2A* (17%); *ERBB2* (15%); and *PTEN* and *NF1* (9%), *NOTCH1* and *MCL1* (8%), *EGFR* (5%), *KRAS* (4%) and *RICTOR*, *HGF*, *FBXW7* and *CDK4* (3%). The greater frequency of *ERBB2* alterations (15%) observed in SAC was significantly higher than observed in 110 similarly studied specialized salivary carcinomas including acinic cell, adenoid cystic and mucoepidermoid carcinomas (1%) ($p = 0.0001$). A similar increase in *HRAS* alterations of 18/92 (20%) SAC vs 4/110 (4%) in the specialized tumor group was also observed ($p = 0.008$). *PIK3CA*was altered in 25% of SAC vs. 5% in 110 specialized tumors ($p = 0.001$). **Conclusions:** SAC are a clinically aggressive and pathologically distinctive subset of salivary gland carcinomas. These tumors also differ significantly from the specialized salivary gland tumors in their genomic landscape. The high frequency of clinically relevant alterations in SAC including the 15% *ERBB2* alteration frequency suggests that continued molecular analysis of this tumor type has the potential to lead patients to clinical trials employing both established and novel targeted therapies.

6041 Poster Session (Board #364), Sat, 1:15 PM-4:45 PM

Hepatitis C virus seropositivity and head and neck cancers: A new trio. *First Author: Parag Mahale, Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas M.D. Anderson Cancer Center, Houston, TX*

Background: Hepatitis C virus (HCV) infection is associated with hepatocellular carcinoma [odds ratio (OR), 17] and non-Hodgkin lymphomas (NHL) (OR, 2). In 2009, we established the first clinic in US devoted to managing HCV-infected cancer patients (pts) where we observed a large number of pts with head and neck cancers (HNC). We aimed to test the association between HCV seropositivity (HCV-Ab$^+$) and HNCs. **Methods:** Medical records of cancer pts who were tested for HCV antibodies at MD Anderson between 6/2004 – 5/2014 were identified. Cases had first primary oropharyngeal cancers (OPCs) and non OPCs (cancers of oral cavity, nasopharynx, hypopharynx, and larynx). Lymphomas of OP/non OP region were excluded. Controls had smoking-associated cancers of lung, esophagus, and urinary bladder. Biopsy reports of OPCs tested for HPV by in-situ hybridization were obtained. Multivariable logistic regression models were constructed. **Results:** Of 34,545 cancer pts tested for HCV antibodies, 409 cases [OPC, 164 (40%); non OPC, 245 (60%)] and 694 controls [lung, 378 (55%); esophagus, 168 (24%); urinary bladder, 148 (21%)] were identified. OPC pts were mostly males (82% vs 68%; $p = .001$), with cancer diagnosed at younger age [median (yrs), 59 vs 63; $p < .0001$], better educated [$\geq$ bachelor's degree, 57% vs 38%; $p < .0001$], smoked fewer cigarettes [median pack-years (py), 24 vs 36; $p = .0001$] but more alcohol intake [drinks/week > 28, 23% vs 13%; $p = .002$] than controls. Non OPC pts were mostly males (77% vs 68%; $p = .01$), with cancer diagnosed at younger age [median (yrs), 59 vs 63; $p < .0001$], smoked fewer cigarettes [median py, 30 vs 36; $p = .2$], more alcohol intake [drinks/week > 28, 29% vs 13%; $p = .002$], and more HIV co-infected (4% vs 1%; $p = .05$) than controls. Adjusted models showed significant association of HCV-Ab$^+$ with OPCs (OR 2.1; 95% CI 1.1 – 4.2; $p = .02$) and non OPCs (OR 2.8; 95% CI 1.4, 5.7; $p = .005$). However, it was significant with only HPV$^+$ OPCs (OR 4.4; 95% CI 1.9 – 10.5; $p = .001$) but not HPV$^-$OPCs (OR 1.1; 95% CI 0.4 – 3.1; $p = .82$). **Conclusions:** HCV-Ab$^+$ may be associated with non-liver cancers such as HNCs, particularly HPV$^+$ OPCs. The strength of this association is as high as the one reported for NHLs. Further studies are warranted to explore this association and interaction of HPV with HCV.

6042 Poster Session (Board #365), Sat, 1:15 PM-4:45 PM

The role of cetuximab in induction chemotherapy: Comparison of APF-C (*nab*-paclitaxel, cisplatin, 5-FU + cetuximab) with APF, both followed by chemoradiation therapy (CRT), in patients with locally advanced head and neck squamous cell carcinoma (HNSCC). *First Author: Douglas Adkins, Washington University School of Medicine, St. Louis, MO*

Background: Cetuximab (C) improved overall survival (OS) in patients (pts) with HNSCC when added to definitive RT or to palliative chemotherapy; however, the role of cetuximab in induction chemotherapy is unclear. We hypothesized improved OS, disease-specific survival (DSS), and lower relapse rates with the addition of C to APF given as induction chemotherapy before CRT. A *nab*-Paclitaxel-based induction chemotherapy regimen was chosen because we observed better survival outcomes in comparison to a docetaxel-based regimen (*Cancer Medicine*2014). **Methods:** Two consecutive prospective phase II trials (APF and APF+C) were performed: 30 pts were treated with APF (weekly *nab*-paclitaxel 100 mg/m^2 and every 3 week cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2/day x 3) and 30 pts were treated with APF+C (APF + weekly cetuximab 250 mg/m^2). Pts were scheduled to receive three cycles followed by CRT (with cisplatin). **Results:** Pt and tumor characteristics for all 60 pts are as follows: median age 57 (38-74) yrs, smoking history 83% (50 pts), p16+ Oropharynx (OPSCC) 57% (34 pts), T classification (T2-16 pts; T3-24 pts; T4-20 pts) and N classification (N0/1-11 pts; 2-38 pts; 3-11 pts). The distributions of age, smoking history, p16+ OPSCC, T and N classifications were similar between the two treatment groups. Two year OS (APF-C 90%, APF 93%) and DSS (APF-C 97%, APF 97%) were excellent in both treatment groups and not significantly different (Table); however, disease relapse occurred in five pts in the APF+C group vs 1 pt in the APF group ($p = .61$, log rank). When stratified for p16+ OPSCC and p16-HNSCC, no significant differences in 2 year OS or DSS occurred between the two treatment groups. **Conclusions:** Two year OS and DSS were similar between APF+C and APF, even when stratified for p16 status. These preliminary data do not support the addition of cetuximab to APF. Clinical trial information: NCT01566435 and NCT00736944.

	APF (n = 30)	APF+C (n = 30)	
Survival Endpoint	**%**	**%**	**p value**
2 yr OS	93%	90%	.99*
2 yr DSS	97%	97%	.99
p16+ OPSCC 2 yr OS	94%	94%	.99
p16+ OPSCC 2 yr DSS	94%	100%	.99
p16- HNSCC 2 yr OS	92%	83%	.59
p16-HNSCC 2 yr DSS	100%	92%	.48

*Fisher's Exact test.

6043 Poster Session (Board #366), Sat, 1:15 PM-4:45 PM

A phase I trial of the addition of the CDK 4/6 inhibitor palbociclib to cetuximab in patients with incurable head and neck squamous cell carcinoma (HNSCC). *First Author: Loren S. Michel, Washington Univ School of Medicine, St. Louis, MO*

Background: Overexpression of cyclin D1 and inactivation of p16 occur in the majority ($> 90\%$) of HPV-unrelated HNSCC. Resistance to cetuximab and cisplatin, the two most effective systemic agents in HNSCC, is in part attributable to cyclin D1 overexpression which can be targeted with inhibitors of the cyclin D axis. Palbociclib is a selective inhibitor of CDK4/6. **Methods:** A phase I trial was performed to determine the maximum tolerated dose (MTD) of palbociclib added to cetuximab. Palbociclib was given orally q.d. on days 1-21 of each 28 day cycle and cetuximab was given weekly (400 mg/m^2, then 250 mg/m^2). Palbociclib was given at 100 mg/d (level 1) or 125 mg/d (level 2: max dose). Fibonacci (3+3) design was utilized. Eligible patients (pts) had incurable HNSCC (p16 -or +) and adequate organ function. Correlative studies included total and p- Rb (IHC), p16 (IHC), and PK analysis of palbociclib. Tumor response assessment using RECIST criteria 1.1 was performed every 2 cycles. **Results:** Nine pts were enrolled (5 platin and cetuximab-resistant and 1 cetuximab-resistant ; 5 p16- and 4 p16+): 3 pts on dose level 1 and 6 pts on dose level 2. Mild (grade 1/2) neutropenia and thrombocytopenia occurred in 2 pts on dose level 1 and in 4 and 3 pts, respectively, on dose level 2. The MTD was not reached as there were no dose limiting toxicities and no AE-related treatment discontinuations. Tumor response assessment following cycle 2 showed partial response in 2 pts (both at dose level 2; both p16 – HNSCC; one with cetuximab- and platin-resistant disease), stable disease in 5 pts (one with cetuximab-resistant disease with an 18% decrease in target lesions), progression in 1 pt, and not yet evaluable in 1 pt. Median time-to-progression was 112 (range: 28-182) days. **Conclusions:** The MTD of palbociclib was not reached during the phase I study; 125 mg/d given on days 1-21 of a 28 day cycle when added to cetuximab, was determined as the recommended phase II dose. Impressively, tumor responses occurred in pts with cetuximab- and platin-resistant HNSCC. Phase II of the trial is enrolling pts with p16-/Rb+ HNSCC on Arm 1 (platin-resistant disease) and Arm 2 (cetuximab-resistant disease). Clinical trial information: NCT02101034.

6044 Poster Session (Board #367), Sat, 1:15 PM-4:45 PM

Augmenting pre-operative risk of recurrence stratification in differentiated thyroid carcinoma using machine learning and high dimensional transcriptional data from thyroid FNA. *First Author: Steven I. Sherman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In addition to improving survival, a risk adapted approach to thyroid cancer therapy should minimize risk of recurrence. Currently, patients are classified post-operatively as high, intermediate or low risk of recurrence using 2009 ATA staging. Though clinically useful, this anatomic staging cannot be assessed pre-thyroidectomy, and does not include molecular predictors of outcome. Our goal was to determine if transcriptional data obtained from FNA of malignant thyroid nodules augment risk stratification before thyroidectomy. **Methods:** We used FNA material from 81 samples preoperatively collected in a previous study and post-surgically diagnosed as PTC. Each patient was categorized as either ATA low risk or ATA intermediate/high risk using established guidelines for recurrence risk stratification. Microarray expression data were obtained on all samples and supervised learning was used to train classifiers (Support Vector Machine (SVM), Random Forest (RF), penalized logistic regression (PLR), and an ensemble of the 3). Performance was measured using 10-fold cross-validation on the training cohort. **Results:** Classifiers were built using the top 70 genes from LIMMA models that controlled for BRAF status. Maximum classification performance of ATA low risk vs. ATA intermediate/high risk was observed for an ensemble classifier with a maximal area under the ROC curve (AUC) of 0.83. All the classifiers achieved similar AUCs: SVM 0.82, RF 0.82, and PLR 0.82. Genes useful in classification belong to transmembrane signaling pathways including ECM-receptor interaction, focal adhesion, and cell adhesion molecules. When applied to the training cohort, the ensemble classifier correctly identified 72.4% (21/29) of ATA low risk tumors and 82.6% (43/52) of ATA intermediate/high risk tumors. **Conclusions:** Transcriptional data from FNA of thyroid nodules may improve the pre-operative prediction of risk for post-operative recurrence. If independently validated in a sufficiently large number of patients, such molecular classifiers may augment initial risk stratification and individualization of patient care.

6045 Poster Session (Board #368), Sat, 1:15 PM-4:45 PM

Prognostic value of HPV detection with three primer sets in 255 Head-Neck cancers. *First Author: Cristiana Lo Nigro, Laboratory of Cancer Genetics and Translational Oncology, Oncology Dept, S. Croce Teaching Hospital, Cuneo, Italy*

Background: HPV-related patients (pts) with locally advanced head and neck cancers (LA-HNCs) have a better prognosis than the HPV-negative ones. This study aimed to investigate the prevalence of HPV infection in a series of LA-HNCs and to compare the prognostic value of E1, E6 and L1 genomic viral fragments, each other, in order to find the best prognosticator among them in terms of Overall Survival (OS) and Progression Free Survival (PFS). **Methods:** HPV was searched in 255 LA-HNC pts, 89 Oropharyngeal cancers (OPCs) and 166 non-OPCs, by DNA-PCR on formalin-fixed paraffin-embedded (FFPE) tissues using three specific primer pairs for type 16. Each pt was analysed simultaneously for the three viral primer sets and for a housekeeping gene to determinate the integrity of tumour DNA samples. **Results:** One hundred and thirty six out of 255 pts (53.3%) were HPV positive with at least one of the primer pairs used; pos E6 (51%) and L1 (29.8%) samples were the most common; while pos E1 samples were lower (13.7%). OPCs showed a significant higher % of pos samples compared to non-OPCs for each primer set tested and the prevalence proportions for each fragment analysed were kept in both groups, with the highest for E6 and the lowest for E1. Therefore each pt highlighted variable positivity for E1, L1 and E6 viral fragments. In this sense OPCs showed the higher % of pos pts for the three viral fragments concurrently (31.5%) compared to non-OPCs (4.2%), moreover E1 detection was always associated with E6 and L1 one. In term of prognostic value analysed for each fragment by itself, only E1 pos OPC pts showed improved OS ($p = 0.012$) and PFS ($p = 0.036$), while pos L1 and E6 ones did not show any gain according with either viral status. **Conclusions:** Though prevalence in HPV infection by DNA-PCR was significantly higher for E6 and L1 primer sets, the detected pos viral fragments seemed very weak prognosticators; on the contrary E1 might become a stronger prognostic marker for OS and PFS in OPC pts. In conclusion E1 by DNA-PCR appears to be clinically relevant in the present series of pts.

6046 Poster Session (Board #369), Sat, 1:15 PM-4:45 PM

Association of head and neck cancer (HNSCC) subgroups defined by HPV RNA status, gene expression patterns, and *TP53* mutations with lymph node metastasis and survival. *First Author: Andreas Dietz, University of Leipzig, Leipzig, Germany*

Background: Classification of HNSCC based on HPV16 DNA and RNA status, gene expression patterns, and mutated candidate genes may facilitate patient stratification. **Methods:** We compared tumors differing in HPV16 DNA and RNA (E6*I) status from consecutively recruited HNSCC patients by gene expression profiling (n = 270, Illumina HT12) and targeted sequencing (n = 226; 50 genes, Ion Torrent). Gene expression was analyzed unsupervised using consensus clustering. **Results:** HPV16 DNA+RNA+ tumors are molecularly distinct from HPV-negative (HPV DNA-) HNSCC, have elevated expression of cell cycle genes and carry rarely *TP53* mutations (3.6%, 1/28). HNSCC without transcriptionally active HPV16 (DNA+RNA-) are similar to HPV DNA- tumors in gene expression and *TP53* mutation frequency (47%, 8/17, and 43%, 72/167). We identify four gene expression clusters significantly differing in overall survival (OS; P = 0.04, adjusting for UICC stage, age, tumor site, treatment, pack-years smoked, alcohol use, HPV16 status). One cluster with high expression of immune response genes (IR) contains most (77%, 27/35) HPV16 DNA+RNA+ HNSCC. The IR cluster and disruptive *TP53* mutations ($TP53^{mut}$) are associated with lymph node metastasis (OR = 5.7; CI95% 2.2-18.0; P < 0.001, and OR = 2.6; CI95% 1.2-6.0; P = 0.01) independent of HPV16 status and tumor site. This validates the associations identified by Walter et al. (2013). Consistent with earlier studies, $TP53^{mut}$ has unfavorable prognosis (OS: HR = 2.0; CI95% 1.1-3.6; P = 0.03; PFS: HR = 1.9; CI95% 1.2-3.2; P = 0.01), adjusting for the UICC stage, age, tumor site, treatment, pack-years smoked, alcohol use, HPV16 DNA RNA status. **Conclusions:** Elucidation of HPV16 E6*I and $TP53^{mut}$ status are required for patient stratification. The IR gene expression cluster and $TP53^{mut}$ in HNSCC are associated with lymph node metastasis.

6047 Poster Session (Board #370), Sat, 1:15 PM-4:45 PM

Prognostic value of mid-treatment total lesion glycolysis in p16+ oropharyngeal cancer. *First Author: Erqi L. Pollom, Stanford University Medical Center, Stanford, CA*

Background: To determine whether total lesion glycolysis (TLG) measured during radiation for locally advanced oropharyngeal cancer (OPC) correlates with outcomes. **Methods:** Patients with Stage III-IVB, intact OPC treated with definitive chemoradiation were included if they underwent both pre- and mid-treatment planning PET scans. The TLG, defined as summation of the total standardized uptake values within the tumor volume, was extracted from within the primary and nodal tumor volumes contoured by the treating physician. TLG velocity was defined as the relative difference between pre- and mid-treatment TLG divided by weeks between the scans. **Results:** In total, 67 patients who fulfilled inclusion criteria were treated from February 2009 to January 2014 at Stanford. Median age was 59 years (range 27-83). p16 status was positive in 58 patients, negative in 8 patients, and unknown in 1 patient. Ten patients received induction chemotherapy; the majority of patients (58%) received platinum-based chemotherapy concurrently. Patients were treated to a median dose of 70 Gy (range 63.6-70 Gy, in 30-35 fractions). Median follow-up was 18.8 months (range 3.3-67.2 months). Two-year progression-free survival (PFS) and overall survival (OS) were 90% and 98%, respectively. Age, smoking status, p16 status, stage and chemotherapy did not predict for PFS or OS. Higher pre- and mid-treatment nodal TLG predicted for worse PFS/OS, while higher pre- and mid-treatment combined primary and nodal TLG predicted for worse PFS, regardless of receipt of induction chemotherapy. For the entire cohort, faster decrease in nodal TLG trended toward improved PFS (p = 0.09, HR 0.004, 95% CI 0-2.5). In the p16+ subset, faster decrease in nodal TLG predicted for improved PFS (p = 0.049, HR 0.001, 95% CI 0-0.98). When dichotomized by the lower quartile of nodal TLG velocity, p16+ patients who had > 3% decrease of nodal TLG/week had better PFS than those who did not (p = 0.009, HR 0.23, 95% CI 0.09-0.7), even with controlling for type of chemotherapy. **Conclusions:** Metabolic response, as characterized by nodal TLG velocity, during radiotherapy predicts for PFS in p16+ OPC patients and may aid with risk-adapting treatment.

6048 Poster Session (Board #371), Sat, 1:15 PM-4:45 PM

Effect of age and lenvatinib treatment on overall survival for patients with ^{131}I-refractory differentiated thyroid cancer in SELECT. *First Author: Marcia S. Brose, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: Lenvatinib (LEN) significantly prolonged progression-free survival (PFS) vs placebo (PB) in the phase 3 SELECT trial of patients (pts) with ^{131}I-refractory differentiated thyroid cancer (RR-DTC)–a benefit maintained in both younger ($\leq$ 65, median 56 years [y]) and older ($>$ 65, median 71 y) pts. In SELECT, median overall survival (OS) was not reached at data cutoff, and OS was not significantly different between LEN and PB (HR 0.73; 95% CI 0.50-1.07; $P = 0.103$). Here we examine the effect of age on OS in SELECT. **Methods:** Pts with RR-DTC and independent radiologic documentation of disease progression were stratified by region, prior VEGF-targeted therapy, and age (younger: LEN, n = 155; PB, n = 81 vs older: LEN, n = 106; PB, n = 50) and randomized 2:1 to LEN or PB. Median follow-up was 17.1 months at primary data cutoff (Nov 15, 2013); 83% of pts on PB crossed over to LEN following confirmed disease progression. **Results:** Median OS was not reached in any group except in older PB-treated pts (18.4 months; 95% CI, 13.3-20.3). A significant difference in OS was observed in older pts, favoring LEN (HR 0.53; 95% CI 0.31-0.91; $P = 0.020$). In a related analysis, there was no difference in OS between older and younger pts who received LEN (HR 0.78; 95% CI 0.49-1.26; $P = 0.304$), but there was a statistically significant difference in the PB arm, favoring younger pts (HR 0.48; 95% CI 0.27-0.85; $P = 0.010$). We examined possible reasons for this difference. There were no statistically significant differences between the age groups for the following factors: baseline ECOG performance status (LEN, $P = 0.56$; PB, $P = 0.46$), proportion of pts with prior VEGF-targeted therapy (LEN, $P = 0.270$, PB, $P = 0.757$), proportion of PB-treated pts who crossed over to receive LEN ($P = 0.441$), or the proportion of pts who received post-SELECT anticancer therapy (LEN, $P = 0.567$, PB, $P = 0.112$). Older pts did have a nonsignificant larger baseline median sum of target lesions (older: 64.9 mm; younger: 58.3 mm; $P = 0.113$). **Conclusions:** Older PB-treated pts with RR-DTC had worse OS than younger PB-treated pts in SELECT. This effect of age was completely mitigated by LEN treatment resulting in improved overall survival for pts $>$ 65 y treated with LEN. Clinical trial information: NCT01321554.

6049 Poster Session (Board #372), Sat, 1:15 PM-4:45 PM

Clinical trials outcomes of combined BKM120 and cetuximab compared to BKM120 in recurrent and/or metastatic squamous cell carcinoma of head and neck (R/M-SCCHN). *First Author: Hye Ryun Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*

Background: To investigate clinical activity, safety and biomarkers of a pan-PI3K inhibitor BKM120 in R/M-SCCHN and identify optimal combinations by conducting co-clinical trials. **Methods**: Patients with R/M-SCCHN who had progressed on platinum chemotherapy were eligible and treated with BKM120 100mg/day. The primary endpoint was DCR at 8 weeks. Secondary endpoints were RR, PFS, OS and safety. Patient-derived xenografts (PDXs) and cell lines (H01, H02) with genomic annotations were established from study patients to evaluate novel drug combinations. **Results:** A total of 37 patients were enrolled and evaluable for efficacy and toxicity. Patient characteristics included median age (55years); male (84%); ECOG 0/1 (19%/76%); locoregional/metastatic (30%/38%); oral cavity/oropharynx (38%/27%); prior chemotherapy regimens 1/ $\geq$ 2 (40%/60%). DCR at 8 weeks was 64.8% and RR was 2.7%. A responder harboring *PIK3CA*^{E542K}mutation had response duration of 53 weeks. Common toxicities were anorexia (62%) and hyperglycemia (59%). Median PFS and OS were 7.4 weeks and 19.2 weeks. In 3 PDXs established from patients showing progression, BKM120 was tested alone or in combination with cetuximab, afatinib, paclitaxel. All PDXs showed resistance to single-agent BKM120, resembling the responses of corresponding human cancers. Combined treatment of BKM120 and cetuximab showed strong synergistic inhibition of tumor growth, compared with either agent alone. Cell viability assay showed synergistic growth inhibition with combined BKM120 and cetuximab, compared with either agent alone. BKM120-induced AKT suppression did not attenuate FoxO phosphorylation, suggesting FoxO-mediated transcriptional upregulation of EGFR may not be responsible for synergy of combined PI3K and EGFR inhibition. Based on the integrated clinical and preclinical data, study protocol had been revised to combine BKM120 and cetuximab to explore whether cetuximab increases the efficacy of BKM120 in R/M-SCCHN. **Conclusions:** BKM120 showed modest efficacy in R/M SCCHN.A co-clinical trial provided a rationale to combine BKM120 and cetuximab for the treatment of R/M-SCCHN. Clinical trial information: NCT01527877.

6050 Poster Session (Board #373), Sat, 1:15 PM-4:45 PM

Response-adapted volume de-escalation (RAVD) of radiotherapy (RT) using induction chemotherapy (IC) in locally advanced head and neck squamous cell cancer (LA-HNSCC). *First Author: Victoria Meucci Villaflor, University of Chicago Med Ctr, Chicago, IL*

Background: Risk stratified treatment approaches are needed in LA-HNSCC. This study determined if RT volumes can be significantly reduced in IC responders without compromising disease control. **Methods:** Patients (pt) with measurable LA-HNSCC regardless of HPV status were treated with 2 cycles of IC (cisplatin 75 mg/m2, paclitaxel 175 mg/m2 day 1, and weekly cetuximab, with or without everolimus). Response to IC determined the extent of RT reduction. Pt with "good" response (GR), $\geq$ 50% reduction in the sum of gross tumor diameters, received TFHX (paclitaxel, fluorouracil, hydroxyurea, and twice daily RT to 75 Gy), with the planning target volume (PTV1) encompassing exclusively gross disease (RAVD). Pt with $<$ 50% response (NR) were treated with volumes encompassing PTV1 and the next nodal station at risk (PTV2) to 45 Gy, followed by a sequential boost to PTV1 to 75 Gy. **Results:** 94 pt were enrolled 5/2010 – 3/2014, median age 58 (range 27-76), 84% male, 58 pts HPV+ oropharynx (OP), 11 pt HPV- OP, 53% $>$10pk yrs tobacco use, 97% stage IV (56% T3/T4, 84% $\geq$ N2b). Everolimus was discontinued for futility at interim analysis after 25 pt. There were 37 (39%) GR to IC.At a median follow-up of 2 years, 79 pts are alive, 20 patients experienced failure. Site of first failure was locoregional in 10 (1 GR, 9 NR), distant in 7 (2 GR, 5 NR), and both in the remaining 3 pt (1 GR, 2 NR). Ultimate LRC was 91.5% on intention to treat analysis. Of 15 pts who experienced a component of LRF at any time, 14 (2 GR, 12NR) were within the RT treatment volume. One GR experienced LRF both within and outside the treated RT volume. Acute grade 3+ toxicities included 10% neutropenia, 22% dermatitis, 53% stomatitis. Rate of gastrostomy tubes (PEG) placement was 24% less during RT and 14% less at 1-yr follow up in RAVD pt. **Conclusions:** RAVD is a novel approach that uses response to IC to guide extent of RT volume reduction in both HPV (+) and (-) LA-HNSCC. In this trial, it appears that outcomes with RAVD are not compromised and long term toxicity may be improved. Further investigation is warranted. Clinical trial information: NCT01133678.

	1-year	2-year
OS	88.4% + 3.5	80.8% + 4.6
PFS	87.6% + 3.5	79.1% + 4.6
GR- PFS	89% + 5.1	86% + 5.8
NR-PFS	79% + 5.8	70% + 7.3

6051 Poster Session (Board #374), Sat, 1:15 PM-4:45 PM

Randomized phase II study of cabazitaxel versus methotrexate in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) previously treated with platinum-based therapy. *First Author: Sylvie Rottey, Ghent University Hospital, Ghent, Belgium*

Background: Cabazitaxel (caba) is a second-generation taxane that improves overall survival (OS) of patients with metastatic castrate resistant prostate cancer who progress on/after docetaxel. Caba has activity in SCCHN cell lines as well as in taxanes-resistant cell lines. We investigated cabazitaxel in recurrent SCCHN patients. **Methods:** Patients with non-curable SCCHN with an ECOG 0-2 and progressive disease within 1 year after platinum-based therapy were randomized between caba every 3 weeks (1st cycle : 20 mg/m2, increased to 25mg/m2 for the subsequent cycles, if no adverse event (AE) $>$ grade 3 during the 1st cycle) and methotrexate (MTX) (40 mg/m2/week). Stratification parameters were ECOG PS (0-1vs 2) and prior chemotherapy given for palliation versus the curative treatment. The primary endpoint was the progression free survival rate (PFSR) at 18 weeks (central review). This trial was a randomized phase II trial (P0 = 0.15, P1 = 0.3, a = 0.1, b = 0.1; Fleming one stage). **Results:** 101 patients (53 in caba and 48 in MTX) were randomized. The median age was 58 years (range 46-80), 63% had received prior platinum for recurrent disease and 37% as part of the multimodal therapy. 17% were ECOG PS 2. 37% had been previously treated with taxanes. PFSR at 18 weeks was 13.2 % (95% IC : 5-25%) for caba and 8.5% (95% IC : 2-20%) for MTX. Median PFS was 1.9 months in both arms. Median OS was 5 and 3.6 months for caba and MTX, respectively. No objective responses were recorded in both arms. More patients experienced Serious AE in caba than in MTX (54 vs 34%). The most common grade ¾ AE in the caba arm was febrile neutropenia (17.3%). Otherwise, the toxicity profile was as expected in both arms. **Conclusions:** This study did not meet the primary endpoint. Caba has low activity in recurrent SCCHN. Clinical trial information: NCT01528163.

6052 Poster Session (Board #375), Sat, 1:15 PM-4:45 PM

Predictive and prognostic values of post chemoradiotherapy PET/CT and the effect of salvage surgery on survival in head and neck squamous cell carcinoma (HNSCC). *First Author: Ryul Kim, Seoul National University Hospital, Seoul, Korea, Seoul, South Korea*

Background: The accuracy of ^{18}F-fluorodeoxygluocose positron emission tomography/computed tomography (PET/CT) for predicting immediate failure after radical chemoradiotherapy (CRT) in HNSCC remains poorly characterized. The purpose of this study was to evaluate 1) predictive and prognostic values of PET/CT for immediate failure after CRT, and 2) their impact on clinical decision making for salvage surgery. **Methods:** From 2005 to 2013, medical records of 132 consecutive LA-HNSCC patients who received radical CRT were analyzed. PET/CTs were taken before CRT and 3-months after CRT. Immediate failure was defined residual disease or locoregional/ systemic relapse within one year. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of SUV for predicting immediate failure were estimated. Overall survival (OS) of patients who had/had not salvage surgery according to SUV were compared. **Results:** Of the 132 patients, 71 (53.8%) achieved metabolic complete response (mCR) in post CRT PET/CT. mCR group had better OS comparing with non-mCR group (3-year OS rate 95.8% *vs.* 66.6%, $P < 0.001$), as well as progression-free survival (PFS) (3-year PFS rate 89.5% vs. 56.9%, $P < 0.001$). Immediate failure occurred in 4/71 patients with mCR, 24/61 patients with non-mCR ($P < 0.001$). Among the various metabolic values, the post CRT maximum SUV (postSUVmax) was found to be optimal for predicting immediate failure with corresponding cutoff point of 3.9. The area under the receiver operating curve was 0.82 (95% confidence interval [CI] 0.73-0.92). The sensitivity, specificity, NPV, and PPV were 71.4%, 83.7%, 91.6%, and 54.1%, respectively. Salvage surgery was conducted in 9 of 37 patients with postSUVmax $\geq$ 3.9. There was no significant difference in OS by immediate salvage surgery based on post CRT PET/CT compared with no immediate salvage operation (3-year OS rate 66.7% *vs.* 58.1%, $P = 0.719$). **Conclusions:** Post CRT PET/CT has prognostic value for OS and is useful for predicting immediate failure with high NPV. However, early detection of immediate failure and salvage surgery based on post CRT PET/CT does not seem to lead OS benefit.

6053 Poster Session (Board #376), Sat, 1:15 PM-4:45 PM

Quality of life (QOL) in a phase III randomized trial of standard fractionation radiotherapy (SFX) with concurrent cisplatin (CIS) versus accelerated fractionation radiotherapy (AFX) with panitumumab (PMab) in patients (pts) with locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): NCIC Clinical Trials Group HN.6 (NCT00820248). *First Author: Jolie Ringash, Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Addition of concurrent anti-EGFR monoclonal antibody to radiotherapy alone did not worsen QOL (Curran 2007). We compared standard chemoradiotherapy (cRT) to bioradiotherapy (bRT). **Methods:** Pts with T any N+M0 or T3-4N0M0 untreated LA-SCCHN were randomized 1:1 to receive SFX (70Gy/35/7 weeks) plus CIS at 100 mg/m^{2}intravenous (IV) for 3 doses on weeks 1, 4 and 7 versus AFX (70Gy/35/6 weeks) plus the anti-EGFR monoclonal antibody PMab at 9 mg/kg IV for 3 doses on weeks -1, 3 and 6. QOL was collected at baseline, end of RT, and 2, 4, 6, 12, 24 and 36 months post-RT using validated instruments FACT-H&N, MDADI and SWAL-QOL. All analyses were intent-to-treat. We hypothesized a 6-points more favourable change in FACT-H&N score from baseline to 1 year post-treatment in the bRT arm relative to cRT. **Results:** From 12/2008 to 11/2011, 320 pts were randomized, 160 to cRT and 160 to bRT, with median follow-up of 46.4 (range: 0.1-64.3) months. Median age 56, 84% male, ECOG PS 0 (71%), 1 (29%). Primary site was oropharynx in 81% (p16 +68%, - 11%, missing 21%), larynx (11%), hypopharynx (6%), oral cavity (2%). Smoking history was $>$ 10 pack-years in 58%, $<=$ 10 in 12%; 28% were never-smokers. All compliance exceeded 80%. Baseline scores did not differ by arm (cRT/bRT): FACT-H&N 110/110, MDADI Global 83/77, SWAL-QOL General 67/68. At 1 year, no statistically or clinically significant difference was seen between arms in FACT-H&N change from baseline: cRT 4.23, bRT 1.88, p = 0.129. Differences were only seen during the last week of radiotherapy, for (cRT: bRT): FACT-Physical Well-Being (-11.6, -10, p = 0.049), MDADI Physical subscale (-40.4, -33.9, p = 0.045), and SWAL-QOL Eating Duration (-61.2, -51.2, p = 0.02), Eating Desire (-53.3, -43.9, p = 0.031) and Mental Health (-42, -32.6, p = 0.009). No differences by arm on any scale were seen post-treatment. **Conclusions:** Despite transient benefits at the end of RT, the combination of PMab with AFX did not durably improve QOL as compared to SFX with CIS. Clinical trial information: NCT00820248.

6054 Poster Session (Board #377), Sat, 1:15 PM-4:45 PM

Long-term outcomes for radiotherapy alone verse combined chemoradiotherapy for patients with stage II nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy. *First Author: Man Hu, Department of Radiation Oncology, Shandong Cancer Hospital, Jinan, China*

Background: The use of chemotherapy (CT) in the treatment of stage II nasopharyngeal carcinoma (NPC) is controversial. And the reports especially about intensity-modulated radiotherapy (IMRT) have been limited. The purpose of this study is to evaluate the long-term survival outcomes for stage II NPC treated with radiotherapy alone verse combined chemoradiotherapyin the era of IMRT. **Methods:** We reviewed records between January 2002 and December 2013 and identified 182 patients who were histologically diagnosed as stage II NPC received RT with or without CT in Shandong Tumor Hospital. Among these patients, 52 were restaged $T_2N_0M_0$ and the other 130 were restaged $T_{1\text{-}2}N_1M_0$. One hundred and fifty-nine (38 in $T_2N_0M_0$ and 121 in $T_{1\text{-}2}N_1M_0$) received RT with CT (RT/CT) and 23 (14 in $T_2N_0M_0$ and 9 in $T_{1\text{-}2}N_1M_0$) underwent RT alone. The overall survival (OS), progression-free survival (PFS), locoregional failure-free survival (LRFF), and disease metastasis-free survival (DMF) were calculated with Kaplan-Meier method. **Results:** With a median follow-up of 63.6 months (range 9.4 to 145.7), the 3-year, 5-year and 10-year OS of all stage II patients were 93.2%, 87.5% and 65.4%. For patients with staged $T_2N_0M_0$, the corresponding rates were 92.3%, 89.9%, 82.6% and for those with $T_{1\text{-}2}N_1M_0$, they were 93.6%, 86.6%, and 63.2%, respectively. No significant difference in OS, PFS, LRFF and DMF were observed between RT/CT group and RT alone group ($p = 0.217, 0.768, 0.340$ and 0.415, *respectively*). All locoregional recurrence occurred in the first 3 years and all distant metastases were developed in patients staged $T_{1\text{-}2}N_1M_0$, referring more aggressive therapy such as chemotherapy may be indicated for these patients. **Conclusions:** This is the largest cohort of patients with stage II NPC in the era of IMRT with long follow-up. Chemotherapy showed no additional benefit for patients with stage II NPC. Patients staged $T_2N_0M_0$ had an excellent outcome treated with RT alone. And for those staged $T_{1\text{-}2}N_1M_0$ who had a higher risk for distant metastasis, additional chemotherapy may be perferred.

6055 Poster Session (Board #378), Sat, 1:15 PM-4:45 PM

Concurrent chemoradiation using weekly versus tri-weekly cisplatin in locally advanced squamous cell carcinoma of the head and neck (SCCHN): A comparative analysis. *First Author: AMR MOHAMED, Morehouse School of Medcn, Atlanta, GA*

Background: Cisplatin based chemoradiation (CRT) is the standard of care for most patients with locally advanced SCCHN. We conducted a systemic review to compare the efficacy and safety profile of weekly versus tri-weekly cisplatin administration in patients with locally advanced SCCHN **Methods:** All prospective studies between 1970- 2013 were independently identified by three authors for inclusion. Studies were excluded if induction therapy was part of the treatment regimen, 5-FU or other targeted therapy was used, cisplatin has been used intra-arterially, orally or in the post-operative setting or if the total dose of cisplatin was less than 180mg/m^2, or radiation dose of less than 60 GY. Clinical outcomes were extracted and analyzed using weighted estimates. Two-tailed T-test was used for all comparisons with a significance level of 0.05 **Results:** Out of 120 studies, 23 with a total of 2,303 patients qualified for inclusion. The number of patients treated with weekly cisplatin was 915 (84% males) and tri-weekly was 1388 (84% males). Both groups received median dose of radiation of 70 Gy. Overall response rate for weekly cisplatin was 88% (CI 0.73-0.95) and 63.5% (CI 0.47-0.76) for tri-weekly cisplatin (P = 0.06). The 2-y, 5-y survival rate (SR) and weighted median overall survival (OS) for weekly vs. tri-weekly cisplatin were 89% vs. 75% (P = 0.28), 81% vs 63% (P = 0.18), and 28 vs 27 mos. (P = 0.33), respectively. The 2-y PFS rate was 81% vs 62%, P = 0.26 for weekly and tri-weekly cisplatin, respectively while locoregional failure free rate was 39% (CI 0.16- 0.67) vs. 44% (CI 0.24-0.65); P = 0.8. Grade 3-5 toxicity was 46% in weekly vs 56.5% in tri-weekly cisplatin (P = 0.23) **Conclusions:** Weekly cisplatin combined with radiation in locally advanced SCCHN is comparable in efficacy and safety to tri-weekly based regimens. Our analysis provides supportive evidence for the use of either weekly or triweekly regimens. Based on our results, tolerability ought to be a key factor in determining the choice of cisplatin schedule in locally advanced SCCHN

6056 Poster Session (Board #379), Sat, 1:15 PM-4:45 PM

Genomic landscape of salivary gland tumors. *First Author: Sheryl Krevsky Elkin, N-Of-One, Inc., Lexington, MA*

Background: Effective targeted treatment options for advanced salivary gland tumors are lacking. In order to better understand these tumors, we assessed their genomic landscape. **Methods:** We studied 117 patients with salivary gland tumors that were, on physician request, tested in a Clinical Laboratory Improvement Amendments (CLIA) laboratory (Foundation Medicine, Cambridge, MA) using next-generation sequencing (182 or 236 genes), and analyzed by N-of-One, Inc. (Lexington, MA). **Results**: There were 354 total aberrations, with 240 distinct aberrations identified in this patient population. Only 10 individuals (8.5%) had a molecular portfolio that was identical to any other patient (with four different portfolios amongst the ten patients). The median number of aberrations/patient was three (range, 0 to 10). The most common abnormalities involved the *TP53* gene (36/117 [30.8% of patients]), cyclin pathway (*CCND1*, *CDK4/6* or *CDKN2A/B*) (31/117 [26.5%]) and PI3K pathway (*PIK3CA, PIK3R1*, *PTEN* or *AKT1/3*) (28/117 [23.9%]). In multivariate analysis, statistically significant co-existing aberrations were observed as follows: *TP53* and *ERBB2* ($p = 0.01$), cyclin pathway and *MDM2* ($p = 0.03$), and PI3K pathway and *HRAS* ($p = 0.0001$). We were able to identify possible cognate targeted therapies in most of the patients (107/117 [91.5 %]), including FDA-approved drugs in 80/117 [68.4%]. **Conclusions:** Salivary gland tumors are characterized by multiple aberrations that mostly differ from patient to patient. Significant associations between aberrations in *TP53* and *ERBB2*, the cyclin pathway and *MDM2,* and *HRAS* and the PI3K pathway were identified. Most patients had actionable alterations. These results provide a framework for tailored combinations of matched therapies.

6057 Poster Session (Board #380), Sat, 1:15 PM-4:45 PM

The phase III clinical study about the effect of Kangfuxin Solution (Chinese herbal medicine compound preparation) on the radiation induced oral and upper gastrointestinal mucositis in nasopharyngeal carcinoma patients. *First Author: Jin Yi Lang, Sichuan Cancer Hospital and Institute, Chengdu, China*

Background: The incidence of oral mucotitis was high in NPC patients treated with radiation. Till now, there was no efficient drug to prevent and treat it. Kangfuxin solution was the Chinese herbal medicine compound preparation, and it could promote angiogenesis and repair mucosa. We aim to observe the effect of it on radiotherapy-induced oral mucositis (OM) and upper gastrointestinal mucositis in NPC patients. **Methods:** 240 pathological confirmed squamous NPC patients from five multi-centers clinical departments were included in this study. They were randomized divided into the control group and treatment group in. Stage I, II, III and IV were all included (AJCC 2010). All the patients received radical chemoradiotherapy. The treatment group used the traditional Chinese medicine (Kangfuxin Solution, 10ml tid) for mouthwash from the beginning of radiotherapy. The control group used Compound Borax Solution (10ml tid) for mouthwash. CTCAE v3.0 and verbal rating scales (VRS) was used to evaluate the incidence and OM grade, upper gastrointestinal mucositis and the pain grade during in different phases of radiation. **Results:** 230 effective patients were used for clinical effects evaluation in the study. Compared to control group, the incidence and grade of OM was significantly lower in treatment group ($p< 0.01$). The time from beginning of radiation to different grade of mucositis occurance (Grade 1, 2, 3) was longer in treatment group ($p< 0.05$), and the accumulated radiation dose was also higher in treatment group comparing to the control group ($p< 0.05$). For upper gastrointestinal mucositis and pains, the grade was lower in treatment group during radiation comparing to the control group ($p< 0.05$). There was no side effect of Kangfuxin solution in the study. **Conclusions:** Kangfuxin solution could prevent and treat the radiotherapy-induced oral and upper gastrointestinal mucositis to some extent. The incidence and grade were all decreased in the Kangfuxin group. This traditional Chinese medicine was safe and effective, and it might be widely used in the clinical practice in the future.

6058 Poster Session (Board #381), Sat, 1:15 PM-4:45 PM

Mucoadhesive clonidine (Clonidine Lauriad) in the prevention of severe radiomucositis in head and neck cancer patients: A phase II randomized trial. *First Author: Jordi Giralt, Hopital General Val D Hebron Barcelone, Barcelone, Spain*

Background: Oral mucositis (OM) is the most frequent and severe complication of chemoradiotherapy (CRT) in head and neck cancer patients. There is currently no effective mechanistically-targeted intervention for CRT-induced OM. NF-κB plays a central role in the signaling cascades and pathways responsible for OM. Clonidine reduces NF-κB activation and the subsequent expression of pro-inflammatory cytokines. In preclinical studies, topical clonidine reduced the incidence and duration of severe OM (SOM). The safety and efficacy of 2 doses of clonidine MBT were evaluated in patients with head and neck cancer receiving postoperative CRT. **Methods:** This phase 2, multicenter, double-blind, randomized, placebo-controlled, 3-arm study compared clonidine MBT 50μg, 100μg, and placebo. Clonidine MBT and matching placebo were applied to the gum once daily 1-3 days prior to RT until the end of CRT. The primary endpoint was the cumulative radiation dose at the onset of SOM (WHO grade 3 or 4) analyzed by the Kaplan-Meier method and the log-rank test. Safety was evaluated by monitoring AEs, clinical laboratory parameters, vital signs, and physical examinations. **Results:** Clonidine MBT was administered to 121 patients and placebo to 62. SOM developed in 45.3% of patients in the clonidine MBT group and in 60.0% of patients in the placebo group ($p = 0.064$). Patients developed SOM at a median radiation dose of 60.0 Gy and 48.0 Gy for the clonidine MBT and placebo groups, respectively (HR = 0.754 [0.484; 1.175]; $p = 0.211$). The percentage of AEs was similar between placebo (98.4%) and clonidine MBT groups (90.8%) with less nausea (49.6% vs 71%) and dysphagia (32.8% vs 48.4%) in the clonidine MBT groups vs placebo. **Conclusions:** Here, we present for the first time, that clonidine MBT treatment in head and neck cancer patients undergoing postoperative CRT reduces SOM with minimal toxicity. However not statistically significant, the observed differences in the incidence and time to occurrence of SOM support the initiation of future confirmatory studies. Clinical trial information: NCT01385748.

6059 Poster Session (Board #383), Sat, 1:15 PM-4:45 PM

Molecular profiling of tumour budding to implicate TGF-β mediated epithelial-mesenchymal transition as a therapeutic target. *First Author: David Hebbelstrup Jensen, Rigshospitalet, Copenhagen, Denmark*

Background: Tumor budding is an adverse prognostic factor in many types of cancer and understanding of the molecular basis of this phenomenon may provide new therapeutic options. **Methods:** The number of tumor buds in 199 oral squamous cell carcinoma (OSCC) patients was correlated to metastases, disease-free and overall survival. Tumor buds and paired central-tumor areas were laser-capture-microdissected from 5 OSCC specimens and examined with RNA-sequencing and miRNA-qPCR arrays. Results were validated with immunohistochemistry in 199 and *in situ* hybridization (ISH) in 20 OSCC samples. **Results:** The number of tumor buds was predictive of the presence of lymph node metastasis at presentation, and was an *independent* predictor of overall survival. Compared to cells in the central parts of the tumors, budding cells exhibited a particular gene expression signature comprising factors involved in epithelial-to-mesenchymal transition (EMT) and activated TGF-β signaling. Transcription factors *ZEB1* and *PRRX1* were upregulated concomitantly with a decreased expression of mesenchymal-to-epithelial (MET) transcription factors such as *OVOL1* in addition to Krüppel-like factors and Grainyhead-like factors. Moreover, the *miR-200* family members, was identified to be down-regulated in budding tumor cells. Five markers of the EMT/MET process were validated with immunohistochemistry and ISH. **Conclusions:** Taken together the results imply that therapeutics based on the inhibition of TGF-β signaling may prove useful in the treatment of oral squamous cancers.

6060 Poster Session (Board #384), Sat, 1:15 PM-4:45 PM

A randomized phase II trial of the MET inhibitor tivantinib + cetuximab versus cetuximab alone in patients with recurrent/metastatic head and neck cancer. *First Author: Everett E. Vokes, Department of Medicine, University of Chicago, Chicago, IL*

Background: MET signaling has been proposed as a mechanism of resistance to anti-EGFR therapy. MET expression is common in Head and Neck Squamous Cell Carcinomas (HNSCC) (*Seiwert et al, Cancer Res 2009*). We compared the oral MET inhibitor tivantinib (ARQ197) (T) in combination with cetuximab (C), with C monotherapy, in patients (pts) with recurrent/metastatic (r/m) HNSCC. **Methods:** 78 cetuximab-naïve pts after platinum failure were enrolled from 2012-2014, 40 on the T+C arm, and 38 on the C control arm. 31 pts (40%) were HPV-positive/p16-positive oropharyngeal (OP) cancers. T was given orally 360mg BID, C 500mg/m2 every two weeks. Cross-sectional imaging was performed every 8 weeks. Primary outcome was response rate (RECIST 1.1), and secondary outcomes included survival. **Results:** In 75 pts currently assessable for response, the response rate in the T+C arm was 8.5% (N = 3, including one CR), and 5.3% (N = 2) in the C alone arm (NS). Of note the response rate in HPV-positive/p16-positive oropharyngeal HNSCC pts was 0% in both arms in a combined 31 HPV-positive/p16-positive OP HNSCC. The response rate in HPV-negative pts was 12.5% (T+C)/ 8.5% (C) (NS). Median PFS in both arms was 4 months (NS), median OS 8 months (NS). Both treatments were well tolerated with a trend towards increased hematological toxicities in the T+C arm (12.5% of pts experience grade 3 leukopenia). **Conclusions:** Tivantinib + Cetuximab given in an unselected population of r/m HNSCC pts does not significantly improve response rate and survival. Consistent with other recent reports (Fayette et al ESMO 2014; Machiels et al ESMO 2014), EGFR inhibitors, including cetuximab appear to be less active/inactive in HPV-positive/p16-positive oropharyngeal HNSCC patients. Clinical trial information: NCT01696955.

6061 Poster Session (Board #385), Sat, 1:15 PM-4:45 PM

Evaluation of the impact of tumor HPV status on outcome in patients with locally advanced unresectable head and neck squamous cell carcinoma (HNSCC) receiving cisplatin, 5-Fluorouracil with or without docetaxel: retrospective analysis of EORTC24971 study. *First Author: Amanda Psyrri, Attikon Hospital National Kapodistrian University of Athens, Athens, Greece*

Background: EORTC 24971 was phase III trial demonstrating superiority of induction regimen TPF over PF, in terms of progression-free (PFS) and overall survival (OS) in locally advanced unresectable HNSCC. We conducted prospective-retrospective analysis with the aim to evaluate whether only HPV negative patients(pts) derive benefit from adding docetaxel to PF, in which case de-intensifying induction treatment in HPV+ patients could be considered. **Methods:** HNSCC specimens were collected from 1999 until 2002. Pre-therapy tumor biopsies (blocks or slides) were assessed for high risk (HR) HPV by p16 immunohistochemistry, PCR and quantitative PCR (qPCR). HPV DNA+ and/or p16+ tumors were subjected to in situ hybridization (ISH) and HPV E6/7 oncogene expression analysis by quantitative reverse transcriptase. The primary and secondary objectives were to evaluate the value of HPV/p16 status as predictive factor of treatment benefit in terms of PFS and OS, respectively. The predictive effect was analyzed based on the model used in the primary analysis of the study with the addition of a treatment by marker interaction term and tested at two-sided 5% significance level. **Results:** A total 120 of 358 patients had available tumor samples and 59 of them had oropharyngeal cancer. Median follow-up was 8.7 years and data updated through 2011. Sixteen of 119 (13%) evaluable samples were p16 positive and 20 of 79 (25%) evaluable tumors were HPV+ by PCR or qPCR. 12/31 pts assessed with HPV DNA ISH were positive and 12 of 28 pts assessed for HPV16mRNA were positive. The pre-planned analysis showed no statistical evidence of predictive value of p16/HPV status for PFS ($p = 0.287$) or OS ($p = 0.118$). **Conclusions:** The incidence of HPV positivity was low in EORTC 24971 cohort. In this prospective- retrospective analysis only powered to detect a large treatment by marker interaction there was no statistical evidence that treatment effect found overall was different in magnitude in HPV positive or HPV negative patients. These results do not justify selection of TPF versus PF according to HPV status.

6062 Poster Session (Board #386), Sat, 1:15 PM-4:45 PM

Treatment-associated mortality in head and neck cancer receiving chemotherapy and radiation: Meta-analysis of published trials. *First Author: Paolo Bossi, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Concurrent chemoradiation (CTRT) produces an advantage in survival as compared with RT alone in locally advanced head and neck squamocellular cancer (HNSCC), while exposing patients (pts) to more severe toxicities. CTRT associated early mortality rate (during and until 90 days after treatment end) has not been consistently described. **Methods:** We conducted a meta-analysis of phase II-III randomized controlled trials (RCTs), observational studies or case series of HNSCC matching these criteria: concurrent CTRT; conducted in both radical and postoperative setting; published from 1/2000 to 6/2014; involving 100+ pts; with available toxicity data. Case series were considered only if presenting homogeneous treatment modalities. Early death incidence was analyzed and related to the following variables: radical vs postoperative setting, induction chemotherapy, poly vs mono CT concurrent with RT, conventional vs altered RT fractionation and study design (RCT vs observational vs case series). **Results:** Of 732 papers identified, 36 were included in the analyses (13 case series, 7 observational, 16 RCTs). Data regarding population, acute toxicities and deaths were extracted. A total of 9164 pts were considered with 183 early deaths (incidence rate 2.1% (95% CI 1.5% – 2.8%). Subgroups analyses on the basis of type of study design revealed differences between treatment-associated deaths reported in observational studies (0.8%; 95% CI 0.5% – 1.5%) compared to RCTs (2.7%; 95% CI 1.8% - 4.0%) and case series (2.7%; 95% CI 1.7% - 4.2%). A quantitative interaction seems to exist when the size of the effect is related to the radical intent with respect to postoperative setting (mortality rate 2.4% vs 0.2%; p value 0.03), but no interaction is found with induction chemotherapy, poly or mono CT and conventional or altered RT regimens. **Conclusions:** CTRT in HNSCC resulted in about 2% of early death, with higher rate in the radical setting. Observational studies underestimate mortality, probably due to bias selection or to inconsistent reporting. Early mortality rate reduction may imply better patient selection and more intensive supportive care programs.

6063 Poster Session (Board #387), Sat, 1:15 PM-4:45 PM

***MLH1*, *MSH2*, *MSH3* and *EXO1* polymorphisms and head and neck squamous cell carcinoma risk and prognosis.** *First Author: Gustavo Jacob Lourenco, Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil*

Background: *MLH1* c.-93G > A, *MSH2* c.211+9C > G, *MSH3* c.3133G > A, and *EXO1* c.1765G > A polymorphisms have been associated with inefficient DNA mismatch repair (MMR). However, it is unknown whether they are involved with increased risk and prognosis of head and neck (HN) squamous cell carcinoma (SCC), therefore, this study aimed to clarify this issue. **Methods**: Genomic DNA from 450 HNSCC patients and 450 controls was analyzed by PCR-RFLP or real time PCR for discrimination of genotypes. The differences between groups were analyzed by χ^2 or Fisher's exact test. Multivariate analysis using the logistic regression model served to obtain age and tobacco status adjusted crude odds ratios with 95% confidence intervals (CI), and to assess the associations between genotypes and HNSCC. Relapse-free survival (RFS) and overall survival (OS) times were calculated using Kaplan-Meier estimate probabilities and differences between survival curves were analyzed by the log-rank test. The prognostic impact of genotypes was examined using univariate and multivariate Cox regression analyses. **Results**: *MSH2* GG plus *MSH3* GG (31.7% vs. 18.7%, P= 0.003) genotypes were higher in laryngeal SCC (LSCC) patients than in controls. Carriers of the respective combined genotype were under a 3.69 (95% CI: 1.54-8.81)-fold increased risk of LSCC. The median follow-up time of overall HNSCC patients enrolled in study was 46.0 months (1.6-166.0). At 60 months of follow-up, RFS was shorter in patients with *EXO1* GG genotype (54.8% vs. 61.1%, P= 0.03) and OS was shorter in patients with *MSH3* GG genotype (42.8% vs. 52.5%, P= 0.02) compared to those with other genotypes, respectively. After multivariate Cox analysis, patients with *EXO1* GG and *MSH3* GG genotypes had worst RFS (HR: 1.50, 95% CI: 1.03-2.20, P= 0.03) and OS (HR: 1.59, 95% CI: 1.19-2.13, P= 0.002) than those with the remaining genotypes, respectively. **Conclusions**: Our data present, for the first time, evidence that inherited *MLH1* c.-93G > A, *MSH2* c.211+9C > G, *MSH3* c.3133G > A, and *EXO1* c.1765G > A abnormalities of DNA MMR pathway are important determinants of HNSCC and predictors of patient outcomes. Our findings, once validated in additional studies, will contribute to personalize the therapy of HNSCC patients.

6064 Poster Session (Board #388), Sat, 1:15 PM-4:45 PM

Outcomes of head and neck squamous cell carcinomas (HNSCC) treated with reirradiation (RRT) at Mayo Clinic. *First Author: Kelly Kevelin Curtis, Mayo Clinic, Scottsdale, AZ*

Background: RRT is offered as definitive (DRRT) or post-operative (PRRT) treatment for patients (pts) with loco-regionally recurrent (LRR) or new primary (NP) HNSCC in previously irradiated volumes. We report the results of a retrospective chart review of all consecutive pts with LRR and NP HNSCC treated with DRRT and PRRT at Mayo Clinic. **Methods:** We included LRR and NP HNSCC pts treated with DRRT/PRRT from 2003-2011 at all Mayo Clinic campuses. Patient and treatment related data were collected. Loco-regional recurrence rate (LR) and distant metastases rate (DM) at 2 years, and overall survival (OS) from end of RRT using Kaplan-Meier methods, were calculated. **Results:** We identified 89 pts (68 M, 21 F). 67 pts had LRR; 22 NP. Treatment included salvage surgery with PRRT (47 pts) and DRRT (42 pts). 30 pts received concurrent chemotherapy (CT) with PRRT; 33 DRRT pts received CT. Median prior RT dose was 66 Gy (26.4 – 79.2 Gy). Median PRRT dose was 60 Gy (11 – 70 Gy). Median DRRT dose was 69.6 Gy (18 – 76.8 Gy). LR occurred in 42 pts (47%) after RRT; 35 pts (39%) had LR by 2 years (95% CI, 30 – 50%). DM occurred in 20 pts (22%) after RRT; 16 pts (18%) had DM by 2 years (95% CI, 11 – 27%). Median OS was 22.2 mos (95% CI, 17.0 – 29.8 mos), with 2- and 5-year OS 47% and 16%. No difference in OS between LRR- and NP-HNSCC or PRRT and DRRT was found. CT was associated with shorter time to LR (4.3 vs. 12.1 mos, $p = 0.008$), but not with time to distant metastases or OS. At last follow-up (median 78.1 mos) 21 pts (24%) were alive, with 43.3 mos (95% CI, 27.6 – 52.9 mos) median OS from time of LRR/NP. Among surviving pts, 2 cases of osteoradionecrosis (10%) and 1 carotid artery pseudoaneurysm with sentinel bleed (5%) were reported, with no reported spinal cord injuries. OS was better among 70 pts treated to at least 60 Gy ($n = 70$) vs. pts treated with less than 60 Gy (median OS 25.2 mos, 95% CI, 19.4 – 32.0 mos; vs. median OS 9.5 mos, 95% CI, 6.8 – 28.7 mos; $p = 0.06$). **Conclusions:** RRT cures a small number of pts. 2-year OS of LRR/NP HNSCC pts treated with RRT in the time frame of this study appears superior to published outcomes. Shorter time to LR among pts receiving CT warrants further study, but may signify selection bias toward more aggressive therapy for pts with high risk LRR/NP HNSCC.

6065 Poster Session (Board #389), Sat, 1:15 PM-4:45 PM

Use of chemotherapy with IMRT reirradiation: MDACC experience. *First Author: Mark A. Edson, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The benefits of adding chemotherapy to radiation, combined with the ability to spare more normal tissue with conformal radiation techniques have led to an increased interest in reirradition of head and neck cancers (HNC). However, similar to the use of chemotherapy in unirradiated patients with HNC, the use and delivery of systemic therapy in the reirradiation setting is not standardized. We evaluated our 15-year institutional experience using intensity modulated radiation therapy (IMRT) for reirradiation of recurrent HNC, focusing on chemotherapy-related outcomes. **Methods:** We retrospectively reviewed the records of 206 patients treated between 1999-2014 with IMRT reirradiation to definitive doses ($>$ 60 Gy). The Kaplan-Meier method was used to estimate locoregional control (LRC), progression-free survival (PFS), and overall survival (OS). The log-rank test was used to compare variables of interest. **Results:** Median follow-up was 25 months. Of the 134 patients (65%) who received chemotherapy (CT), 124 (93%) received concurrent chemotherapy (CCT), and 50 (37%) received induction chemotherapy (iCT). The use of CT was associated with worse OS (5Y 35% vs 49%; $P = 0.04$), but not LRC (N.S.) or PFS (N.S.). The use of CCT was associated with improved LRC (5Y OS 55% vs 69%; $P = 0.05$) but not PFS (N.S.) or OS (N.S.). Sub-group analysis of patients who received CCT showed that the use of platinum-containing doublets ($n = 24$) was associated with improved LRC (5Y 82% vs 57%; $P < 0.05$). The use of iCT did not impact clinical outcomes. However, patients who experienced a radiographic complete response after iCT had improved 5-year PFS (5Y 43% vs 9%; $P < 0.01$) and OS (5Y 44% vs 18%; $P < 0.01$) but not LRC (N.S.). CT use was associated with increased grade 3 toxicity (5Y 59% vs 345; $P = 0.02$), and for those receiving concurrent chemotherapy platinum-based CCT was associated with increased grade 4-5 toxicity (28% vs 8%; $P < 0.05$). Prior CT use, and type or number of cycles did not affect clinical outcome or toxicity after reirradiation. **Conclusions:** Chemotherapy given concurrently with IMRT-based reirradiation for HNC appears to improve LRC but not OS. The potential for increased toxicity associated with combined modality treatment warrants careful patient selection.

6066 Poster Session (Board #390), Sat, 1:15 PM-4:45 PM

Double blind multicenter phase III GORTEC trial evaluating the efficacy of oral immune modulating formulae therapy during adjuvant radiochemotherapy in head and neck squamous cell carcinoma (HNSCC). *First Author: Pierre Boisselier, Institut régional du Cancer Montpellier, Montpellier, France*

Background: A previous phase II study showed that an oral immunomodulating formula could reduce severe toxicities and increased survival for HNSCC with concomitant cisplatin and irradiation treatment (1). We conducted a double blind prospective phase III multicenter trial. **Methods:** In 20 GORTEC centers after surgery with curative intent and previous standard radiochemotherapy (2, 3), 180 patients were randomly assigned to receive oral supplementation (3 bags/day, a formula enriched with L-arginine, ω-3 fatty and ribonucleic acids *vs* an isocaloric isonitrogenous control) for 5 days before each cycle of cisplatin. Statistical analysis was done according to an intent-to-treat (ITT) and per protocol (PP) principle. Acute mucositis (RTOG and WHO scales) and 24-months survival were analyzed. **Results:** ITT included 172 patients and PP, the 109 patients with a product compliance $\geq$ 75%. No difference was identified one month after the end of radiochemotherapy on grade 3-4 mucositis, for ITT and for PP, with both scales, RTOG (p = NS) and WHO (p = NS). In accordance with the phase II study, disease-free survival was significantly improved by the immunomodulating formula ($p = 0.004$) in PP patients, and a statistical trend was observed in overall survival ($p = 0.07$). In ITT patients, both overall and disease-free survivals were not significant ($p = 0.22$ and $p = 0.07$, respectively). Median disease-free and overall survivals were not reached. **Conclusions:** Oral supplementation with an immunomodulating formula did not reduce grade 3-4 mucositis but showed significant increase of disease-free survival in product compliant patients (PP). Long term follow-up of our study along with further investigations are needed to confirm these findings and perhaps could open a new avenue for standard treatment of HNSCC. Acknowledgements: We thank the Ligue Nationale contre le Cancer and the Fondation Xavier Leverve for funding and Nestlé International for the product. (1) Assenat E et al. Eur J. Clin Nut Met 2011 (2) Cooper JS et al. NEJM 2004 (3) Bernier J et al. NEJM 2004 Clinical trial information: 2009-A00384-53.

6068 Poster Session (Board #392), Sat, 1:15 PM-4:45 PM

Is there a role for induction chemotherapy in the setting of concomitant chemoradiation in locally advanced head and neck cancer: A systematic review and meta-analysis of randomized controlled trials. *First Author: Aron Popovtzer, Davidoff Cancer Center, Rabin Medical Center, Petach Tiqva, Israel*

Background: :There is a controversy regarding the role of induction chemotherapy (IC) prior to concomitant chemoradiation (CCRT) in locally advanced head and neck cancer (LAHNC). We performed a systematic review and meta-analysis(MA) of all randomized controlled trials (RCTs) which assessed the addition of IC in this setting. **Methods:** We included RCTs that compared IC followed by CCRT to CCRT alone for LAHNC. The Cochrane Library, MEDLINE and conference proceedings were systematically searched (2000-11/2014). The primary outcome was overall survival (OS). Secondary outcomes were progression free survival (PFS), disease control (DC), complete response (CR) rate and adverse events. Relative risk (RR) for dichotomous data and hazard ratio (HR) for time to event data were estimated and pooled. **Results:** Five RCTs met the inclusion criteria, with a total of 1229 patients with stage III or IV LAHNC. Median age was 55y (35-75). IC consisted of docetaxel, platinum and 5FU (TPF) in 4 trials, and platinum-5FU (PF) in one trial. No statistically significant effect on OS was shown, though a trend towards the IC-CCRT group was observed - HR 0.85 (95%CI 0.71-1.02,$p = 0.07$). There was no significant difference in PFS HR 0.84 (0.57-1.24). Yet, patients treated with IC had a better DC compared to CCRT alone (HR of progression, treatment failure or death 0.64 (95%CI 0.52-0.8). The rate of CR improved with IC compared to CCRT, RR 1.66 (95%CI 1.02-2.69). The risk of any grade 3-4 adverse event, fever and neutropenia increased in the IC-CCRT group. The risk of mucositis (4 trials, 922 patients) increased with IC followed by CRT- RR 1.24 (95%CI 1.05-1.46, I2 of heterogeneity73%). In a sensitivity analysis using a random-effects model no such difference was shown RR 1.30 [0.91-1.85] **Conclusions:** MA of RCTs showed no significant effect on OS or PFS. However, the advantage in CR and DC, as well as a trend to improved OS in the IC group, imply that selected patients may benefit from the addition of IC. Since the patient population varied in the extent of disease, future studies are warranted to evaluate the role of IC in subpopulations of patients with LAHNC.

6069 Poster Session (Board #393), Sat, 1:15 PM-4:45 PM

Combination of everolimus and sorafenib in the treatment of thyroid cancer: Update on phase II study. *First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Everolimus is an oral inhibitor of the mammalian target of rapamycin complex 1 (mTORC1). Laboratory data suggests that mTORC1 activity is required for the growth promoting effects of the oncoproteins RET/PTC, RAS, and BRAF in rat thyroid PCCL3 cells. Sorafenib, an oral kinase inhibitor with activity against multiple targets, is FDA-approved for the treatment of radioactive iodine-refractory (RAIR) thyroid cancer. We conducted a clinical trial evaluating everolimus plus sorafenib for RAIR follicular cell derived thyroid cancers (DTC) and medullary thyroid cancers (MTC). **Methods:** This single institution study used a two-stage phase II design and was initiated on 9/21/10. Primary objective was response rate. Eligible patients (pts) had progressive, RAIR/fluorodeoxyglucose (18-F)-avid, recurrent/metastatic, non-anaplastic, thyroid cancer; RECIST measurable disease. Sorafenib was given at 400 mg orally twice a day and everolimus at 5 mg orally once daily. 41 pts were enrolled; 38 were eligible for the primary endpoint of response and 3 were evaluable for toxicity only at the data cutoff date of 1/21/15. 7 pts are still on study. **Results:** Of the 41 eligible pts, median age-61 years (35-79). 15 patients received prior VEGF-targeted systemic therapy. Grade 4-5 adverse events at least possibly related to drug: grade 4- hepatic enzyme increase (1 pt): grade 4- Hyperglycemia (1 pt): grade 4-Hypertriglyceridemia (1 pt). Histology and response data by partial response, confirmed and unconfirmed, (PR), stable disease (SD), progression of disease (POD), and days on study (DOS) are shown in the Table. **Conclusions:** The combination of sorafenib and everolimus demonstrates activity that rivals the best reported data, and surpasses that for sorafenib alone, in all evaluated thyroid cancer subgroups. A randomized study of sorafenib +/- everolimus is indicated in both pts with DTC and MTC. Clinical trial information: NCT01141309.

Histology	#	PR	SD	POD	Median DOS (range)
Papillary	9	5 (56%)	3 (33%)	1 (11%)	484 (27-854+)
Hurthle Cell	9	7 (78%)	2 (22%)	0	553 (55-1419+)
Follicular	2	1 (50%)	1 (50%)	0	136 (80-192)
Poorly Diff	8	4 (50%)	4 (50%)	0	262 (142-863+)
MTC	10	4 (40%)	4 (40%)	2 (20%)	209 (31-1517+)
DTC only	28	17 (61%)	10 (36%)	1 (4%)	430 (27-1419+)
Total	38	21 (55%)	14 (37%)	3 (8%)	373 (27-1517+)

6070 Poster Session (Board #394), Sat, 1:15 PM-4:45 PM

Characteristics of PD-L1, PD-1 expressions and CD8+ tumor infiltrating lymphocyte in EBV-associated nasopharyngeal carcinoma. *First Author: Komkrit - Mahaprom, Ramathibodi Hospital, Bangkok, Thailand*

Background: Early phase clinical studies showed promising activities of anti-PD1/PD-L1 antibody in squamous cell carcinoma of head and neck (SCCHN). PD-L1 expression is a potential biomarker of these drugs. Tumor Infiltrating Lymphocyte (TIL) was a prognostic marker of HPV+ SCCHN and potentially associated with response of immunomodulatory drugs. Most clinical trials of anti-PD1/PD-L1 often excluded nasopharyngeal carcinoma (NPC). We evaluated characteristics of PD-L1 expression and CD8+ TIL for a future development of anti-PD1/PD-L1 antibody in NPC. **Methods:** NPC patients were identified through the Ramathibodi Cancer Registry database between 1/2007 and 12/2012. PD-L1 and PD-1 expressions were characterized by immunohistochemistry (IHC) from formalin-fixed paraffin-embedded tumor samples. PD-L1 expression was defined by using a cut-off of ≥1% (≥1-9%=1+, 10-49%=2+, ≥50%=3+). Mean number of CD8+TILs following the analysis of 2-4 images was assessed quantitatively by 2 individual pathologists blinded to outcomes. Tumor EBV status was analyzed by using EBV encoded RNA (EBER) in situ hybridization. **Results:** 119 NPC samples were analyzed. Overall, PD-L1 expression was positive in 72% (13% IHC 3+). PD1+ was observed in 11% of patients. Most patients had EBER+ tumors (96%). Characteristics were summarized in the table. PD-L1+ was highly observed in male (p=0.02). Mean CD8+ TIL count was significantly deceased with stage at diagnosis (p=0.02). There was no significant correlation between PD-L1 and CD8+ TILs observed. **Conclusions:** More than 70% of EBV+ NPC expressed PD-L1. These results support future development of anti-PD1/PD-L1 antibody in NPC.

Characteristics	PD-L1 (%) -	PD-L1 (%) +	P-value	Mean CD8+ TIL count (±SD)	P-value
Median Age	48	53.5	0.86	52	n/a
(range)	(24-69)	(17-81)	0.34	(17-81)	0.74
<65 years	28(93)	68(85)		60±35	
≥65 years	2(7)	12(15)		57±30	
Male	15(50)	59(74)	0.02	62±34	0.35
Female	15(50)	21(26)		55±34	
Smoking	15(63)	29(52)	0.38	54±30	0.45
Never	9(37)	27(48)		59±34	
Yes					
EBV+	32(97)	82(95)	1.00	59±34	0.44
EBV-	1(3)	4(5)		47±19	
PD1+	3(9)	10(12)	1.00	71±47	0.14
PD1-	30(91)	76(88)		57±31	
Stage	5(18)	12(15)	0.68	77±40	**0.02**
1-2	22(82)	67(85)		56±31	
3-4					
Median OS (months)	44.2	54.0	0.76	n/a	

6071 Poster Session (Board #395), Sat, 1:15 PM-4:45 PM

A pilot, single arm, prospective trial using neoadjuvant rapamycin prior to definitive therapy in head and neck squamous cell carcinoma. *First Author: Keisuke Shirai, Medical University of South Carolina, Charleston, SC*

Background: Deregulated PI3K-AKT-mTOR signaling is one of the most common abnormalities in head and neck squamous cell carcinoma (HNSCC). We previously showed that mTOR inhibition with rapamycin significantly inhibited the growth of human HNSCC xenografts and oral cancers in multiple genetically-defined and chemically-induced mouse models. A pilot trial of neoadjuvant rapamycin treatment was developed to assess its effect on clinical response and mTOR signaling. **Methods:** Patients with untreated stage II-IVA HNSCC received 21 days of rapamycin treatment (15 mg on day 1, 5 mg on days 2-21) prior to definitive treatment with surgery or chemoradiation. Treatment responses were assessed clinically and radiographically with CT and FDG-PET. Pre- and post-treatment biopsies and blood were obtained for toxicity, immune monitoring and immunohistochemical assessment of mTOR signaling. **Results:** Sixteen patients (8 oral cavity, 8 oropharyngeal) completed rapamycin and definitive treatment (15-surgery, 1-chemoradiation). Half of patients were p16 positive. Fifteen of 16 patients showed clinical improvement. One patient had pathological CR. two met RECIST criteria for response (1 CR, 1 PR, 14 SD). Treatment was well tolerated with no grade 4 or unexpected toxicities. Two grade 3 toxicities (1 post-operative wound complication, 1 hypokalemia) and 3 grade 2 toxicities (1 wound infection, 1 mucositis, 1 hyperglycemia) were seen. The most common toxicity was grade 1 thrombocytopenia (n = 5). Two asymptomatic patients required dose reduction due to elevated rapamycin levels. No significant immune suppression was observed. The level of phosphorylated S6 (pS6) showed statistically significant decrease in all evaluable (13/16) patients (34-87% decrease). Inhibition of phosphorylated AKT^{S473} ($pAKT^{S473}$) was observed in 12/13 evaluable patients (27-97% decrease in 12 patients, 16% increase in one patient). **Conclusions:** Rapamycin treatment was well tolerated and resulted in significant clinical responses despite the brief treatment duration. Significant reduction in pS6 and $pAKT^{S473}$ supported successful inhibition of mTOR signaling. Clinical trial information: NCT01195922.

6072 Poster Session (Board #396), Sat, 1:15 PM-4:45 PM

A phase II study of everolimus (E) and sorafenib (S) in patients (PTS) with metastatic differentiated thyroid cancer who have progressed on sorafenib alone. *First Author: Marcia S. Brose, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: Recently, S became the first drug FDA-approved in 40 years to treat progressive, RAI-refractory thyroid cancer. S inhibits VEFR, PDGFR, Kit and RET. With S, patients achieve a median PFS of 10.8 months. We observed that pts may progress in some sites while maintaining stability in others. We hypothesized that progression on S may depend on increased activity of the AKT/MTOR pathway. Therefore we conducted a Phase II study to see if the addition of everolimus (E), an oral mTOR inhibitor, to S would have activity in pts who had progressed on S alone. **Methods:** 35 pts with evidence of progression by RECIST criteria on S were enrolled. Pts were started on a dose of S 200mg/d lower than their previously tolerated dose, combined with E 5mg/d. Pts were followed for toxicity; if tolerated, the dose of E and then S were incrementally increased to a maximum daily dose of S 800mg/day and E 10mg/day. The primary endpoint was progression-free survival (PFS). Response was evaluated by RECIST every 8 weeks. **Results:** Of 35 pts enrolled, 33 were evaluable for PFS and response. 17 pts had papillary, 9 had Hu¨rthle Cell, 1 had follicular and 6 had poorly differentiated subtypes. 13 pts were successfully dose escalated to full dose of both agents: S 800mg/d and E 10mg/d, 5 pts reached S 600mg/d and E 10mg/d, and 8 pts reached S 600mg/d and E 7.5 mg /d. While increased severity of hand foot skin reaction was anticipated, it was rarely seen. The median PFS was 13.7 mos (95% CI: 7.15-24.75). No complete responses were observed, 1 pt achieved a partial response and 18 achieved a best response of stable disease for > = 6 mos. for a clinical benefit rate (CR+PR+SD > = 6 mos.) of 58%. **Conclusions:** The addition of everolimus to sorafenib at the time of progression was tolerable and allowed pts an additional median of 13.7 mos. of disease stability. The addition of everolimus did not result in dose-limiting hand foot skin reaction as had been seen in prior studies in which both were started at the same time, demonstrating that these agents may be successfully combined if started sequentially. Our approach may have implications in other diseases where the combination of a VEGFR inhibitor and mTOR inhibitor may have added activity. Clinical trial information: NCT01263951.

6073 Poster Session (Board #397), Sat, 1:15 PM-4:45 PM

Landscape of genetic alterations in non-smoking patients with oral tongue carcinoma: An analysis of The Cancer Genome Atlas (TCGA) head and neck squamous cell carcinoma data. *First Author: Nabil F. Saba, Winship Cancer Inst Emory Univ, Atlanta, GA*

Background: Despite the overall decreased incidence of oral cavity carcinoma a recent surge in the diagnosis of oral tongue cancers (OTC) in younger predominantly female non-smokers has been noted. We sought to explore the landscape of mutational and transcriptional alterations in non-smoking patients with OTC using the TCGA data. **Methods:** We queried the TCGA data utilizing a novel R-based software Cancer Genome ExploreR (http://sourceforge.net/projects/cancergenomeexplorer/) to compare coding mutations, mutation spectra, gene expression and copy number profiles between groups of interest. **Results:** Sixty two female lifelong non-smokers or current reformed smokers ($>$ 15 years) having cancers of the oral cavity including OTC (n = 29), oral cavity not otherwise specified (n = 17), floor of mouth (n = 6), alveolar ridge (n = 4), buccal mucosa (n = 3) or hard palate (n = 3) were identified in the TCGA clinical data. Seventy life-long non smoker or reformed smoker male with a similar distribution of oral site cancers were also identified (n = 33, 18, 5, 8, 5, 1 cases respectively). Female versus male OTC exhibited very similar genomic profiles, as did a combined analysis of all of the above sites between males and females. The genomic differences we did detect came primarily from expression and mutation of X and Y chromosome genes. However, male and female OTC (n = 62) had several genomic features that distinguished them from other oral cavity sites (n = 77). These included relative differences in the frequency of CDKN2A, CASP8 and NOTCH1 coding mutations and differential rates of deletion of chromosomes 11q and 13q. **Conclusions:** Our results point to genomic differences in non-smoking OTC patients when compared to all other oral cavity tumors from non-smokers regardless of gender. These results present an opportunity to develop better understanding of the biology of OTC in non-smokers in addition to an exploration of targeted therapeutic approaches in this group. (This research was supported by a grant NCI R21 CA182661-01A1 to NFS and GZC).

6074 Poster Session (Board #398), Sat, 1:15 PM-4:45 PM

Phase I study of cetuximab, intensity-modulated radiotherapy (C-IMRT), and intratumoral EGFR antisense (AS) DNA in patients with locally advanced head and neck cancer (HNC). *First Author: Julie E. Bauman, University of Pittsburgh, Pittsburgh, PA*

Background: Epidermal growth factor receptor (EGFR) is a validated therapeutic target in HNC. The combination of C-IMRT is a standard for locally advanced HNC; however, failure of locoregional control (LRC) remains the primary cause of cancer-related death. Intratumoral injection of EGFR-AS DNA oligonucleotide was safe and associated with promising lesional response in a phase I study. We conducted a phase I trial to evaluate the safety of C-IMRT and EGFR-AS DNA injections in patients with locally advanced HNC. **Methods:** Eligible patients had Stage IVa-IVc HNC, ECOG 0-2, no prior RT, and a measurable lesion accessible for repeated injection. Treatment course was 9 wks. C was loaded wk 1 then administered 250 mg/m^2/wk for 8 wks. EGFR-AS DNA (11.92mg/1.78mL; no dose modifications) was injected weekly into the selected lesion starting wk 1 until complete response (CR) or a maximum of 7 injections. IMRT (70 Gy; 2 Gy/fraction) was delivered wks 3-9. Biopsies of injected lesions were obtained at baseline and after 2 injections. The primary endpoint was safety; a $\geq$ 20% rate of grade 3/4 adverse events (AEs) attributable to EGFR-AS DNA was considered unsafe. EGFR signaling in paired biopsies was evaluated by reverse phase protein array (RPPA). **Results:** Between Apr 2013 and June 2014, 6 patients (4 male; 2 female) were treated. Stage: IVa (4); IVc (2). Primary site: oropharynx (4; HPV+/HPV-/HPV$_{unk}$ 1/1/2); hypopharynx (1); oral tongue (1). Lesion selected for injection: lymph node (LN; 2); oropharynx (3); oral tongue (1). No grade $\geq$ 2 AEs were attributed to EGFR-AS DNA; 2 of 6 reported grade 1 injection site pain. Expected rates of acneiform rash, RT dermatitis, and mucositis were observed. All patients completed IMRT and 8-9 doses of C. Best lesional response was CR (4), partial response (1), or progression (1). A patient with T2N2cM1 hypopharynx primary had CR in the injected 5 cm LN but only PR in a contralateral 1.5 cm non-injected LN. RPPA results will be presented. **Conclusions:** The combination of C-IMRT plus EGFR-AS DNA injections was well tolerated. The lesional response pattern is intriguing. A phase II efficacy trial evaluating LRC as the primary endpoint is planned. Clinical trial information: NCT00903461.

6075 Poster Session (Board #399), Sat, 1:15 PM-4:45 PM

Effect of the extent of lymph node dissection on overall survival in patients treated for oral cavity squamous cell carcinoma. *First Author: Jennifer Lobo Shah, Stanford Cancer Inst, Stanford, CA*

Background: Limited recently published data has suggested that resection of at least 18 lymph nodes improves outcomes for patients treated with oral cavity cancer. We sought to determine if further survival benefit could be derived from a more extensive nodal dissection in these patients. **Methods:** We retrospectively reviewed 551 consecutive patients treated at the Stanford Cancer Institute from 1998-2013 for oral cavity squamous cell carcinoma with surgical resection followed by adjuvant therapy if indicated. Patients treated for recurrent disease and metastatic disease were not included. Of this cohort, 278 patients underwent neck dissection as a component of their initial surgical management. For this study, we defined a select neck dissection as 0-19 lymph nodes, a standard dissection as 20-39 lymph nodes, and a comprehensive dissection as 40 or more lymph nodes. **Results:** Within the 278 patients who underwent neck dissection, 85 patients had a select dissection, 100 patients had a standard dissection, and 93 patients had a comprehensive dissection. In this cohort, there was an overall survival benefit to having a comprehensive dissection compared to a select or standard dissection (p = 0.05). Of the patients who underwent adjuvant radiation therapy (RT), 24% had a select dissection, 35% had a standard dissection, and 40% had a comprehensive dissection. For patients who had RT, there was overall survival benefit to having a comprehensive dissection compared to select or standard (p = 0.05). This survival benefit was further seen patients with T2 and T3 tumors (p = 0.005, p = 0.04), N2 nodal involvement (p = 0.01), extracapsular extension (p = 0.04), and perineural invasion (p = 0.06). The extent of neck dissection did not impact survival for patients who did not undergo radiation therapy, even when analyzed by T and N stage. **Conclusions:** For patients requiring radiation therapy for oral cavity squamous cell carcinoma, a comprehensive neck dissection including the resection of at least 40 lymph nodes confers overall survival benefit.

6076 Poster Session (Board #400), Sat, 1:15 PM-4:45 PM

Outcomes of elderly patients treated for oral cavity squamous cell carcinoma. *First Author: Jennifer Lobo Shah, Stanford Cancer Inst, Stanford, CA*

Background: Implementing standard treatment recommendations for oral cavity cancer in the elderly population can be challenging due to the comorbidities seen in this population. We sought to compare outcomes in patients of age 70 years or older compared to their counterparts. **Methods:** We retrospectively reviewed 551 consecutive patients treated at the Stanford Cancer Institute from 1998-2013 for oral cavity squamous cell carcinoma with surgical resection followed by adjuvant therapy if indicated. Patients treated for recurrent disease and metastatic disease were not included. Of this cohort, 188 patients were elderly, defined as age 70 years or above, and 363 patients were younger than age 70. Survival estimates were determined using the Kaplan-Meier method, and recurrence rates were determined using cumulative incidence estimates including competing-risk analyses. **Results:** At 2 years after diagnosis, overall survival was 55% in the elderly group compared to 75% in those younger than age 70 ($p < 0.0001$). Loco-regional recurrence at 2 years was 29% in the elderly group compared to 34% in the younger group (p = 0.09). Freedom from progression was 32% in the elderly group compared to 36% in the younger group (p = 0.11). Within the elderly group, 69 patients underwent neck dissection as a component of their initial surgical resection. Overall survival at 2 years was 50% for elderly patients who underwent neck dissection compared to 58% for elderly patients who did not (p = 0.09). **Conclusions:** Consistent with life expectancy, elderly patients age 70 years or older treated for oral cavity cancer had worse overall survival compared to younger patients. Loco-regional recurrence and freedom from progression, however, were lower in the elderly population. Less aggressive management may be acceptable in this population.

6077 Poster Session (Board #401), Sat, 1:15 PM-4:45 PM

Low pre-operative absolute monocyte count to predict overall survival benefit for oral cavity squamous cell carcinoma. *First Author: Timothy Bui, Stanford University, Stanford, CA*

Background: With the advent of immunotherapy, the role of the immune system in cancer patients is increasingly being investigated. The role of lymphocytes as indicators of the adaptive immune response has been reported; however, the relevance of the innate immune response is unclear. Monocytes are the precursor cells to dendritic cells and macrophages. As a crude metric, we sought to determine the predictive value of the pre-operative absolute monocyte count (AMC) in patients being treated for oral cavity squamous cell carcinoma. **Methods:** We retrospectively reviewed 551 consecutive patients treated at the Stanford Cancer Institute from 1998-2013 for oral cavity squamous cell carcinoma with surgical resection followed by adjuvant therapy if indicated. Patients treated for recurrent disease and metastatic disease were not included. The reference range for AMC is 0.3-0.95 K cells per microliter. For this study, a low AMC was defined as less than 0.5 K cells per microliter. Survival estimates were determined using the Kaplan-Meier method, and recurrence rates were determined using cumulative incidence estimates including competing-risk analyses. **Results:** In this cohort, 160 patients had a low AMC, and 391 patients had an AMC greater than or equal to 0.5 K cells per microliter. There was no statistically significant difference in T stage and N stage between patients with a low AMC compared to the remainder of the cohort. For the 119 patients who underwent adjuvant radiation therapy, those with a low AMC had improved overall survival at 2 years, 83% vs 53%, and at 5 years, 62% vs 33% ($p = 0.02$). For patients who did not undergo adjuvant radiation therapy, low AMC did not impact overall survival ($p = 0.24$). **Conclusions:** In addition to the adaptive immune system, the innate immune system may be relevant to cancer outcomes. Further investigation is required to understand the mechanisms leading to these observations.

6078 Poster Session (Board #402), Sat, 1:15 PM-4:45 PM

Patterns of CD8+ T-cell infiltration and immune escape mechanisms in head and neck cancer. *First Author: Vassiliki Saloura, University of Chicago, Chicago, IL*

Background: Immunotherapy with PD-1/PD-L1 axis blockade has shown promising preliminary results in patients with head and neck squamous cell carcinomas (HNSCC) (Seiwert ASCO 2014). Using a 12-gene chemokine expression signature (Harlin/Gajewski 2009) 33-47% of HNC have a T-cell inflamed phenotype (TCIP-High) characterized by CD8+ TIL enrichment and PD-L1 expression in both HPV(+) and HPV(-) HNC. In this study, we sought to identify patterns of CD8+ tumor infiltration and describe immune escape mechanisms. **Methods:** We evaluated the patterns of infiltration of CD8+ TILs in a subset of tumors ($N = 73$) from the Chicago HNC Genomics (CHGC) cohort using IHC. 58 were also stained for PD-L1 expression. 55 tissues were evaluated with dual CD8/FOXP3 staining. To assess potential mechanisms of immune escape, we interrogated the different patterns of CD8+ TIL infiltration in conjunction with the TCIP-high signature. **Results:** 27% (20/73) of CHGC tumors showed either no CD8+ T-cells (Immunologic Ignorance (II), 8%, 6/73) or CD8+ T-cells limited to the tumor periphery (Excluded Immune Infiltrate (EII), 19%, 14/73). Of these tumors, 75% (15/20) were PD-L1 negative and 25% (5/20) were PD-L1+. 73% (53/73) of tumors showed intratumoral CD8+ TILs. Of these tumors, 38 had available PD-L1 staining results and 63% (24/38) were PD-L1+ (Functional Immune Response (FIR)), while 37% (14/38) were PD-L1 negative (Non-Functional Immune Response (NFIR)). FIR tumors (intratumoral CD8+, PD-L1+) with strong PD-L1 positivity showed significantly higher immune cytolytic activity, by *GZMA* and *PRF1* gene expression, compared to NFIR tumors. Tumors with intratumoral CD8+ TIL infiltrate correlated with the TCIP-High phenotype in both HPV(+) and HPV(-) tumors. FOXP3 staining was significantly higher in HPV(+) tumors. **Conclusions:** 73% of HNC attract intratumoral CD8+ TILs and 63% of these tumors seem to activate a functional immune response. PD-L1 upregulation may serve as a compensatory immune escape mechanism, making this subset a rational target for PD-L1 blockade. T-regulatory cells seem to play an additional role in immune evasion of HPV+ HNC, suggesting that a combinatorial approach with a T-reg depleting strategy warrants clinical investigation.

6079 Poster Session (Board #403), Sat, 1:15 PM-4:45 PM

Correlation of specific genetic aberrations and signaling pathways with T-cell inflamed phenotype (TCIP) in head and neck cancer and as novel candidate biomarkers for checkpoint blockade therapy. *First Author: Zhixiang Zuo, The University of Chicago, Chicago, IL*

Background: Anti-PD-1/PD-L1 blockade is active in patients (pts) with head and neck squamous cell carcinoma (HNSCC) (Seiwert ASCO 2014). The T-cell inflamed phenotype (TCIP)/INF-g driven gene expression delineates a group of HNSCC that are likely to benefit from anti-PD-1 therapy (Seiwert ASCO 2015). We examined the genetically annotated TCGA cohort to determine genetic aberrations and signaling pathways associated with TCIP HNSCC, and validated findings *in vitro*, in order to identify novel candidate genetic biomarkers for immunotherapy and possible combination strategies. **Methods:** 416 HNSCC tumors from the TCGA cohort were used to calculate T-cell inflamed phenotype (TCIP) (Saloura ASCO 2014). Mutation/copy number data, expression intrinsic subtypes (Keck CCR 2015), and KEGG pathways were evaluated for correlation with TCIP in a hypothesis-forming analysis. In-vitro validation was performed in cell lines with similar genetic background. **Results:** Aberrations in the histone-methyl-transferase NSD1, altered in 41% of HNSCC via mutation/deletion. Considering HPV(-) tumors only, both NSD1 mutation and NSD1 deletion were strongly correlated with non-TCIP ($p = 0.0035$ and $p = 6.60e-09$, respectively). NSD1 mutation distribution suggested loss of function. Secondly, EGFR amplification occurred in non-TCIP tumors ($p = 3.88e-11$) and overlapped with active EGFR signaling in the Basal (BA) intrinsic subtype. BA cell lines treated with an EGFR inhibitor (gefitinib) consistently showed an increase in PD-L1 expression by immunoblotting. Pathway analysis identified WNT signaling as significantly associated with non-TCIP. CD274 (PD-L1)/JAK2 co-amplified in 101 out of 416 HNSCC tumors, which was significantly enriched in TCIP ($p = 5.93e-13$). **Conclusions:** NSD1 aberration,EGFR amplification, basal subtype, and WNT signaling are biomarkers of non-TCIP tumors, CD274/JAK2 amplification of TCIP tumors. These newly identified candidate biomarkers for immunotherapy require additional clinical and functional validation. Combination therapy with anti-EGFR and anti-PD-1/PD-L1 should be further explored.

6080 Poster Session (Board #404), Sat, 1:15 PM-4:45 PM

Comparison of two large, genetically and clinically annotated head and neck cancer (HNC) cohorts (TCGA, CHGC) and differential treatment effects on TP53 mutated, as well as oral cavity cancers. *First Author: Johannes Bragelmann, Medical Clinic III; Department of Oncology, Hematology and Rheumatology; University Hospital Bonn, Bonn, Germany*

Background: Whileeffects of specific genetic aberrations on outcome in HNC have been described (Poeta 2007, Gross 2014), the impact of therapies in genetic subgroups remains unknown. We therefore examined in an exploratory, hypothesis-forming analysis two large, genetically annotated cohorts, which preferentially employed different treatment regimens, with respect to impact on outcome in certain genetic backgrounds. **Methods:** Data of 238 patients (pts) from the Cancer Genome Atlas (TCGA), and 131 pts of the Chicago HNC Genomic Cohort (CHGC) receiving curative intent treatment for locoregionally-advanced HNC were included. Subgroups of patients were analyzed evaluating anatomic site, HPV status, TP53 mutation status, and survival in an exploratory, hypothesis-forming study. **Results:** Pts in both cohorts were largely treated at high-volume North American referral centers. Pts in CHGC received more frequently induction chemotherapy and primarily taxane/FHX, non-platinum containing regimens and less frequently surgery. The genetic profiles were very similar when controlling for HPV status. In both cohorts HPV-positive and HPV-negative tumors 5-year survival rates were similar (NS), however with improved outcomes in the HPV-positive pts in CHGC compared to HPV-positive pts in TCGA ($p = 0.02$). In HPV-negative tumors in TCGA TP53 mutations conferred a negative prognosis, while in CHGC pts with TP53 mutations showed an increased survival. Furthermore in CHGC outcome in oral cavity cancers was improved (5-year survival CHGC 59%, TCGA 41%, $p = 0.046$). **Conclusions:** While bias due to differences in cohort composition and lack of standardization of treatment cannot be controlled for, this analysis provides for the first time hypotheses regarding the interaction of treatment choices with genetic background in the curative intent setting. In particular the possible impact of taxane-containing induction chemotherapy or non-platinum based taxane/FHX regimens on worse prognosis TP53 mutant tumors, as well as non-surgical approaches for oral cavity/laryngeal Stage IV tumors deserves additional study.

6081 **Poster Session (Board #405), Sat, 1:15 PM-4:45 PM**

Notch1 mutations to define a subgroup of adenoid cystic carcinoma (ACC): Tumor stage, propensity to bone and liver metastasis, risk of relapse, and overall survival. *First Author: Renata Ferrarotto, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ACC is chemotherapy refractory and there is no standard of care treatment for patients (pts) with metastatic disease. ACC genotyping revealed alterations in the Notch (N) pathway in 13-29% of cases. An ACC patient identified in our institution with an activating Notch1 (N1) mutation achieved a partial response after 2 cycles of a N1 inhibitor in a phase I trial. In this study, we investigate the clinical and pathologic characteristics of N1 mutant ACC. **Methods:** N1 sequencing was performed in 97 pts (71 using whole-exome sequencing and 26 using a 50 gene panel including N1 exons 26, 27, 34). Comparisons between tumor characteristics and clinical outcomes in pts with or without activating N1 mutations (PEST or HD domain) were performed. **Results:** N1 mutations were identified in 13 pts. Pathway activation was confirmed by IHC for N1 intracellular domain. N1 ACC pts had significantly higher disease stage at diagnosis ($p = 0.009$, Fisher's exact test), and solid histologic subtype ($p = 0.027$). Only 1/38 pts who presented with stage I-III disease had N1 mutation compared with 4/12 pts (33%) who presented with distant metastasis. Although lung is the most common site of metastasis in ACC, N1 mutants developed bone (odds ratio [OR] = 7) and liver (OR = 4.5) metastasis more frequently than lung (OR = 0.44). Recurrence-free survival and OS were significantly shorter in the N1 mutant subgroup (p-value = 0.025, Log-rank test). The clinical correlations identified for the N1 mutants were maintained in an extended analysis that included SPEN and N2 mutations (4 pts), with an even higher impact in OS ($p = 0.007$). **Conclusions:** A subgroup of ACC harbors N1 (13.4%) or other N pathway activating mutations (17%). N activation defines a more aggressive phenotype, with a distinct pattern of metastatic spread, higher risk of relapse, and shorter OS. The identification of genetic events that activate N and the encouraging response observed in an index case suggest an immense opportunity to further explore this pathway as a therapeutic target in ACC.

6082 **Poster Session (Board #406), Sat, 1:15 PM-4:45 PM**

Systematic review and meta-analysis of the safety and efficacy of minimally invasive compared to open thymectomy for thymic malignancies. *First Author: Adam J. Friedant, Fox Chase Cancer Center, Philadelphia, PA*

Background: Complete resection is the standard of care for the treatment of thymoma. The use of minimally invasive surgery remains controversial. **Methods**: We searched online databases and identified studies from 1995 to 2014 comparing minimally invasive (MIS) (video assisted or robotic-assisted) to open thymectomy for thymic tumors. Study endpoints included operative blood loss, operative time, pulmonary complications, atrial fibrillation, length of stay (LOS), R0 resection, and tumor recurrence. We summarized outcomes across studies using random-effects meta-analysis to account for study heterogeneity. We calculated odds ratios (OR) for binary outcomes and standardized mean differences for continuous outcomes. We calculated incidence rate ratios (IRR) for the number of recurrences, accounting for total person-time observed in each study. **Results**: 36 studies (with 935 patients) were analyzed. Masaoka stage I-II comprised 88.5% (n = 522) of MIS patients and 80.4% (n = 413) of open. Mean tumor size was 4.49 cm (MIS) and 4.99 (open). 32/522 (6.13%) MIS cases were converted to open. MIS patients had significantly less blood loss (226 vs. 169 mL, std diff = -0.78, 95% CI -0.97 – 0.57, $p < 0.01$) but no significant difference in operating time (164.92 vs. 147.18 min, std diff = 0.13, 95% CI -0.28 – 0.54, $p = 0.53$), cardiac complications (7 MIS vs. 21 open, OR = 0.73, 95% CI 0.28 – 1.92, $p = 0.52$), respiratory complications (13 MIS vs. 38 open, OR = 0.79, 95% CI 0.29 – 2.16, $p = 0.64$), or overall complications (32 MIS vs. 63 open, OR = 0.90, 95% CI 0.41 – 1.93, $p = 0.78$). LOS was shorter for MIS patients (8d MIS vs. 9d open, std diff = -0.88, 95% CI -1.52 – -0.24, $p < 0.01$). Analyzing Masaoka I - II patients only, there was no difference in R0 resection rate (97.36% vs. 97.25%, OR = 0.98, 95% CI 0.23 – 4.14, $p = 0.88$) or overall recurrence rate (2.86% vs. 2.91%, IRR = 2.10, 95% CI 0.39 – 11.25, $p = 0.39$). There was one postoperative death (open group). **Conclusions**: The results of this unadjusted meta-analysis of published reports comparing MIS to open thymectomy suggest that MIS thymectomy is safe and can achieve similar oncologic outcomes to open thymectomy in selected patients with thymic malignancy.

TPS6083 **Poster Session (Board #407a), Sat, 1:15 PM-4:45 PM**

A phase I study to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary clinical activity of MEDI0562 in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). *First Author: Rom Samuel Leidner, Earl A. Chiles Research Institute, Providence Cancer Center, Portland, OR*

Background: Co-stimulatory signals delivered via binding to OX40 on T cells increase T-cell survival, proliferation, and effector function, and result in the generation of long-lived memory T cells. Experience to date with a human OX40 agonist murine antibody (MEDI6469) suggests targeting this pathway may provide antitumor activity with a manageable safety profile. In a Phase I study in advanced solid tumors, a single cycle of MEDI6469 had both an acceptable toxicity profile and regression of ≥ 1 metastatic lesion in 12 of 30 treated patients (pts)(Curti B, et al. Cancer Res 2013;73:7189–98). Humanized OX40 agonists are anticipated to have reduced immunogenicity relative to murine antibody, which may allow for repeat-dosing, potentially enhancing biologic and antitumor activity. MEDI0562 was developed through humanization of MEDI6469, and specifically binds to and activates signaling by human OX40. **Methods:** This is a Phase I, multicenter, open-label study (NCT02318394) in adults with R/M SCCHN. The primary endpoint is safety. Secondary endpoints include antitumor activity (objective response and disease control by immune-related RECIST, duration of response, progression-free survival, and overall survival), PK, immunogenicity, and pharmacodynamics. In the dose-escalation phase, sequential cohorts will receive 1 of 6 dose levels (3+3 design) of MEDI0562 IV for up to 48 weeks or until progressive disease (PD). Based on available data, any dose level not exceeding the maximum tolerated dose can be expanded. A dose-expansion phase may be initiated at the sponsor's discretion in SCCHN pts to further examine MEDI0562 at the dose level and treatment schedule determined during dose escalation. Upon evidence of PD in follow up, pts in both dose escalation and expansion cohorts may have 1 round of MEDI0562 re-treatment according to their previous regimen. All pts will be followed for survival through to study end. Enrollment of ~50 pts (≤ 36 in dose escalation; ≤ 14 in dose expansion) is ongoing. Clinical trial information: NCT02318394.

TPS6084 **Poster Session (Board #407b), Sat, 1:15 PM-4:45 PM**

KEYNOTE-040: A phase III randomized trial of pembrolizumab (MK-3475) versus standard treatment in patients with recurrent or metastatic head and neck cancer. *First Author: Ezra E. W. Cohen, UC San Diego Moores Cancer Center, La Jolla, CA*

Background: Prognosis of patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is poor, with limited treatment options and survival rates of 6-9 months following standard-of-care (SOC) therapies. Pembrolizumab, a humanized IgG4 monoclonal antibody against PD-1 designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2, has demonstrated clinical efficacy by investigator review (confirmed and unconfirmed responses) in a phase I study of R/M HNSCC. Preliminary PD-L1 biomarker data suggest that response rate may be greater in PD-L1–positive patients. **Methods:** In this global open-label, phase III KEYNOTE-040 (NCT02252042) trial, 466 subjects with recurrent or metastatic HNSCC that have failed prior platinum therapy will be randomized (1:1) to pembrolizumab (200 mg Q3W) vs investigator's choice SOC (single-agent methotrexate, docetaxel, or cetuximab). Randomization will be stratified by ECOG PS (0 vs 1), human papillomavirus (HPV) status in oropharyngeal cancer by p16 immunohistochemistry testing (positive vs negative), and centralized PD-L1 status (positive vs negative). Pembrolizumab will be given for ≤ 24 months or until disease progression, unacceptable toxicity, or investigator decision. AEs will be assessed according to NCI CTCAE, v4.0. Imaging will occur per RECIST v1.1 at 9 weeks and every 6 weeks thereafter. Modified RECIST, which allows for continued treatment after initial radiographic progression until confirmation imaging ≥ 4 weeks, will be used to account for unique responses seen with pembrolizumab. Radiographic responses will be confirmed by independent central review by RECIST v1.1 and modified RECIST and analyzed in real time for verification of progressive disease by RECIST v1.1. Survival follow-up will occur every 12 weeks. Primary end points are progression free survival (PFS) and overall survival (OS); secondary end points include ORR, DOR and PFS, OS, and ORR in PD-L1$^+$ patients. Treatment differences in PFS and OS will be assessed using stratified log-rank test; Hazard ratios with 95% confidence intervals will be estimated using stratified Cox proportional hazard models. Clinical trial information: NCT02252042.

TPS6085 **Poster Session (Board #408a), Sat, 1:15 PM-4:45 PM**

Ceritinib in anaplastic thyroid cancer (ATC) with ALK abnormalities. *First Author: Saad A. Khan, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: ATC is a rare tumor of thyroid epithelium affecting several hundred patients annually, but causing death in almost 100% of them. It has a dismal prognosis with currently ineffective treatment options, particularly in metastatic disease. BRAF V600E mutations have been identified and then targeted with novel agents, which led to striking activity in patients (Rosove et al, NEJM 2013). ALK overexpression and mutation have also been identified in ATC in 11% of patient samples (Murugan et al, Cancer Res 2011). Patients treated with ALK inhibitors show dramatic tumor response (Godbert et al, JCO 2014). Ceritinib is a well-tolerated, highly potent oral ALK-inhibitor that is FDA-approved for use in ALK-rearranged lung cancer. It is critical to develop a framework by which anaplastic tumor samples can be collected, actionable mutations identified and novel agents rapidly tested. **Methods:** This multicenter, open label trial (NCT02289144) is collecting tissue from 100 patients with ATC/UTC. A genomic profile will be created by next generation sequencing of all 100 tumor samples. 10 of these patients are predicted to demonstrate ALK abnormalities; either by overexpression, mutations or rearrangements. Upon confirmation of metastatic or unresectable disease, patients with ALK-abnormalities will get 750 mg ceritinib daily. Prior therapy does not affect eligibility. Primary endpoint is progression free survival of 3.5 months, compared to historical controls. As patients are screened, their tumor tissue genomic profile will be collected and analyzed for future targets. As genomic profiling provides more information about actionable targets in ATC patients, additional therapeutic arms/sub-studies with other novel agents will be added to this trial. This protocol may serve as the basis by which newer therapies may be tested in this challenging disease. Clinical trial information: NCT02289144.

TPS6086 **Poster Session (Board #408b), Sat, 1:15 PM-4:45 PM**

A Phase 2, multicenter, single-arm, global study of MEDI4736 monotherapy in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): HAWK (NCT02207530). *First Author: Dan Paul Zandberg, University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD*

Background: Patients (pts) with R/M SCCHN have a poor prognosis, with current systemic therapy options after failure of first-line platinum-based chemotherapy yielding objective response rates (ORRs) of approximately 10% and an overall survival (OS) of 6 months. In SCCHN, tumors create a highly immunosuppressive environment and evade immune detection by exploiting inhibitory immune checkpoints such as the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis. Upregulation of PD-L1 by SCCHN tumor cells is associated with inhibition of antitumor T-cell responses. Thus, therapeutic intervention with immune-modulating agents targeting this pathway holds promise. MEDI4736 is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD-80 with high affinity and selectivity. Evidence of clinical activity for MEDI4736 in R/M SCCHN has been seen in a Phase 1 study (NCT01693562), with initial data indicating that PD-L1 expression is associated with a higher ORR. A comprehensive clinical development program of MEDI4736 in SCCHN is underway. Here we describe the HAWK study (NCT02207530), a trial with registrational potential, assessing MEDI4736 monotherapy in pts with PD-L1$^+$ R/M SCCHN. **Methods:** In this Phase 2, open-label, single-arm, multicenter study, 112 PD-L1$^+$ pts will be enrolled from North American and European sites to investigate the efficacy and safety of MEDI4736 (10 mg/kg IV every 2 weeks for up to 12 months). Eligible pts, who are immunotherapy naïve and have tumor progression or recurrence during or after treatment with 1 platinum-containing regimen for R/M disease, will receive MEDI4736 monotherapy. The primary outcome measure is ORR (RECIST v1.1), based on independent central review. Secondary outcome measures will further assess disease control rate, duration of response, progression-free survival, and OS (using RECIST v1.1 and immune-related RECIST criteria); safety (CTCAE v4.03) and tolerability; and health-related quality of life. Exploratory outcomes include PK, immunogenicity, and potential biomarkers of response to MEDI4736. Recruitment is ongoing. Clinical trial information: NCT02207530.

TPS6087 **Poster Session (Board #409a), Sat, 1:15 PM-4:45 PM**

TPExtreme randomized trial: TPEx versus Extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma. *First Author: Joel Guigay, Centre Antoine-Lacassagne, Nice, France*

Background: The EXTREME regimen (6 cycles of 5FU–cisplatin-cetuximab followed by cetuximab maintenance) is currently the standard first line in recurrent/metastatic (R/M) HNSCC. The GORTEC trial evaluating the TPEx regimen (4 cycles of docetaxel–cisplatin-cetuximab followed by cetuximab maintenance) demonstrated good results (median OS 14 months, ORR 54%) with acceptable safety profile, excellent dose intensity, high rate of patients who started maintenance. The aim of the current trial is to compare TPEx and EXTREME regimens. **Methods:** International, randomized, open-label trial. Main inclusion criteria are: histologically confirmed R/M HNSCC not suitable for locoregional treatment, age 18-70 years, PS $<$ 2, creatinine clearance $>$ 60 ml/min, prior total dose of cisplatin $<$ 300 mg/m^2. The control arm EXTREME : 6 cycles, every 21 days, of cisplatin 100 mg/m^2 day1, 5FU 4000 mg/m^2 continuous infusion day1-4, and weekly cetuximab 250 mg/m^2 (1st loading dose 400 mg/m^2) followed by weekly cetuximab 250 mg/m^2 maintenance. The experimental arm TPEx: 4 cycles, every 21 days, of docetaxel 75 mg/m^2 day1, cisplatin 75 mg/m^2 day1, and weekly cetuximab 250 mg/m^2 (1st loading dose 400 mg/m^2), followed by cetuximab 500 mg/m^2 maintenance every 2 weeks. If cisplatin is not tolerated or its total cumulative dose reaches 600 mg/m^2, it must be replaced by carboplatin AUC5. G-CSF prophylactic administration is mandatory for each cycle in the TPEx arm. Only patients with CR/PR/SD will continue the cetuximab maintenance until PD or unacceptable toxicity. The primary endpoint is OS. Assuming a 2-sided type I error of 0.05, observing 295 deaths will provide a 80% power to detect a hazard ratio of 0.72. 295 deaths are expected out of 416 patients (208 per arm). Secondary endpoints are ORR, best response rate, PFS, TTP, toxicity and QoL. Tumor response assessments (Weeks 6, 12 and 18, then every 8 weeks until PD) will be reviewed by a blinded central image review committee. HPV central analysis and cost-effectiveness study are ancillary studies. GORTEC (France), AIO-Studien-gGmbH (Germany), TTCC (Spain) joint trial in collaboration with French GETTEC, GERCOR, H&N UNICANCER groups. Unrestricted grant from Merck Serono. Clinical trial information: NCT02268695.

TPS6088 **Poster Session (Board #409b), Sat, 1:15 PM-4:45 PM**

Window of opportunity trial of HPV E7 antigen-expressing *Listeria*-based therapeutic vaccination prior to robotic surgery for HPV-positive oropharyngeal cancer. *First Author: Brett Miles, Department of Otolaryngology, Mount Sinai Medical Center, New York, NY*

Background: The incidence of human papilloma virus-associated oropharyngeal cancer (HPVOPC) has rapidly risen over the past two decades. Foreign viral antigens make HPVOPC an attractive target for immunotherapy. One exciting approach is the use of live attenuated *Listeria monocytogenes* bioengineered to express the HPV16 E7 protein (LmE7) and elicit a vigorous immune response. We designed a phase II "window of opportunity" trial with robust correlative endpoints to determine the effect of LmE7 vaccination on anti-tumor immunity in the tumor microenvironment and peripheral blood, as well as safety and tolerability in the HPVOPC population. **Methods:** **Trial Design:** Non-randomized single-arm phase II clinical trial utilizing a Simon's two-stage design. HPVOPC patients receive two cycles of LmE7 over 5 weeks prior to standard-of-care transoral surgical resection of their tumor with or without neck dissection. The primary objective is to determine the rate of post-vaccination T cell responses by measuring the pre- and post-treatment mean frequency of peptide-specific IFN-γ expressing T cells in the peripheral blood by ELISPOT. We will conclude that LmE7 is likely highly immunogenic and worth further investigation if post-treatment responses are seen in $>$ 75% of patients. **Inclusion Criteria:** Previously untreated surgically-resectable stage II-IV HPVOPC, HPV-positive by PCR-based testing. **Exclusion Criteria:** Prior history of cancer within 3 years, or any history of systemic cancer therapy; immunosuppressive disorder or medications; medical contraindications to therapy. **Correlative Studies:** The pattern of immunocyte infiltration in the tumor and draining lymph nodes will be assessed by multiplex immunofluorescence; expression profile of immune-related genes assessed by nanostring; and T cell receptor diversity by deep sequencing. These tissue-based changes will be correlated with comprehensive analysis of immune changes in the peripheral blood **Status:** Open, actively accruing. 8 of a maximum 22 (9 in first stage, 13 in second stage) vaccinated patients, and 0 of a maximum 10 untreated observational cohort patients have been enrolled. Clinical trial information: NCT02002182.

6500 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

The Technology Enhanced Navigation (TEN) Trial among low-income patients with breast cancer. *First Author: Kathy J. Helzlsouer, The Prevention and Rsrch Ctr, Baltimore, MD*

Background: Socioeconomic disparities negatively impact adjuvant breast cancer treatment completion. A web-based knowledge application was developed in collaboration with breast cancer survivors and evaluated in a randomized clinical trial for the impact on treatment adherence with and without virtual navigator support. The application provides direct links to vetted websites for both study arms, and, for the intervention arm, tailored documents, short instructional videos, and navigator visits via videoconference or phone are provided. **Methods:** Eligible patients were newly diagnosed with non-metastatic breast cancer, low-income (U.S. Department of Housing and Urban Development guidelines) Maryland residents, and recommended to have adjuvant treatment. Patients were given a netbook computer, training, and 12 months of wireless Internet access and randomized to either the application alone (control arm) or to the application and nurse/social worker navigation support (intervention arm). Adherence was assessed by medical record review and measured by percent initiating/completing recommended treatment. Baseline characteristics and results were compared by study arm using t-tests, chi-square, and Poisson regression analyses. **Results:** Of 150 eligible patients, 101 were enrolled; 49 on each arm evaluable. The majority were non-white (67%) and unemployed/on disability (68%); 47% had a high school education or less. Over 70% of participants on both arms agreed that the computer application was easy to use; confidence in using the application was high (71% intervention arm; 67% control arm). On the control arm, 10 adjuvant treatments were refused totally or in part among 6 patients; 2 on the intervention arm ($p = 0.04$). Three control-arm patients refused multiple treatments: one refused surgery and radiation; another refused radiation and hormone therapies and discontinued chemotherapy; another refused chemotherapy and hormone therapy. One patient on the intervention arm refused post-mastectomy radiation and another completed chemotherapy, initiated hormone therapy, but discontinued radiation therapy. **Conclusions:** Among low-income patients with breast cancer, adherence to adjuvant therapy was improved with navigator support compared to application-access alone. Clinical trial information: NCT01596179.

6501 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Financial burden of cancer clinical trials: Impact of an equity program intervention. *First Author: Ryan David Nipp, Dana-Farber / Harvard Cancer Center, Boston, MA*

Background: Cancer patients (pts) often experience financial burden, but little is known about the additional burden of clinical trial (CT) participation. Additionally, CT enrollment among underserved groups is lacking. We sought to examine the impact of a cancer care equity program (CCEP) on CT enrollment and to assess pt-reported barriers to CT participation. **Methods:** We implemented a CCEP at Massachusetts General Hospital (MGH) in 2014 to help fund non-clinical expenses related to CTs (e.g. travel, lodging). To determine the impact of the CCEP on CT enrollment, we compared CT enrollment in 2014 (after initiating the CCEP) to 2012 and 2013. We used multiple regression analysis to evaluate changes in CT enrollment. To assess financial barriers to CT participation, we administered surveys to CCEP pts and a comparison group of non-CCEP pts. We used chi-square tests to compare CCEP and non-CCEP pts. **Results:** In 2014, cancer CT enrollment increased by 17% and 40% compared to 2012 and 2013. Adjusting for CT availability, phase, and cancer type, CT enrollment increased significantly from 2013 to 2014 ($p = 0.02$). In 2014, CT enrollment increased among racial minorities ($p < 0.01$) and those living > 50 miles from MGH ($p < 0.01$). Comparing CT pts who enrolled in CCEP to those who did not, more CCEP pts were female (68% vs 51%, $p < 0.01$), under age 65 (74% vs 64%, $p = 0.05$), with metastatic disease (90% vs 72%, $p < 0.01$), incomes $<$ \$50k/yr (24% vs 15%, $p = 0.03$), and in phase I CTs (76% vs 50%, $p < 0.01$). Of 87 pts who completed the financial barriers survey (61% response rate), we received responses from 49 CCEP pts and 38 non-CCEP pts. More CCEP pts reported financial concerns (56% vs 11%, $p < 0.01$). Compared to non-CCEP pts, more CCEP pts reported concerns with medical costs (47% vs 14%, $p < 0.01$), travel (69% vs 11%, $p < 0.01$), lodging (60% vs 9%, $p < 0.01$), and insurance coverage (43% vs 14%, $p = 0.01$) related to CT participation. **Conclusions:** CT enrollment increased after the implementation of a CCEP, particularly among underserved groups. While CTs often represent the best option for pts with cancer, pts served by the CCEP report significant financial barriers to CT participation. These findings stress the need to recognize and address the financial burden of CT participation.

6502 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Trends in resource utilization and costs during implementation of a lay navigation program. *First Author: Gabrielle Betty Rocque, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

Background: Lay navigators provide support to patients from diagnosis through survivorship or end of life. We hypothesized that integrating lay navigators into the care team would lead to reduced healthcare utilization and cost. **Methods:** Medicare claims data were obtained for patients ≥ 65 years old diagnosed with cancer in 2008-2014 within the UAB Health System Cancer Community Network (UAB CCN) (12 cancer centers in AL, MS, TN, GA, FL) to identify the percentage with ≥ 1 ER visit, hospitalization, ICU admission, or hospice admission. Analysis period runs from 1/1/2012 to 6/30/14. The first patient was enrolled in the navigation program in March 2013, and ~30% of patients were navigated by June 2014. Costs for Medicare were assessed, excluding prescription drugs. We used general linear models to evaluate changes in both health care utilization and cost from the pre- (1/1/12-2/28/13) to the post- implementation period (3/1/13-6/30/14). **Results:** We observed decreases after implementation from 13.4% to 11% for hospitalizations (18% decrease, $p < 0.01$), 8.0% to 7.1% for ER visits (12% decrease, $p < 0.01$), 2.9% to 2.5% for ICU admissions (14% decrease, $p = 0.04$) and an increase of 3.9% to 4.3% for hospice (9.2% increase $p = 0.37$). Costs decreased about \$158 per quarter per beneficiary over the analysis period. A significant pre-post decrease of \$952 per beneficiary ($p < 0.01$) lead to an estimated total reduction in Medicare costs of \$18,406,920 for the 19,335 beneficiaries in the UAB CCN for the five quarters post-implementation. **Conclusions:** Thislay health navigator program may increase hospice use and reduce health care use and costs. Further analysis of its direct impact is warranted. *The project described was supported by Grant Number 1C1CMS331023 from the Department of Health and Human Services, Centers for Medicare & Medicaid Services. The contents of this abstract are solely the responsibility of the authors and do not necessarily represent the official views of the U.S. Department of Health and Human Services or any of its agencies.*

6503 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

How should we estimate costs of care attributable to cancer? *First Author: Aileen B. Chen, Dana Farber Cancer Inst, Boston, MA*

Background: Costs of care attributable to cancer are distinct from total costs of medical care, and transparent methods are needed to inform decisions about value of interventions. We measure how alternative strategies for specification of cancer-free control cohorts influences estimation of cancer-attributable costs. **Methods:** Using SEER-Medicare data, we calculated mean Medicare spending from one month prior until 11 months following diagnosis among patients > 66 diagnosed with lung, breast, prostate, and colorectal cancers from 2007-2009. Cancer attributable costs were estimated by subtracting monthly costs for cancer patients from one of 3 alternative reference cohorts: 1) non-cancer Medicare patients individually matched by age, gender, race, and SEER region, 2) non-cancer Medicare cohort matched on demographic factors with the addition of modified Charlson comorbidity score, 3) monthly costs from 2 to 13 months prior to diagnosis, using cancer patients as their own control. **Results:** Cancer-attributable costs were highest for all patients when using their own pre-diagnosis costs as comparison. Cancer-attributable costs were higher among breast and prostate, but lower among lung and colorectal patients, when using non-cancer controls and matching by comorbidity in addition to demographic characteristics. The greatest variation was seen for prostate cancer, with 39-73% of total costs attributed to cancer depending on reference cohort. Meantotal and cancer-attributable costs are summarized in the Table. **Conclusions:** Choice of reference group can have a substantial impact on proportion of total costs attributed to cancer and should be clearly delineated in analyses of cost and value.

Mean Medicare costs in year 1 (\$).

		Cancer-attributable costs, by reference group (% total costs attributed to cancer)		
	Total costs	Non-cancer patients, demographic match	Non-cancer patients, demographic and comorbidity match	Cancer patients as own control, year prior to diagnosis
Lung n = 43,196	47,366	31,703(67)	28,725(61)	35,476(75)
Breast n = 33,674	30,958	14,653(47)	15,242(49)	22,749(73)
Prostate n = 42,079	25,126	9,774(39)	11,048(44)	18,320(73)
Colorectal n = 29,075	54,144	38,184(71)	37,235(69)	43,621(81)

6504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Cost of chemotherapy for metastatic colorectal cancer with either bevacizumab or cetuximab: Economic analysis of CALGB/SWOG 80405. *First Author: Deborah Schrag, Dana-Farber Cancer Institute, Boston, MA*

Background: CALGB/SWOG 80405, a phase III trial, found that adding either bevacizumab or cetuximab to standard first-line chemotherapy for metastatic colorectal cancer (mCRC) resulted in similar survival. We compared the economics of treatment on each arm. **Methods:** Patients were assigned to standard chemotherapy (Cx) and randomized to either bevacizumab (B, N = 559) or cetuximab (C, N = 578).Quality of life was assessed at baseline and at 8 week intervals using the EQ5D on a representative subgroup of participants (N = 56 for B and N = 55 for C) to estimate utilities. Because survival and quality of life were similar in each arm, cost-minimization rather than cost-effectiveness analysis was performed. Chemotherapy utilization was tracked from randomization to progression and drug costs were estimated using 4thquarter 2014 average sales price from the US Center for Medicare and Medicaid Services. Resource utilization of acute care including hospitalizations, emergency room visits and ICU care were tracked while patients were on study and costs assigned based on CMS estimates for mCRC patients. End of life and downstream costs were assumed to be comparable per survival month. Out of pocket costs were not tracked. All cost estimates are in 2014 USD. **Results:** Acute care costs were similar but drug costs were higher in the cetuximab arm (Table). Results were robust to sensitivity analyses and did not change whether the chemotherapy backbone included oxaliplatin or irinotecan. **Conclusions:** For first-line chemotherapy treatment of patients with kras wild type mCRC, based on US 2014 drug costs, bevacizumab is preferable to cetuximab from a health economic standpoint. Clinical trial information: NCT00265850.

Mean Costs of treatment for participants in CALGB 80405	Chemo+B N=559	Chemo+C N=578	Difference (95% CI)
Protocol-directed chemotherapy	$37,124	$75,845	$-38,720 (-45,699 to -31,740)
Acute care on study	$28,951	$29,494	$-543 (-2831 to +1,745)
Chemo and acute care costs	$66,076	$105,339	$-39,264 (-46,521 to -32,005)

6505 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Necitumumab in metastatic squamous non-small cell lung cancer (mSqN-SCLC): Establishing a value-based cost. *First Author: Daniel A. Goldstein, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: The SQUIRE trial demonstrated that adding necitumumab to chemotherapy for patients with mSqNSCLC produces a median overall survival benefit of 1.6 months (hazard ratio 0.84). The objective of this study was to evaluate the range of drug costs for which adding necitumumab to chemotherapy could be considered cost-effective. **Methods:** We developed a Markov model to compare the incremental cost-effectiveness of standard chemotherapy with or without necitumumab in the first-line treatment of mSqNSCLC. In the model, patients received gemcitabine and cisplatin for 6 cycles or gemcitabine, cisplatin, and necitumumab for 6 cycles followed by maintenance necitumumab. The clinical inputs were the survival benefits and frequency of adverse events (AEs) described in the SQUIRE trial. Weibull models were fitted to the survival curves in the SQUIRE trial. The cost inputs included drug costs based on the Medicare average sale prices, and costs for drug administration and the management of AEs based on Medicare reimbursement rates (all in 2014 US $). Model robustness was addressed by probabilistic sensitivity analyses (PSA) in which we ran 10,000 Monte Carlo simulations sampling from the distributions for all variables. We performed multiple model simulations each time varying Willingness To Pay (WTP) values to evaluate the incremental cost effectiveness ratio (ICER) across a range of values for the cost of necitumumab. **Results:** In the base case analysis, the addition of necitumumab produced an incremental survival benefit of 0.15 life years (LY) and 0.11 quality-adjusted life years (QALY). The PSAs established that: when necitumumab cost < $563 per cycle there was 90% confidence that the ICER for adding necitumumab would be < $100,000/QALY; when necitumumab cost $1309 per cycle there was 90% confidence that the ICER would be < $200,000/QALY; and when the cost of necitumumab was > $6,628 per cycle there was > 99% confidence that the ICER would be > $500,000/QALY. **Conclusions:** These findings provide a value-based range for the cost of necitumumab from $563 to $1309 per cycle. This study provides a framework for establishing value based pricing for new oncology drugs entering the US marketplace.

6506 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Value of information analyses for real-time prioritization decisions within a cancer clinical trials cooperative group. *First Author: Caroline Savage Bennette, University of Washington, Seattle, WA*

Background: Cancer clinical trials groups face excess demand for limited research funds and patient populations. Value of Information (VOI) analyses are an emerging methodology that can help align research investments with areas that could have the greatest impact on patient outcomes, but many questions remain concerning its feasibility and acceptability to inform real-world research prioritization decisions. Our objective was to develop and assess a process for calculating VOI in "real time" to inform trial approval decisions within SWOG, a large US-based cancer clinical trials cooperative group. **Methods**: We developed a rapid, reproducible modeling approach to estimate VOI, and applied the method to nine phase II/III trial proposals for breast, gastrointestinal (GI) and genitourinary (GU) cancer that were reviewed by SWOG leadership between 2008-2013. The decision models for each trial proposal were based on the trial design and informed from the literature. "Clinical" (benefits only) and "economic" (treatment and trial costs) VOI estimates were calculated using Bayesian updating methods. We customized the process using stakeholder input. **Results**: VOI modeling was feasible for 8 of 9 trial proposals. Model construction and calculations took <1 week per proposal. Net VOI results varied widely from proposal to proposal (Table). SWOG leaders felt that VOI analyses would likely be useful to inform future trial proposal evaluations. **Conclusions:** We developed an efficient and customized process to calculate the expected VOI for cancer clinical trial proposals that is feasible for use in real-time decision-making and acceptable to SWOG stakeholders. Prospective use and assessment of this approach is currently underway within SWOG.

Net VOI metrics for 9 retrospective trial proposals.

Proposal ID	Phase	Sample Size	Committee	Per-Patient VOI	Population-level VOI
A	3	630	GU	$42,000	$3,100,000,000
B	3	1486	GU	-$77,300	-$4,222,364,596
C	2	200	GI	-$23,000	-$1,210,000,000
D	2	120	GI	-$14,476	-$1,900,000,000
E	2	92	GI	-$ 6,400	-$ 700,000,000
F	3	690	Breast	-$ 5,900	-$ 700,000,000
G	3	720	Breast	$ 2,600	$ 400,000,000
H	3	3400	Breast	$ 5,400	$ 400,000,000
I	3	680	Breast	-	-

6507 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Physician-driven variation in non-recommended imaging for women with early stage breast cancer. *First Author: Allison Nicole Lipitz Snyderman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Some women at low risk for metastasis receive imaging for staging of early breast cancer, despite ASCO Choosing Wisely recommendations and NCCN guidelines supporting the contrary. The objective of this study was to assess the extent to which the observed variation in use of imaging in this context reflects physician-driven practice. **Methods:** Retrospective analysis using population-based SEER-Medicare data to examine the likelihood that a woman would receive a non-recommended imaging test (i.e., CT scan, PET scan, or bone scan) if her physician's last patient received one. The cohort included women ages 66 and over diagnosed with early stage breast cancer between 2000 and 2007, who had surgery within 6 months of diagnosis (n=66,149 women). We also assessed the extent of variation in imaging between physicians using a non-linear random-effects model. **Results:** Fourteen percent of our cohort received at least one imaging test between diagnosis and surgery. Over 3,800 physicians had at least two patients assigned, representing approximately 98% patients, and were included in the analysis. The likelihood that a woman would receive an imaging test was over three fold higher if her physician's prior patient received an imaging test, adjusting for patient characteristics (adjusted odds ratios ranged by imaging test from 3.05 to 6.54) (Table). From the random effects models, a test of whether the estimated variance of the random effects is significantly different from zero provides indication of significant unexplained variation across physicians ($p<0.0001$ for all models). **Conclusions:** We observed a substantial physician-driven influence on imaging for women with early stage breast cancer. Our findings support intervening at the physician level, specifically targeting high users, to help reduce the use of these potentially harmful and costly services.

Adjusted odds ratio [95% confidence interval] of patient receiving non-recommended imaging test if the physician's prior patient received imaging test.

	Any imaging	CT scan	PET scan	Bone scan
Prior patient received imaging test	3.27 [3.09-3.45]	3.05 [2.83-3.29]	5.79 [4.63-7.24]	6.54 [6.11-7.01]

6508 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Prevalence and consequences of second opinions from medical oncologists for early-stage breast cancer: Results from the iCanCare study. *First Author: Allison W. Kurian, Stanford University Medical Center, Stanford, CA*

Background: A second medical oncology opinion (SMO) may facilitate increasingly complex decision-making about use of chemotherapy. However, little is known about use of SMOs in the community or the interplay between SMOs and the quality of decision-making or chemotherapy use. **Methods:** We surveyed women newly diagnosed with early-stage invasive breast cancer in 2013-2014, accrued approximately 5 months after diagnosis through two population-based SEER registries (Georgia and Los Angeles), about their experiences with medical oncologists, their decision-making, and their use of chemotherapy. We evaluated demographic, clinical and decisional factors associated with SMO using logistic regression. **Results:** Among 1350 surveyed patients with invasive disease who consulted with a medical oncologist and answered questions about second opinions, 9.5% had SMO and 3.3% received chemotherapy from the SMO provider. On multivariable analysis that included an extensive list of demographic covariates and clinical factors, younger age (odds ratio, OR = 0.96, 95% confidence interval, CI 0.92-0.99), usage of a web-based support group (OR = 1.32, 95% CI 1.05-1.67) and education (p-value = 0.03) were significant predictors of SMO. On univariate analysis, compared to non-recipients, SMO recipients less strongly wanted their doctor to tell them what to do (none or little of the time: 27.0% vs. 18%, p-value = 0.008). Patient ratings of satisfaction with chemotherapy decision-making were high and did not differ between those who did versus did not receive an SMO (86.3% quite or totally satisfied vs 85.8%, p-value = 0.87). Chemotherapy use did not differ between SMO recipients vs. non-recipients (p-value = 0.7). **Conclusions:** SMO use and treatment by SMO clinicians was remarkably low among early-stage breast cancer patients. High decision satisfaction and no difference between SMO receipt groups suggest little unmet demand. While chemotherapy use did not vary between SMO recipients vs. non-recipients, additional measures of treatment quality will be presented. Funding: P01-CA-163233

6509 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Financial insolvency as a risk factor for mortality among patients with cancer. *First Author: Aasthaa Bansal, University of Washington, Seattle, WA*

Background: Patients with cancer are more likely to file for bankruptcy than the general population, but the impact of severe financial distress on health outcomes among cancer patients is not known. **Methods:** We linked Surveillance, Epidemiology and End Results (SEER) cancer registry records and federal bankruptcy records for Western Washington and identified patients who were diagnosed with cancer from 1995 to 2009. We used propensity score matching to account for differences between patients who filed for bankruptcy and those who did not, with respect to age, gender, race, marital status, residence type, income, stage at diagnosis, and treatment(s) received. In the propensity score matched sample, we used Cox proportional hazards models to compare overall survival between patients who filed and those who did not. **Results:** Compared to patients who did not file for bankruptcy (n = 226,868), those who filed (n = 4,728) were more likely to be younger, female, non-white, have local or regional (vs. distant) stage disease at diagnosis and have received treatment. After propensity score matching, 7,682 patients remained in the analysis, 3,841 subjects in each group. Both groups had a mean age of 53 (SD 14.7), more men than women (54%), a mean income of $49,000 (SD $12,000), and majorities of white (86%), married (60%) and urban (91%) patients. Most patients in both groups were diagnosed with local or regional stage cancer (84%) and both groups received similar first courses of treatment. Compared to cancer patients who did not file for bankruptcy, the adjusted hazard rate for mortality among patients who filed was 75% higher [HR 1.75, 95% CI (1.61, 1.91)]. Excess mortality risk following bankruptcy varied by cancer type, with colorectal, prostate, lung and thyroid cancers having the highest risk. Excluding patients who were distant stage at cancer diagnosis from the analysis had little impact on the mortality risk. **Conclusions:** Severe financial distress requiring bankruptcy protection following cancer diagnosis appears to be a risk factor for mortality. Further research is needed to understand the process by which extreme financial distress influences survival after cancer diagnosis, and to find factors that could mitigate this risk.

6510 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

The impact of patient navigation on racial and ethnic disparities: Results from the patient navigation research program. *First Author: Naomi Ko, Boston Med Ctr, Boston, MA*

Background: Disparities in cancer outcomes for racial and ethnic minorities are an ongoing problem, in part due to persistent delays in timely care for at-risk patient populations. Patient navigation was developed to address barriers to timeliness. This study explores whether patient navigation reduces racial and ethnic disparities in timely cancer care. **Methods:** This is an analysis of the multi-site Patient Navigation Research Program. Participants were age 18 or older, had an abnormal cancer screening test, and were allocated to either the navigation arm or control arm (usual care). The outcome was time to diagnostic resolution of a screening abnormality. Unadjusted median time (25^{th}, 75^{th} percentile) to resolution was calculated for each racial/ethnic group by navigation and control. Multivariable Cox proportional hazards models were fit, adjusting for sex, age, cancer screening type, and health insurance, stratifying by center of care. **Results:** Among a sample of 7,514 participants, average age was 45.1, 89% were women, 43% Hispanic, 29% Non-Hispanic White (NHW) and 28% Black. Median time to resolution was similar across control and navigated arms for NHW patients [65 days (31, 220) for control and 67 days (33, 196) for navigation] and Hispanic patients [68 days (31, 208) and 62 days (34, 120)]. Black patients had longer median time to resolution in the control arm [108 days (42, 315)], still lagging in the navigated arm [97 days (49, 230)]. In the multi-variable adjusted models of the control arm, Black race was significantly associated with increased risk of delay (HR = 0.77; 95% CI: 0.69, 0.84) compared the NHW (reference) group. Hispanic race showed a non-significant increased risk (HR = 0.98; 95% CI 0.89, 1.07). There was borderline significance of an increased benefit of navigation among the navigated Hispanic group (HR 1.10; 95% CI: 0.998, 1.2), but a continued delay in diagnostic resolution among navigated Black patients (HR = 0.85; 95% CI: 0.77, 0.94) when compared to the NHW group. **Conclusions:** This study demonstrated significant delays in timely diagnostic care among Black participants. While navigation benefited minority groups, it did not eliminate all disparities in timely care for Black populations.

6511 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Effect of organizational approaches on safety-net hospitals' cancer care quality. *First Author: Nina A. Bickell, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Safety-net hospitals, historically at higher risk for delivering poor-quality care, provide a disproportionate amount of care to vulnerable populations. Some safety-net institutions deliver excellent quality cancer care. We undertook this study to determine the impact of organizational factors on breast cancer care quality. **Methods:** We abstracted charts of 389 breast cancer patients treated in 2009-12 at 9 inner-city safety-net hospitals with high proportions of minority breast cancer patients to measure underuse of needed adjuvant treatment. We interviewed 90 key informants (n = 59 clinical; n = 16 administrative; n = 12 clerical; n = 3 other) about how care is coordinated and delivered. Using Qualitative Comparative Analysis, we defined "conditions"—handoffs, no-shows, organizational culture—that particularly impact care coordination, categorized hospitals into low (< 10%), intermediate (10-20%) and high (> 20%) underuse of needed adjuvant therapies, and calibrated each of the "conditions." Hierarchical models assess impact of organizational and patient factors on underuse. **Results:** Underuse ranged from 8% to 29%. Higher quality sites designated individuals to track & follow-up no-shows; shared clinical information during handoffs; had fully integrated EHRs enabling providers and clerks to transfer responsibility across specialties; had strong system support; paid close organizational attention to clinic patients; and allocated adequate resources for the cancer clinics. Organizations with a patient-centered culture focused on making processes easier for patients. Poor quality sites lacked these organizational characteristics. Multivariate modeling found that beyond older patient age (RR = 1.89; 1.14-3.15), hospitals with strong approaches to follow-up affect underuse rates (RR = 0.24; 0.08-0.738). **Conclusions:** At safety-net hospitals, underuse of needed cancer therapies is affected by older patient age and organizational approaches to track and follow-up treatment. These findings offer strategies to safety-net hospitals to improve cancer care quality.

6512 Poster Discussion Session; Displayed in Poster Session (Board #69), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Development of cost and quality composites for the 2012 ASCO Choosing Wisely measures: Methods and evidence. *First Author: Melora K Simon, Stanford University's Clinical Excellence Research Center (CERC), Stanford, CA*

Background: Oncology clinics, health care systems, and payers are considering how to gauge performance for the ASCO Choosing Wisely (CW) program. We sought to develop a clinic-level composite CW metric that accounts for adherence to the 2012 CW measures. We also measured total cost of care. **Methods:** SEER cancer registry records for western Washington State from January 2007 to May 2014 were linked with claims from a large regional commercial insurer to develop algorithms to characterize each CW measure and assign patients to their primary oncology provider. In addition, a time-based episode was developed to capture total cost of care related to each CW measure. For each clinic, we looked at the observed to expected ratio across the CW measures and the total cost of care measures, with expected defined as the average clinic rate for each measure. A composite score for each was derived by dividing the weighted observed/expected ratio by the clinic volume. **Results:** Among the 14 clinics with the highest patient volume, the number of eligible commercially insured patients ranged from 531 to 1532 depending on the CW measure. Clinic scores on the CW measures ranged from 25% to 100%. The observed to expected adherence composite scores ranged from 0.77 to 1.13 (SD-0.11) while the cost composite scores ranged from 0.68 to 1.40 (SD-0.21). Adherence and cost of care were not well-correlated. Three clinics had better than expected composite adherence score and lower than expected costs. We identified these as "high value outliers." Five clinics had better than expected composite adherence score and higher than expected costs. 3 clinics each had lower than expected composite adherence scores and either higher or lower than expected costs. **Conclusions:** Identifying high performing clinics using individual CW metrics is complex - clinics vary widely in their adherence across metrics. We intend to assess convergence between the composite score and expert opinion through site visits, while using a similar approach in other geographies to increase our sample. Our composite score approach may assist decision makers in identifying the best clinics. To better gauge value, costs of care should also be considered alongside performance.

6513 Poster Discussion Session; Displayed in Poster Session (Board #70), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Trends in antineoplastic receipt after Medicare payment reform: Implications for future oncology payment design. *First Author: Helen M. Parsons, The University of Texas Health Science Center at San Antonio, San Antonio, TX*

Background: The Medicare Modernization Act (MMA) changed antineoplastic reimbursement from average wholesale price to average sales price +6%, reducing many outpatient reimbursement rates and altering practice patterns for lung cancer. To further evaluate the MMA's effect, we focus on colon cancer, where longstanding fluorouracil-based regimens were augmented in 2004 with 3 newly-approved drugs (oxaliplatin, bevacizumab, and/or cetuximab). **Methods:** Using the 2000-2009 SEER-Medicare data, we examined trends in chemotherapy use and type of antineoplastic received among 59,642 stages II-IV colon cancer patients. Logistic regression models tested the effect of time (pre-post the 2005-2006 reimbursement change) and setting (physician offices implemented reimbursement changes in 2005 vs hospital outpatient departments (OPD) in 2006); interaction terms tested for differential effects of MMA implementation in the 2 settings. Models controlled for patient demographic and tumor characteristics. **Results:** Overall, 16.3% of stage II, 52.4% stage III and 39.6% stage IV colon cancer patients received antineoplastics. After the reimbursement change in 2007-09 relative to 2000-03, stages II (marginal probability (MP) = -0.06, $p < 0.01$) and III (MP = -0.04, $p < 0.01$) patients decreased antineoplastic use, while stage IV patients increased use (MP = 0.03, $p < 0.01$). While use of fluorouracil-based therapy decreased slightly after reimbursement changes (MP:-0.07 stage II; -0.04 stage III; -0.04 stage IV; $p < 0.01$ for all), use of new drugs increased substantially (MP: 0.47 stage II; 0.67 stage III, 0.77 stage IV; $p < 0.01$ for all). Use of new drugs for stage IV cancer occurred earlier in physician offices compared to OPDs ($p < 0.01$). **Conclusions:** Colon cancer patients saw small decreases in treatment with fluorouracil-based chemotherapy, but large increases in newly approved drugs after the MMA. Trends suggest slightly earlier increases in physician office settings for stage IV patients, consistent with an MMA effect. The identifiable effects of the MMA are relatively small, but highlight the responsiveness of providers to changes in reimbursement, and the need to integrate new drugs into payment schema.

6514 Poster Discussion Session; Displayed in Poster Session (Board #71), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A randomized controlled trial (RCT) to improve enrollment to cancer clinical trials. *First Author: Catriona Parker, Cancer Council Victoria, Melbourne, Australia*

Background: The proportion of adults with cancer recruited to clinical trials is low. Cancer Council Victoria awards funding to clinical trial sites through its Clinical Trials Management Scheme (CTMS). With this state-wide scheme, there appeared to be a temporal relationship between growth or stability in funding and the number of patients recruited. We undertook a RCT to evaluate the hypothesis that additional funding would improve trial recruitment. **Methods:** Participating sites (n = 34) were stratified into four strata based on 2011 recruitment numbers. Control sites (n = 18) received usual CTMS funds only while intervention sites (n = 16) received usual funds plus additional funds, proportional to the number of patients recruited in 2011. Additional funding was a median increase of 300% (IQR: 112.5%, 459%) relative to usual CTMS funds and was an average 11.8% (IQR: 8%, 12.3%) increase in a site's budget. Additional funds were provided in early 2013. Sites were to use funds with the aim of increasing recruitment. The primary study endpoint was the number of new participants recruited to clinical trials in 2013 relative to recruitment in 2012. Negative binomial regression analysis was used to model the endpoint in intention-to-treat analysis adjusting for any imbalance in randomized groups' features and historical recruitment. An online survey was used to assess strategies employed to increase recruitment. **Results:** The median number of new trial recruits in 2013 was 21 (IQR: 5, 39) in the control arm and 12.5 (IQR: 3.5, 44.5) in the intervention arm. The ratio of the annual recruitment rate of new trial recruits at the intervention sites compared to control sites in 2013 adjusting for 2012 numbers and institution type was 0.99 (95%CI: 0.69, 1.43, p = 0.96). We found no evidence of a differential intervention effect across strata of higher pre-trial recruitment ($\chi^2_3 = 2.27$, p = 0.5). The survey revealed most intervention sites utilized funds for increased staffing. **Conclusions:** Additional funding at a site level did not lead to a contemporaneous increase in trial recruitment. A lag-effect may become apparent. In our setting, simply providing more funding without targeting and managing its use does not immediately increase trial accrual.

6515 Poster Discussion Session; Displayed in Poster Session (Board #72), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Psychosocial outcomes of the electronic self-report assessment for cancer-II randomized trial. *First Author: Donna Lynn Berry, Dana-Farber Cancer Institute, Boston, MA*

Background: TheElectronic Self-Report Assessment for Cancer (ESRA-C), a web-based intervention, is known to improve patient-provider communication and reduce overall cancer symptom distress in adults on active cancer therapy. ESRA-C provides patients with self-monitoring of cancer symptoms and quality of life, self-care instructions, and communication coaching, and gives clinicians a color coded summary. **Methods:** Secondary data analysis of the ESRA-C II randomized trial data explored the effect of ESRA-C on psychosocial outcomes during therapy in 581 adults with various cancers.Role (RF), social (SF) and emotional function (EF) were assessed with the Quality of Life Questionnaire-Core 30 (QLQ-C30) (higher score, better function), and depression outcomes by the Patient Health Questionnaire -9 (PHQ9) (lower score, less depression). Outcome scores were compared between groups using analysis of covariance (ANCOVA) and regression adjusting for baseline scores and selected variables. **Results:** Significantly lower PHQ9 scores were observed (p = 0.02) for the intervention group. Marginally significant higher functional scores in the intervention group were detected for RF (p = 0.07) and SF (p = 0.1). Results remained after adjusting for age, clinical service and working status. Working at enrollment contributed to higher role (p = 0.008), emotional (p = 0.09) and social function (p = 0.02) and lower depression (p = 0.05). **Conclusions:** Self-monitoring, self-care education, communication coaching plus a simple clinician summary, resulted in significantly better psychosocial outcomes for patients receiving active cancer therapy.The association of working status with positive outcomes may reflect a benefit for work-able individuals. Clinical trial information: NCT00852852.

	RF		EF		SF		PHQ9	
	Est	P-val	Est	P-val	Est	P-val	Est	P-val
Univariate ANCOVA								
Group (ESRA-C vs. control)	3.40	0.07	0.95	0.43	3.01	0.10	-0.60	0.02
Baseline score	0.49	<.0001	0.55	<.0001	0.55	<.0001	0.57	<.0001
Multivariable ANCOVA								
Group (ESRA-C vs. control)	3.54	0.07	0.79	0.54	3.49	0.07	-0.56	0.04
Age	-0.06	0.51	0.05	0.34	-0.03	0.72	0.01	0.40
Service		0.27		0.19		0.11		0.25
Working (No vs. yes)	-5.91	0.008	-2.48	0.09	-5.31	0.02	0.62	0.05
Baseline score	0.49	<.0001	0.53	<.0001	0.52	<.0001	0.55	<.0001

6516 Poster Discussion Session; Displayed in Poster Session (Board #73), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Patient-reported care coordination and outcomes of colorectal cancer surgery. *First Author: Sarah T. Hawley, University of Michigan, Ann Arbor, MI*

Background: Care coordination is an essential component of effective, patient-centered cancer care. Yet little is known about the impact of patient reported care coordination on clinical outcomes, such as postoperative complications following high risk colorectal cancer surgery. **Methods:** In 2011-13, we surveyed Stage III colorectal cancer patients from Detroit and Georgia SEER registries 4-12 months after diagnosis. The primary outcome was self-report of a postoperative complication. We adapted a validated 6-item scale to assess perceived coordination across the overall continuum of cancer care (range 6-30). We used a separate 7-item scale to assess perceived care coordination specifically pre- and postoperatively (range 7-35). We compared the association between postoperative complications and overall and pre- /postoperative care coordination with chi-square tests. We assessed associations between complications and coordination in each phase of care in separate models, using logistic regression to control for age, race, education and insurance. **Results:** Among 1465 patients who returned surveys (RR = 66%), 23.1% reported a postoperative complication. Most respondents perceived their care coordination to be good overall (mean: 25.9, SD: 3.7), as well as pre- (mean: 29.5, SD 4.6) and postoperatively (mean: 30, SD 4.3). Older, minority and those with more comorbidities significantly more often perceived poor care coordination ($P < 0.001$). In adjusted analyses, postoperative complications were inversely associated with perceptions of good care coordination overall (OR: 0.72, 95% CI: 0.59-0.97) and with better pre- and post-operative coordination (OR = 0.96, 95% CI = 0.93-.98; OR = 0.93, 95% CI = 0.91-0.97, respectively). **Conclusions:** Similar to other large studies, complications in this sample were common after colorectal cancer surgery. Reported care coordination was good for most patients, but less so for certain vulnerable subgroups. Better care coordination was associated with lower rates of surgical complications. Such findings indicate that better care coordination may lead to better clinical outcomes, however further work to confirm and expand these results is needed.

6517 Poster Discussion Session; Displayed in Poster Session (Board #74), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Family perspectives on aggressive cancer care near the end of life. *First Author: Alexi A. Wright, Dana-Farber Cancer Institute, Boston, MA*

Background: Advanced cancer patients are receiving increasingly aggressive medical care near death, despite growing concerns that the use of hospital-based services at the end of life (EOL) reflects poor quality of care. **Methods:** We surveyed bereaved family members of 1,159 older patients participating in the Cancer Care Outcomes Research and Surveillance study (CanCORS; a national, prospective, observational cohort study) who were diagnosed with or recurred with advanced lung or colorectal cancer, and who died by 2011. We assessed whether bereaved family members' perceptions of the quality of patients' EOL care were associated with claims-based measures of aggressive medical care before death, adjusted for patients' demographic and clinical characteristics, mental illness, and treatment preferences. **Results:** Bereaved family members of patients who enrolled in hospice ≥ 3 days before death (n = 601) were more likely to report excellent quality of EOL care compared with those who enrolled later or did not receive hospice care (n = 558; adjusted proportion: 58.5% vs. 42.7%, $P < 0.001$). In contrast, family members of patients admitted to the ICU within 30 days of death (n = 153) were less likely to report excellent quality of EOL care than those who were not (n = 1,006; adjusted proportion 44.4% vs. 52.9%, P = 0.03), as were family of patients who died in the hospital (n = 467; adjusted proportion 41.8% vs. 57.1%, $P < 0.001$). Frequent use of the emergency department in the last month of life was not associated with lower family-reported ratings of EOL care quality (n = 92 with ≥ 2 visits; adjusted proportion 50.5% vs. 50.9%, P = 0.79); nor was the receipt of chemotherapy within 2 weeks of death (n = 77; adjusted proportion 48.7% vs. 51.1%, P = 0.80). **Conclusions:** Our findings suggest that efforts to improve earlier hospice enrollment, reduce ICU admissions at the EOL, and avoid terminal hospitalizations are important to improve the quality of cancer care and families' experiences. While existing quality measures characterize the repeated use of emergency visits and chemotherapy near death as poor quality care, we could not detect a difference in family ratings of care by these measures.

6518 Poster Discussion Session; Displayed in Poster Session (Board #75), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Use of online communication and social media by newly diagnosed breast cancer patients: Results from the iCanCare Study. *First Author: Sarah T. Hawley, University of Michigan, Ann Arbor, MI*

Background: Online communication (OC) and social media (SM) could be used to enhance cancer treatment decision-making and care support. Yet, virtually nothing is known about whether and how newly diagnosed cancer patients use different forms of OC and SM during the treatment decision process. **Methods:** A weighted random sample of breast cancer patients newly diagnosed in 2013-14 were identified from Los Angeles and Georgia SEER registries and surveyed approximately 6 months after diagnosis (current response rate 68%). Respondents were asked whether they used different forms of OC (email or texting) or SM (facebook, twitter or blogs), how often, and for what purpose. We evaluated patient factors (age, education, race, stage, family history) associated with some/frequent use using logistic regression. We assessed purpose of OC and SM by patient factors using chi-square tests. **Results:** In a preliminary sample (n=2,021), 37% reported some or frequent use of either OC or SM to discuss the diagnosis, treatment decisions, or care support. There was a strong inverse relationship between increasing age and use (Table). Patients most likely to use any form (vs. never) were younger (age < 45 and 45-54) (OR: 4.0; 95% CI 2.8-5.7 and OR: 2.5; 95% CI 1.8-3.4), more highly educated (OR: 2.5, 95% CI: 1.9-3.5), and white (OR: 2.4; 95% CI 1.8-2.9). Of some/frequent users, the most common reasons were for letting people know about the diagnosis (69%), getting advice about treatments (56%), and for dealing with negative feelings/emotions (46%). Less common reasons were for sharing opinions about doctors (31%) or deciding on doctors (22%). More frequent users more often reported a deliberative decision process and had higher decision satisfaction ($P<0.05$) than never users. **Conclusions:** The substantial use of OC and SM for treatment decision and care support suggests growing opportunities to incorporate these modes into clinical practice. Future research should address optimal ways to incorporate these modes of engagement to improve experiences for all patients. Funding: NCI P01CA163233

	Use of OC or SM for treatment decision or care support (%)		
	Never	Some	Frequent
< 45	37	29	33
45-54	54	22	23
55-64	60	18	21
65+	75	13	12
P<0.001			

6519 Poster Discussion Session; Displayed in Poster Session (Board #76), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Email communication practices and preferences among patients and providers in a large comprehensive cancer center. *First Author: Natalie Cook, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Little is known about how email is currently used in healthcare to facilitate patient care. The objective of our study was to understand current practices and preferences of patients (pts) and physicians (MDs) for email communication. **Methods:** Separate cross-sectional surveys were administered to pts and MDs (staff physicians and clinical fellows) at Princess Margaret Cancer Center. Survey domains included current email and internet use practices, digital literacy skills, perceived barriers and preferences regarding email use to facilitate care. Logistic regression was used to identify factors associated with current email use. Chart review was conducted to assess the impact of email communication on care. **Results:** The survey was completed by 833 pts, of which 50% reported previous email contact with a healthcare professional (HCP) including administrative assistants (52%), MDs (51%: 36% with specialist; 18% with primary care; 3% both) and nurses (45%). Most pts (87%) were satisfied with this method of communication. Patient factors associated with higher likelihood of email contact with a HCP included younger age ($p<0.0001$), higher education ($p<0.0001$) and higher income ($p<0.0001$). Enrollment in clinical trials ($p<0.0001$), receipt of multiple treatments ($p=0.001$) and receipt of chemotherapy ($p=0.0006$) were also associated with higher likelihood of email contact. Pts had less concerns about using email for health care if they had prior email contact with HCPs compared to those with no prior email contact (60% vs. 70%; $p=0.004$). Of the 80 MDs who responded to the survey (response rate 30%), 80% had previous contact with a pt via email although only 24% felt this should be used regularly to communicate with pts. All MDs reported email contact with other HCPs about pt related matters and all felt this to be an effective way to communicate. 962 pt charts were reviewed with email correspondence documented in 9% of cases. **Conclusions:** Email is commonly used for pt care but poorly documented and there may be a mismatch between pt/MD preferences. The use of email in this setting can be developed with appropriate guidance, however there may be concerns about widening the gap for certain groups of pts.

6520 Poster Discussion Session; Displayed in Poster Session (Board #77), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Disease-specific hashtags for online communication about cancer care. *First Author: Matthew S. Katz, Radiation Oncology Associates, Lowell, MA*

Background: A majority of patients and health care professionals are now online. Our hypothesis is that disease-specific cancer hashtags may be a way to access accurate health information and positive interactions. **Methods:** Based upon two de novo hashtags, #bcsm and #btsm, an organized system of hashtags, the cancer tag ontology (CTO) was designed in July 2013 for online use. We conducted a retrospective study of 25 hashtags used on Twitter April 2011 – September 2014 using data from Symplur, LLC. We classified up to 100 most active users of each hashtag as follows: patient; doctor; non-doctor health care professional (HCP); individual NOS (I); healthcare organization (HCO), other organization (OO); or spam. Tweet activity was analyzed quarterly for all tags. **Results:** During the study period, there were a total of 531,765 tweets from 77,454 users. The two original hashtags #bcsm and #btsm had the most use with 249,312 and 110,465 tweets, respectively. The other tags were used almost exclusively starting Q3 2013 onward. Overall, the most active new tags were those with organized Twitter-based chats: #ayacsm; #gyncsm; #lcsm; #mmsm; and #pancsm. These seven accounted for 93% of total Twitter activity. In the cohort, 11% were patients, 20% doctors, 3% HCP, 32% I, 30% HCO, 1% OO, and 3% spam. The most active top users were patients with an median of 46 tweets. Activity increased from 13,778 tweets in Q3 2011 to 75,960 tweets in Q3 2014. For the 23 structured tags, quarterly use increased from 18,098 tweets in Q3 2013 to 39,761 tweets in Q3 2014. **Conclusions:** We have demonstrated the feasibility and growth of organized, cancer-specific hashtags on Twitter used by a variety of stakeholders in cancer care. Use of the CTO indicates potential value of online interaction. Further study is needed to determine whether the CTO has any impact on access, outcomes or as a model for other areas of medicine.

6521 Poster Discussion Session; Displayed in Poster Session (Board #78), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Machine-learning prediction of cancer survival: A prospective study examining the impact of combining clinical and genomic data. *First Author: David M. Ashley, Andrew Love Cancer Centre, Geelong, Australia*

Background: Accurate prediction of survival in patients with cancer remains a challenge due to the ever-increasing heterogeneity and complexity of cancer at the molecular level, in treatment options and patient populations. Data mining using machine learning techniques (MLT) may enhance our ability to deal with such complexity. The current work tests the hypothesis that by combining digital data contained in a rich purpose-built epidemiological and clinical cancer registry with patient specific genomic data, using MLT, we could enhance our previously published methods in predicting clinical outcomes. **Methods:** Cancer 2015 is a large-scale prospective epidemiological, clinical and molecular cohort study in which tumors underwent mutational analysis from using the Illumina TruSeqAmplicon 48 gene Cancer Panel. Data from 1002 patients were used to model survival at 12 months. Machine-learning prediction using comprehensive data that included demography, tumor stream information, co-morbidities, past history and patient presentation details was then compared using the Area Under the Curve (AUC) with a model combining the same data and the mutational status results for each tumor. **Results:** Of the 48 genes examined mutations in only 4 genes present in patient samples significantly contributed as independent risk factors in predictions of survival, these included: FGFR2 (odds ratio = 4.1304), RB1 (odds ratio = 2.7295), BRAF (odds ratio = 2.2513), KIT (odds ratio = 2.2464). However, when considering this entire population the addition of all genomics data did not significantly improve 12 month prediction of survival. Combined clinical and genomics data model yielded an AUC of 0.8502 (0.8468-0.8536) whilst the clinical data model alone yielded an AUC of 0.8464(0.8429- 0.8498). **Conclusions:** Whilst the presence of some specific mutations contributed to the prediction of survival, overall genomic information in this group did not enhance survival prediction by MLT beyond that of clinical and epidemiological data alone.

6522 Poster Discussion Session; Displayed in Poster Session (Board #79), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Predicting low accrual in the Clinical Trials Cooperative Group Program's phase II/III oncology trials. *First Author: Caroline Savage Bennette, University of Washington, Seattle, WA*

Background: Although general barriers to clinical trial accrual are well described, the extent to which trial-level factors differentially influence accrual to individual trials has not been comprehensively studied. Our objective was to study the empirical relationship and predictive properties of a broad set of putative risk factors for low accrual among NCI's Clinical Trials Cooperative Group Program (CTCG), now the National Clinical Trials Network. **Methods**: Data from 787 phase II/III adult CTCG trials that opened 2000-2011 were used to develop a logistic regression model to predict low accrual, defined as trials that closed with or were accruing at < 50% of target; 46 trials opened 2012-2013 were used for validation. Candidate predictors of accrual were identified from a literature review and expert interviews. Model performance was evaluated by calibration and discrimination via the area under the curve (AUC). **Results**: The multivariable model (Table) had good calibration and discrimination to predict trials with low accrual (AUC in trials launched in 2012-2013: 0.73; 95% CI: 0.58, 0.88). Results were robust to different definitions of accrual success and model selection strategies. **Conclusions**: Prospectively, a prediction tool based on multiple trial-level risk factors may help quantify the risk of low accrual for cooperative group trials. Such a tool could inform trial design, aid prioritization decisions, and help target limited resources to support accrual where most needed.

Multivariable model to predict low accrual in CTCG phase II/III trials.

Risk Factor	Odds Ratio	95% CI
Annual incidence of clinical condition(s), per 10,000	0.98	0.95, 1.00
Common solid tumor setting (prostate, breast, lung, colon)	2.11	1.14, 3.88
# Competing trials/10,000 eligible patients	1.86	1.31, 2.66
>1 condition evaluated	1.88	1.17, 3.03
Enrollment as % of eligible population, per %	2.67	1.36, 5.25
Investigational new drug (IND)	0.21	0.09, 0.51
Interaction term (Phase III x IND)	3.41	1.02, 11.45
Metastatic setting	1.46	0.81, 2.63
Phase III (vs II)	2.63	1.52, 4.54
Radiation therapy	2.01	1.26, 3.21
Sample size, per 100	0.96	0.93, 1.00
Targeted therapy	0.54	0.34, 0.87
Tissue sample required to assess eligibility	1.33	0.88, 2.02

6523 Poster Discussion Session; Displayed in Poster Session (Board #80), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Colonoscopy versus less invasive approaches for colorectal cancer (CRC) screening (Scr): A strategic perspective. *First Author: Afsaneh Barzi, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Colonoscopy (CS) is an effective approach to Scr for CRC. Given its invasive nature, interest exists to find other Scr strategies (STs) with DNA stool testing being the most recent. Stool tests (STT) are dichotomous and a positive test typically results in a CS and then a negative CS would dictate the future Scr regime. We compared Scr STs in terms of their effectiveness (E), costs (C), and cost effectiveness (CE) to define the characteristics of a test or ST that can successfully compete or replace CS. **Methods**: Using a societal perspective, 12 STs and No Scr were compared. Using a Markov model 100,000 simulated individuals (SIs) 50 to 75 years of age with average risk of CRC were followed for up to 35 years. E (life years gained- LYG) and C (C of Scr and CRC) were calculated per SI. **Results**: CS dominates all other STs and has the highest LYG and lowest C even compared to No Scr. Under various sensitivity analyses (SA) we find that the results remain stable, primarily due to the high sensitivity (Sen) and specificity (Spe) of CS. DNA testing is not competitive, even among STT, given its high C and minimal improvement on E. For DNA to be competitive compared to other STT, its C must decrease or its Sen must improve. **Conclusions**: CS remains the unrivaled Scr test for CRC. Given CS's impact on incidence by detecting and eliminating precancerous polyps, dichotomous stool testing strategies are at a disadvantage. Value proposition for a new Scr ST is in a departure from dichotomous reporting and providing risk levels that can identify precancerous polyps and influence the Scr regime after a negative CS. This should be regarded as the focus of Scr research and development.

ST	LYG	Costs	ICER
No Scr	14.12	$3,511	#
FO	14.12	$3,419	#
FIT	14.12	$3,523	#
FO+ FS	14.13	$3,322	#
FIT+FS	14.13	$3,409	#
CS	14.14	$3,186	0
FS	14.14	$3,591	#
FO @2	14.12	$3,493	#
FIT @2	14.12	$3,551	#
FO @2+FS	14.13	$3,445	#
FIT @2+FS	14.13	$3,496	#
DNA	14.12	$5,439	#
DNA @3	14.12	$4,315	#

Abbreviations: FO: Fecal Occult Blood Testing, FIT: Fecal Immunochemical Test, FS: Flexible Sigmoidoscopy, @2: at 2 year intervals, @3: at 3 year intervals. Sen for test: FO 64%, FIT: 82%, FS: 75%, CS 95%, DNA 92%. Spe in SA for all tests was 90%. ICER: Incremental Cost Effectiveness Ratio. #: Absolute Dominance.

6524 Poster Session (Board #81), Mon, 1:15 PM-4:45 PM

Developing a CAncer genomics Digital Educational Tool to assess the knowledge and expectations of patients with advanced solid tumors (CADET). *First Author: Herbert H. F. Loong, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Genomic testing in cancer (GTC) is increasingly important to guide therapy for patients (pts) with advanced cancers, as eligibility for many early-phase clinical trials is restricted to patients with specific actionable mutation(s). Using a prospectively administered GTC questionnaire, we previously found that only 48% of pts with advanced solid tumors felt that they had sufficient knowledge to make an informed decision to pursue GTC (Blanchette et al, Cancer, 2014). **Objective:** To develop a digital education tool (DET) to improve pts' knowledge of GTC, and to assess whether such tool can change pts' attitudes and expectations toward GTC. **Methods:** A 5-min video was developed highlighting background information, logistics and rationale for GTC. Pts referred for phase 1 trials and molecular profiling were recruited to view the DET and to complete an identical GTC questionnaire as used in our previous study. These were returned by mail on a voluntary basis. Questionnaire comprised of 12 knowledge of cancer & genomics and 17 attitudes & expectations questions. Results from this cohort (B) were compared with the previously reported cohort (A). **Results:** Between Aug 2013 and Feb 2014, 118 pts consented to the study with 98 pts completing the questionnaire, representing 83% of pts surveyed. Demographics were similar between the cohorts. In terms of knowledge, as an aggregate, more correct answers were identified from questionnaires administered in B vs. A (72% vs. 67%, OR 1.26; 95%CI 1.06 – 1.51, p=0.01). Multivariate analysis adjusting demographics, prior work experience in healthcare or having close family members with cancer confirmed better knowledge score in cohort B vs. A (OR 1.22, 95% CI 1.01 – 1.47; p=0.04). More pts in cohort B felt they had adequate knowledge regarding potential benefits & risks of DNA testing to make an informed decision to purse GTC (66% vs. 48%, p=0.013) and agree that DNA testing may improve cancer treatment (79% vs. 64%, p=0.037). **Conclusions:** This DET helps fulfill the support pts need, enhancing knowledge and affecting attitudes towards GTC. Evaluation of long-term effect of this DET is warranted.

6525 Poster Session (Board #82), Mon, 1:15 PM-4:45 PM

Utilization of palliative chemotherapy for advanced bladder cancer: Patterns of care in routine clinical practice. *First Author: Andrew George Robinson, Kingston General Hospital, Kingston, ON, Canada*

Background: Although palliative chemotherapy for advanced bladder cancer is recommended in clinical practice guidelines, patterns of care in routine care is not described. Here we describe utilization rates of chemotherapy and referral rates to medical oncology in the last year of life among patients who die of bladder cancer. **Methods:** A population based cohort of bladder cancer patients was identified from the Ontario Cancer Registry; the study population included those patients who died of bladder cancer 1995-2009. Electronic records of treatment and physician billing records were used to identify treatment patterns and referral to medical oncology (MO). Log-binomial and poisson regression were used to examine factors associated with chemotherapy utilization and MO consultation. **Results:** 8005 patients died of bladder cancer; 25% (1964/8005) of whom received chemotherapy in the last year of life. Use of chemotherapy was independently associated with patient age (Relative risk (RR) 0.49 70-79 vs < 50 years, $p < 0.001$), comorbidity (RR 0.61 moderate comorbidity vs none, $p < 0.001$), socioeconomic status (RR 0.84 lowest quintile vs highest, $p = 0.01$) and gender (RR 0.91 females vs males, $p = 0.012$). Utilization increased over time (from 22% to 26%, $p < 0.001$) and varied across geographic regions (range 18-30%, $p < 0.001$); these findings persisted on adjusted analyses. 68% (5426/8005) of patients were seen by MO in the last year of life. Factors independently associated referral rates to MO include age (RR 0.82 70-79 vs < 50 years, $p < 0.001$), comorbidity (RR 0.90 moderate comorbidity vs none, $p < 0.001$), socioeconomic status (RR 0.90 lowest quintile vs highest, $p < 0.001$), and gender (RR 0.96 females vs males, $p = 0.023$). Referral rates modestly increased over time (66% to 69%, $p = 0.006$) and varied widely across geographic regions (range (57% to 79%, $p < 0.001$); these findings persisted on adjusted analyses. **Conclusions:** Despite clinical practice guideline recommendations, utilization of palliative chemotherapy for bladder cancer in routine practice remains low. Treatment patterns and referral rates to MO vary substantially across geographic regions.

6526 Poster Session (Board #83), Mon, 1:15 PM-4:45 PM

Is online patient information at NCI cancer centers too complex for broad general readership? *First Author: Stephen Rosenberg, Department of Human Oncology, University of Wisconsin, Madison, WI*

Background: The NIH and the Department of Health and Human Services recommend that online patient information (OPI) be written at a 6th grade level to facilitate broad readership comprehension. We sought to assess the readability of OPI found on NCI Designated Cancer Center websites across the US. **Methods:** Cancer.gov was utilized to identify 68 NCI Designated Cancer Center websites from which we collected both general OPI and specific OPI on breast, prostate, lung, and colon cancer. We then performed a readability analysis with 10 commonly used readability tests: the New Dale–Chall Test, Flesh Reading Ease Score, Flesh-Kinkaid Grade Level, FORCAST test, Fry Score, Simple Measure of Gobbledygook, Gunning Frequency of Gobbledygook, New Fog Count, Raygor Readability Estimate, and Coleman-Liau Index. We sought to test the hypothesis that the readability of OPI from NCI Designated Cancer Centers would be written at the 6thgrade level. As a secondary analysis, we compared readability of OPI between comprehensive and non-comprehensive cancer centers, by geographic region, and to the OPI produced by the American Cancer Society (ACS). **Results:** Data from 40 comprehensive and 18 non-comprehensive NCI Designated Cancer Centers were available for analysis (7 non-clinical centers and 3 without appropriate OPI were excluded). A mean of 30,507 words (range 5,732 – 147,425) were analyzed. A composite measure of grade level was constructed using the 8 readability measures that provide a grade level. These measures were strongly correlated and formed a reliable measure (SI alpha = 0.98). The mean grade level of 12.46 (95% CI: 12.13 – 12.79) was significantly greater than the target reading level ($t(57) = 38.15$, $p < .001$). No statistically significant difference in readability was seen when comparing comprehensive vs. non-comprehensive centers (t range 0.42 – 1.19, $p = 0.24 – 0.69$). Regional differences were identified in 4 of the 10 readability metrics ($p < .05$). The ACS OPI provides easier language, 7-9th grade level, across all tests ($p < .01$). **Conclusions:** OPI found on NCI Designated Cancer websites is more complex for the readership than recommended. This may limit the reach and impact of important cancer information to the public.

6527 Poster Session (Board #84), Mon, 1:15 PM-4:45 PM

A discrete choice experiment to examine the preferences of patients with cancer and their willingness to pay for different types of health care appointments. *First Author: Shu Fen Wong, Deakin University, Waurn Ponds, Australia*

Background: Little comparative data exist on how patients with cancer make choices about accessing health care appointments. Our study used a discrete choice experiment (DCE) to better understand patient preferences regarding their cancer care and potential trade-offs between health care appointment characteristics. **Methods:** Patients diagnosed with cancer at 3 hospitals were recruited to complete a self-administered DCE. Each version of the questionnaire (n = 16) had 8 paired choice scenarios where each health care appointment scenario described 6 attributes (identified through qualitative analysis): expertise of the doctor; familiarity of the doctor with their medical history; waiting time for an appointment; permitted accompaniment by family/friends; travel times to appointments and out-of-pocket costs. Patient preferences were estimated using logistic regression; willingness to pay (WTP) estimates for different aspects were then derived. **Results:** 185 out of 512 patients (36%) returned the questionnaire. Mean age was 61 yrs (22–92 yrs), and the majority was female (60%). Mean time since cancer diagnoses was 34 mths, 90% had received cancer treatment and 61% had early stage disease. The most important attributes for determining patient preferences were the expertise and familiarity of the doctor with their medical history; distance travelled was least likely to influence patient preferences. The WTP analysis found that patients were willing to pay $705 to consult specialists with higher expertise, $572 to consult doctors familiar with their medical history, $464 for shorter waiting times for appointments, $410 to be accompanied by family/friends and $342 for shorter travelling times to appointments. **Conclusions:** Our study could guide the development of patient-centered health care models, with an emphasis on the most important appointment characteristics; models should improve patient access to experienced doctors, and support the role of primary care providers in the community. Interventions to reduce waiting and travel times for appointments and to accommodate medical escorts still influenced patient choices, but to a lesser degree.

6528 Poster Session (Board #85), Mon, 1:15 PM-4:45 PM

Impact of age on the associations between genomic testing in breast cancer (BrCA) and chemotherapy (chemo) use and costs. *First Author: Yu-Ning Wong, Fox Chase Cancer Ctr, Philadelphia, PA*

Background: The 21-gene recurrence score assay (Oncotype Dx) (RS) guides adjuvant chemo use in patients (pts) with BrCA. Since age is associated with chemo appropriateness, we sought to understand if the associations between RS receipt, chemo use, and costs varied by age. **Methods:** We identified 7665 pts diagnosed with node-negative, hormone-receptor-positive BrCA during 2007-2010 using the Pennsylvania Cancer Registry and claims from Independence Blue Cross (IBC) or Medicare for 12 months before and after diagnosis. Propensity-score-weighted regression models were used to assess the independent effect of RS receipt on chemo use and total 1-year post-diagnosis chemo costs by age group, controlling for demographics, insurance, tumor characteristics, and comorbidities. **Results:** Mean age was 71 years (range 23-100). 74% were insured by Medicare. Pts who received RS were younger, had fewer comorbidities, were more likely Stage 1, and were more likely to have IBC coverage ($p < .001$ for all). The proportion of patients undergoing RS testing increased from 17% among pts in 2007 to 28% in 2010. RS use was associated with reduced adjuvant chemo use and lower chemo spending among younger pts, but had minimal effects on chemo use and chemo spending among older pts (Table, * indicates $p < .05$). None of the RS recipients over age 85 received chemo. **Conclusions:** RS testing was associated with lower chemo use in younger pts, but had little effect on chemo use in older pts. The cost savings noted in young pts who underwent the RS test was not seen among older pts. Our results suggest that RS testing is being ordered in many elderly patients for whom chemo is not a realistic treatment option. As additional high-cost genomic tests enter clinical practice, their use should be targeted towards pts in whom the test result will influence clinical decision making.

Age	RS testing	N	Received chemo %	Difference in chemo rate	Mean chemo spending ($)	Difference in chemo spending ($)
< 50	Yes	186	47	-18*	21000	-23000*
	No	297	65		44000	
50-64	Yes	459	34	-9*	9500	-12500*
	No	673	43		22000	
65-74	Yes	794	22	1	4100	-2200*
	No	1987	21		6300	
75-84	Yes	300	14	5*	2100	200
	No	2182	9		1900	
≥ 85	Yes	11	0	-2*	60	-130
	No	776	2		190	

6529 Poster Session (Board #86), Mon, 1:15 PM-4:45 PM

The influence of hospital and surgeon factors on the prevalence of axillary evaluation in ductal carcinoma in situ. *First Author: Ellie J. Coromilas, Columbia University Medical Center, New York, NY*

Background: Axillary lymph node evaluation (LND) is standard of care in the surgical management of invasive breast cancer, but benefit has not been demonstrated in ductal carcinoma in situ (DCIS). We aimed to determine the incidence of LND in women with DCIS undergoing breast conserving surgery (BCS) and mastectomy, and to identify clinical, hospital, and surgeon-related factors associated with LND. **Methods:** Perspectives database was used to identify women ages 18-90 with DCIS who underwent BCS or mastectomy between 2006-2012. Analyses were stratified by surgery type, and multivariable regression analysis was used to identify factors associated with LND. **Results:** Of 35,591 women identified with DCIS, 26,580 (74.7%) underwent BCS and 9,011 (25.3%) underwent mastectomy; 17.7% undergoing BCS and 63% undergoing mastectomy had LND. Rates increased over time with mastectomy (2006: 56.6%, 2012: 67.4%) and were relatively stable with BCS (2006: 18.5%, 2012: 16.2%). In a multivariable analysis, Medicaid insurance (RR 1.17, CI 1.05-1.30) and treatment in a non-teaching hospital (RR 1.13, CI 1.06-1.21) or urban location (RR 1.30, CI 1.09-1.55) were associated with LND with mastectomy. Among women undergoing BCS, Hispanic race (RR 1.32, CI 1.00-1.74) and treatment in a non-teaching hospital (RR 1.17, CI 1.03-1.33) influenced LND. Surgeon volume was the most significant predictor of LND with BCS (mid vs. low: RR 0.87, CI 0.70-0.94; high vs. low: RR 0.54, CI 0.44-0.65). Low volume surgeons performed LND in 26.4% of patients undergoing BCS, compared to 20.4% by mid volume and 10.4% by low volume surgeons. **Conclusions:** Despite guidelines recommending against LND in women with DCIS undergoing BCS and lack of evidence for its use with mastectomy, it is frequently performed. Given the additional morbidity and cost of these procedures, alternative surgical approaches or prospective evaluation of the clinical benefit of LND in women with DCIS is needed.

6530 Poster Session (Board #87), Mon, 1:15 PM-4:45 PM

Improving veteran access to lung cancer care (IVaLuCancerCare): A quality improvement project at the Louis Stokes Cleveland VA Medical Center (LSVAMC). *First Author: Rami Manochakian, Louis Stokes Cleveland VAMC/Case Western Reserve University, Cleveland, OH*

Background: At the LSVAMC, one of the largest VA medical centers in the USA, about 190 new cases of lung cancer are diagnosed yearly and 450 veterans are followed for lung cancer care. **"IVALuCancerCare"** is a quality improvement project supported bya grant from theVA Office of Specialty Care Transformation. Through this project, a new multidisciplinary lung cancer program launched in October 2013 to address three gaps in lung cancer care: timeliness of care, coordination of care and access to palliative care. **Methods:** To address the gaps, we targeted three specific aims and proposed the following goals: 1) Increase percentage of non-small cell lung cancer (NSCLC) patients who receive first treatment within 28 days from diagnosis from 33% to 50%. 2) Increase percentage of medical oncology visits that are associated with 2 or more additional appointments on the same day from 33% to 50%. 3) Increase percentage of advanced lung cancer patients who receive a palliative care consultation from 10% to 75% and percentage of those who receive ongoing collaborative palliative care from 0% to 30%. In order to reach our goals, we implemented through this project, and with help from the VA Center for Applied Systems Engineering, multiple interventions including a new dedicated multidisciplinary weekly lung cancer clinic, dedicated patient navigator, weekly lung tumor board and nodule rounds, new lung cancer education clinic, new lung cancer tracking tools, distress screening and management and others. **Results:** From October 2013 to July 2014, percentage of NSCLC patients who received first treatment within 28 days from diagnosis was 58%. Percentage of medical oncology visits that were associated with 2 or more additional appointments on the same day was 60%. Percentage of advanced lung cancer patients who received a palliative care consultation was 90% and percentage of those who received ongoing collaborative palliative care was 69%. **Conclusions: "IVALuCancerCare"** project at the LSVAMC significantly improved the care for veterans with lung cancer. The project's goals were met. We plan to sustain and spread the above changes and identify new ways to further enhance our program.

6531 Poster Session (Board #88), Mon, 1:15 PM-4:45 PM

Cancer pain management practices and their impact on quality of life for Asian cancer patients. *First Author: Yong-Chul Kim, Department of Anesthesiology and Pain Medicine, Seoul National University School of Medicine, Seoul, Republic of Korea, Seoul, South Korea*

Background: In order to implement more effective policies for cancer pain management, a better understanding of current practices and their effects on patients are needed. The ACHEON study was a survey-based investigation of the impact of cancer pain and management practices on patients' quality of life in 10 Asian countries. **Methods:** Patients experiencing cancer pain were randomly surveyed in 10 Asian countries with a 33-item questionnaire assessing attitudes and perceptions towards cancer pain management. Patients aged ≥ 18 years with a documented history of cancer pain in the preceding month were selected. **Results:** Of the 1,190 patients (median age; 53, male/female 805/385) surveyed, 1,026 reported moderate-to-severe pain (median duration, 12 months). The attribution of the pain was 53% from cancer, 18% from cancer-related therapy and 29% from mixed sources. 1,056 (90%) patients were treated for their cancer pain and only 308 patients were receiving opioids, to their knowledge. Patients agreed that their pain affected activities of daily living (86%), sleeping patterns (87%), concentration and focus (92%), as well as causing too much reliance on other people (67%), while only a small proportion reported having a good quality of life (34%). Only 22% of patients were employed, and 44% of those had been absent from work for more than 7 days over the past 3 months due to their cancer pain. It was reported that 42% of the patients who were unemployed had stopped working due to cancer pain. **Conclusions:** The ACHEON study results show that cancer pain significantly affects multiple aspects of quality of life for patients. The development of more effective management practices for cancer pain will require collaborative efforts from institutional, social and regulatory parties.

6532 Poster Session (Board #89), Mon, 1:15 PM-4:45 PM

State variation in Medicare Part D and choice of initial endocrine therapy for breast cancer. *First Author: Liliana E Pezzin, Medical College of Wisconsin, Milwaukee, WI*

Background: Evidence suggests that drug utilization under Medicare Part D has been uneven, varying significantly by geographic region. We sought to examine the extent to which geographic variation in Part D plan characteristics contribute to the variation in choice of initial hormone therapy agent among women with incident breast cancer. **Methods:** Two-stage multivariate regression analyses applied to 23840 Medicare beneficiaries with incident breast cancer in 06-07. The first stage determined the effect of state of residence on the probability of having an aromatase inhibitor (AI, as opposed to tamoxifen) as the initial endocrine therapy, controlling for confounders. The second stage provided estimates of state-specific Part D plan characteristics on state variation in choice of initial hormone therapy. **Results:** There was substantial *residual* geographic variation in the likelihood of using an AI as the initial endocrine therapy, despite controls for socioeconomic status, breast cancer treatment, and other factors. Regression-adjusted probabilities of starting an AI ranged from 53.4% in Wyoming to 82.4% in New York. Nineteen states (38%) had adjusted probabilities significantly different than the national mean: 13 of those were above, while the remaining six states –WY, MT, MN, IA, NH, AR-- were significantly below the national mean. Results from the second stage revealed that variation in characteristics of Part D plans across states explained over one- third (35%) of the overall state-level variability in initiating endocrine therapy with an AI. A higher number of drug plans with cost sharing above the mean, greater spread in deductible costs and a greater spread in monthly drug premiums were associated with lower adjusted state probabilities of initiating an AI. In contrast, a higher number of drug plans with monthly premiums above the state mean and higher mean cost sharing were both positively associated with likelihood of starting on an AI. **Conclusions:** This study suggests that variability in use of AIs-- the newer, more effective breast cancer oral therapy-- could be significantly reduced by changing the benefit design underlying states' Part D plans.

6533 Poster Session (Board #90), Mon, 1:15 PM-4:45 PM

Analysis of home care coordination activities in oncology: A mixed methods study. *First Author: Fatima Yatim, Gustave Roussy, Villejuif, France*

Background: Many studies point out the importance of care coordination, but there are few descriptive studies about the content of coordination activities and how it responds to the needs of patients and professionals. Objectives: To identify the skills and competencies needed to perform home care coordination activities. **Methods:** The study was conducted at Gustave Roussy (Villejuif, France), into the department coordinating outpatient care for patients who need post-discharge home care. In a first step, a data grid was developed (a focus group with the nurses and the head of the department), and then refined during an observation period. After this qualitative analysis, a quantitative analysis studied the phone calls received at the coordination platform of this department (May-June 2014). The following data were systematically collected (date; caller; reason for the call; procedure performed), and then analyzed by two researchers. They identified five categories of actions, one clinical (F1), and four related to managerial and, organizational solutions (F2 to F5), validated by the staff members of the department. **Results:** 543 calls were analyzed. The callers were patients or their relatives (38%), private nurses (35%), medical devices providers (20%), other primary care providers (7%). Five categories of coordination activities were identified: (F1) Patient monitoring and management of clinical and non-clinical alerts (side effects) (32%); (F2) Helping to understand and navigate through the clinical pathway (information about healthcare professional contacts) (21%); (F3) Managing technical problems linked to the achievement of care (problem about medical devices delivery) (17%); (F4) Explaining some elements of the care protocol (use a medical device)(16%); (F5) Collecting and transmitting the patient medical record information (medical prescriptions) (14%). **Conclusions:** The majority of requirements for patients and professionals are related to managerial and organizational issues (e.g. navigation, lack of information about specific aspects of the clinical pathway). They require the implementation of new professional managerial skills, especially among nurse navigators and other new professions.

6534 Poster Session (Board #91), Mon, 1:15 PM-4:45 PM

Patients with advanced non-small cell lung cancer (NSCLC): Are research biopsies a barrier to participation in clinical trials? *First Author: Charles Henry Lim, University of Toronto, Toronto, ON, Canada*

Background: The evolution of targeted therapy in NSCLC has led to growing complexity of clinical research and a heightened expectation of clinical benefit for participants. Clinical trials in NSCLC increasingly require mandatory tumour samples or research biopsies, both potential barriers for trial participation. We assessed the impact of performing research biopsies in advanced NSCLC on clinical trial enrollment. **Methods:** We conducted a retrospective chart review of patients with advanced NSCLC evaluated for systemic therapy clinical trials at the Princess Margaret Cancer Center from 2010 to 2014. **Results:** Of 26 clinical trials reviewed, 21 required tumour samples for enrolment. Eleven required confirmation of a pre-specified biomarker in order to receive investigational treatment. Trial participation was offered to 151 patients at 293 unique study encounters (some enrolled in multiple trials). Forty-three percent proceeded to receive study treatment. Those considering trials without mandatory biopsies or tissue requirement were more likely to proceed to study treatment than those considering trials with these requirements (75% vs. 40%, $p = 0.009$). For trials requiring mandatory tumour samples, 210 consents for participation were obtained, 170 research biopsies were ordered and 88% were performed. Participants proceeded to study treatment in 57% of encounters; 7% of biopsies yielded insufficient tissue and 34% were "biomarker-negative". The most common barriers to trial enrollment included lack of the pre-specified biomarker (40%), other study exclusion criteria (17%), patient refusal of biopsy (11%), insufficient biopsy tissue (9%), and deteriorating clinical status/death (10%). **Conclusions:** With the evolution of personalized medicine, a growing number of NSCLC trials require tumour tissue for treatment eligibility. This has emerged as a significant barrier to clinical trial enrollment. Potential solutions include routine tissue banking at diagnosis, facilitating use of available diagnostic samples (e.g. fine needle aspirates) for trials, development of circulating DNA assays for trials, and more resources for timely tissue acquisition.

6535 Poster Session (Board #92), Mon, 1:15 PM-4:45 PM

Validation of a clinical trial accrual predictive model. *First Author: Wendy R. Tate, The University of Arizona Cancer Center, Tucson, AZ*

Background: The costly and extensive process to drug approval highlights the need to streamline the drug pipeline process. We previously reported a novel predictive model with the outcome of anticipated accrual to be used when considering a prospective clinical trial at our center. Here, we present the results of the validation study. **Methods:** Eligible studies include treatment and supportive care intervention studies permanently closed to accrual between 10/2013 and 01/2015 at our center. Data abstracted from the clinical trials management system (OnCore, Forte Systems, Madison, WI) included: use of investigational drug, disease management team (DMT), use of local IRB, local start date, DMT accrual prediction value, actual total accrual, and clinicaltrials.gov (NCT) number. Abstracted from clinicaltrials.gov were protocol-specific data: number of national sites, national enrollment goal, national start date, and national date of expected primary endpoint completion. Studies were run through the model and actual accrual plotted against predicted accrual. Actual, team- and model-predicted subjects accrued; percent of trials meeting cut-off values; and model sensitivity and specificity were calculated. **Results:** Sixty-one trials met study inclusion criteria. Total accrual was 373 subjects (mean: 6.1 ± 17.2); 16 (26.2%) studies had zero accrual, 23 (37.7%) accrued 88.7% of the total subjects. The model predicted accrual of 513 subjects (138% of actual) versus the DMT predicted accrual of 1111 subjects (298% of actual). The model correctly predicted whether a study would accrue 4+ subjects 75% of the time. Twenty-seven studies (44.3%) correlated perfectly at the category level. Model sensitivity is 70%; specificity is 78%. For the 17 studies not correctly categorized using a cutoff of four, nine (60%) would have been incorrectly opened (predicted 4+, < 4 accrued) and six (40%) would have incorrectly not opened (predicted < 4, 4+ accrued). **Conclusions:** The identified national and local factors to predict clinical trial accrual at our center are valid, showing it to be an accurate, quick and valuable metric in assessing trial success as well as planning resource allocation. Further research includes national expansion of the model to cancer centers.

6536 Poster Session (Board #93), Mon, 1:15 PM-4:45 PM

Emergency diagnosis of lung cancer: An international problem. *First Author: Thomas Newsom-Davis, Chelsea & Westminster Hospital, London, United Kingdom*

Background: Lung cancer survival in the United Kingdom (UK) is lower than similar healthcare systems in Europe. 40% of UK lung cancer patients are first diagnosed with their disease during presentation to emergency or acute medical services. This emergency presentation (EP) is associated with late diagnosis and lower 1-year relative survival. The gatekeeper role of the general practitioner (GP) has been suggested as a possible cause for the high rates of EP in the UK. We investigated whether EP is a feature of other healthcare systems in Europe. **Methods:** Retrospective data was collected on all lung cancer patients diagnosed in 2012 from 11 hospitals in 8 countries: Austria, Croatia, France, Ireland, Italy, Netherlands, Portugal and UK. Where required, ethical approval was obtained prior to data collection. **Results:** 2,315 patients were included, of which 534 (23.1%) were diagnosed as part of an emergency presentation. EP rates between counties ranged from 13.2% to 47.7% and did not correlate with whether GPs act gatekeepers to secondary care services in that country. EP was associated with older age, lower performance status, higher stage of disease, and certain histological sub-types such as small cell lung cancer. EP patients were less likely to receive a histologicl diagnosis, less likely to receive any anti-cancer treatment and if they did receive treatment it was less likely to be with curative intent. 76% of EP patients had significant medical co-morbidities. 59% presented with thoracic symptoms (dyspnea, chest/shoulder pain, cough, haemoptysis). The median length of inpatient stay was 14.31 days (range 0-68 days). Further comparative analysis between countries demonstrates the inter-country variation in patient demographics, presentation and management. **Conclusions:** The emergency route to lung cancer diagnosis is common across Europe, is associated with specific patient demographics, and represents a significant burden on acute services. The gatekeeper role of the GP does not appear to govern EP rates. Establishing the causes behind EP of lung cancer should allow identification, earlier diagnosis and better outcomes for this vulnerable patient population.

6537 Poster Session (Board #94), Mon, 1:15 PM-4:45 PM

Healthcare resource utilization and cost considerations in patients with soft tissue sarcoma treated with chemotherapy. *First Author: Chris M. Kozma, CK Consulting, St. Helena Island, SC*

Background: Locally advanced or metastatic soft tissue sarcoma(STS) is frequently treated with chemotherapy when symptoms develop. Healthcare resource use(HRU) and cost in patients(pts) with STS have not been widely reported. This study provides real world evidence on HRU and costs associated with initiation of STS chemotherapy. **Methods:** Adult patients whose first claim for STS chemotherapy (doxorubicin, gemcitabine, docetaxel, ifosfamide, cyclophosphamide, paclitaxel, dacarbazine, temozolomide, pazopanib, methotrexate, epirubicin, vinorelbine, vinblastine, vincristine) within 90 days of a STS diagnosis were identified in a 2005-2013 U.S. healthcare claims database. Patients had ≥ 12 months continuous enrollment before and six months after the index date (chemotherapy initiation). STS chemotherapy combination regimens were defined as all STS therapies within 90 days of index date. HRU costs were evaluated for the six months following index date. **Results:** This analysis identified 1206 STS patients. Mean (SD) age was 55 (14) years; 50% were male. Common pre-index comorbidities included hypertension (35%), hyperlipidemia (17%), and diabetes (11%). Doxorubicin-based regimens were reported as initial therapy in 44% of patients and gemcitabine-based regimens in 39%. The mean number of months (SD) a claim for STS therapy was observed during the six month period was 3.6 (1.6) months. The proportion of patients with treatment-related claims included radiation oncology 26%, colony stimulating factors 69%, red blood cell growth factors 21%, red blood cell transfusions 16%. During the observation period, the mean (SD) number of hospitalizations was 1.0 (1.7) and mean number of hospital days was 6.2 (11.0). The overall mean (median) cost was $103,000 ($80,750). Component costs are shown in the table below. **Conclusions:** This analysis reported HRU and costs in patients with STS in the six months following initiation of chemotherapy. Such information is useful to stakeholders in understanding the management of patients with STS and those with interest in episode of care costs.

	Hospitalization	Outpatient	Pharmacy	Emergency Room
Mean component cost	$26,300	$69,100	$6,500	$1,100

6538 Poster Session (Board #95), Mon, 1:15 PM-4:45 PM

Disparity by insurance status and race in receipt of aggressive and advanced treatments for high risk prostate cancer/PCa. *First Author: Brock R. Baker, UNC Chapel Hill, Chapel Hill, NC*

Background: Young and healthy men with high-risk PCa require aggressive treatment. We examined treatment received by these men using the National Cancer Data Base, which contains 70% of incident cancers across the US. We hypothesized a disparity by race and insurance on receipt of aggressive treatment and access to advanced surgical (robotic) and RT (proton or intensity-modulated RT) techniques. **Methods:** 12,778 men age < 65 with Charlson comorbidity score 0 diagnosed with NCCN high-risk PCa from 2010-12 were included. Logistic regression examined factors associated with treatment. **Results:** 97% received definitive treatment (either radical prostatectomy or radiation). However, there was a dramatic difference in use of RP by race (White 73%, Black 50%) and insurance (Private 71%, Medicaid 38%)(Table). On multivariate analysis (MVA) which adjusted for age, facility type and regional sociodemographics, race (Black vs White, OR .45, $p < .001$) and insurance (vs private, Medicaid OR .32, uninsured .39, $p < .001$ for both) remained associated with prostatectomy as primary treatment. Among surgical patients, 73% with private insurance received robotic surgery compared to 54% Medicaid patients (Table). In MVA, insurance was significantly associated with robotic surgery (vs private, Medicaid OR .48, uninsured .42, $p < .001$ for both). In MVA for RT patients, Medicaid vs private insurance was associated with less advanced technology (OR .73, $p = .02$). Black vs White race were not significantly different in receipt of advanced surgical or RT technologies. **Conclusions:** Young/healthy men with high-risk PCa who lack private insurance or were non-white were treated less aggressively. Medicaid and uninsured patients were also less likely to receive advanced surgical and RT technologies. These findings are difficult to explain medically and point to differences in treatment access.

Percentage of patients receiving each treatment.

		Primary Treatment			Surgical Technique			RT Technique		
		Prostatectomy	Not	p	Robotic	Not	p	Advanced	Not	p
Race	White	73	28	< .001	72	28	< .001	71	29	.002
	Black	50	50		68	32		66	34	
	Hispanic	61	39		61	39		67	33	
				p			p			p
Insurance	Private	71	29	< .001	73	27	< .001	70	31	.01
	Medicaid	38	62		54	46		61	39	
	Uninsured	44	56		51	49		68	33	

6539 Poster Session (Board #96), Mon, 1:15 PM-4:45 PM

Impact of health insurance transitions on cancer survivors and those with no cancer history. *First Author: Katherine S. Virgo, Emory University, Atlanta, GA*

Background: 15.4% of the U.S. population was uninsured in 2012. Those without coverage face limited health care access and are more likely to have poor outcomes. Cancer survivors are particularly at risk of insurance gaps due to the long-term nature of the disease. This study examines the association between cancer history and health insurance transition patterns, including insurance gain or loss, and the impact on access to care. **Methods:** Using longitudinal data from the Medical Expenditure Panel Survey (MEPS) for 2008-2012 (panels 12-16), 2386 cancer survivors and 41,211 individuals with no cancer history ages 18-63 upon MEPS survey entry during 2008-2011 were selected. Individuals were categorized as initially uninsured or insured based on first stable consecutive three-month insurance status. Multivariate logistic regressions were used to assess the association between cancer history and insurance loss or gain based on first coverage change, adjusting for the MEPS complex survey design. **Results:** Uninsured cancer survivors were more likely to gain insurance and insured cancer survivors were less likely to lose insurance than those with no cancer history (42.5% and 34.1%; 9.9% and 14.6%, respectively). In adjusted analyses, cancer history was positively associated with insurance gain and negatively associated with insurance loss; but insignificant ($p = 0.06$; $p = 0.11$, respectively). Initially uninsured, younger (18-34), non-Hispanic white, occasionally employed, risk-averse individuals were more likely to gain insurance. Initially insured, younger (18-44), low income, occasionally employed males in fair to poor health were more likely to lose insurance. Those remaining uninsured or losing insurance were more likely to experience problems accessing needed medical care and less likely to have a usual source of care. **Conclusions:** Cancer history is associated with health insurance transition patterns. Different factors impact insurance gain and loss. Cancer survivors need stable health insurance coverage, yet coverage is inconsistent. Providing incentives to those with inconsistent access, such as the young, to enroll in health insurance could decrease volatility in coverage and improve continuity of care.

6540 Poster Session (Board #97), Mon, 1:15 PM-4:45 PM

Comprehensive genomic profiling of rare tumors in a dedicated community clinic. *First Author: William Jeffery Edenfield, Clinical Research Unit – ITOR Greenville Hospital System, Greenville, SC*

Comprehensive genomic profiling of rare tumors in a dedicated community clinic W. Jeffery Edenfield[1], Ryan Fields[1], Siraj M. Ali[2], W. Larry Gluck[1], Julian Chmielecki[2], Jeffrey S. Ross[2], Phillip J. Stephens[2], Vincent A. Miller[2], Ki Chung[1] [1]Greenville Health System Cancer Institute, Greenville,SC. [2]Foundation Medicine, Boston, MA **Background:** Rare tumors by European Union (EU) definition are uncommon (< 6/100,000 patients), but aggregately number more than all other solid cancers. With few prospective trials to guide treatment, therapy is based on minimum merit by case reports and small series. Comprehensive genomic profiling (CGP) may provide insight into tumor biology and identify rational therapeutic choice. **Methods:** In March 2014, the rare tumor clinic began evaluating 4-6 patients/month using CGP. DNA was extracted from 40 micron FFPE sections from 39 patients. All classes of genomic alterations were evaluated. Important alterations identified links to marketed drugs available or agents under evaluation in mechanism driven trials. **Results:** Patients were diverse. Of the 39, 6 each of biliary origin or sarcomas, 5 each neuroendocrine or glandular head and neck, and 3 mixed mullerian tumors. Nearly half had commercial drug options (18/39); 15/39 had available trial choices matched to their alteration. 61% of patients derived actionable information. 9 patients had both off-label and trial options. Marked clinical response to pazopanib in a patient with metastatic hemangioendothelioma and VHL mutation as well as a novel melanoma *ALK-OTAF* fusion will be reported separately. 3 potential germ line mutations were identified. **Conclusions:** CGP of tumors from 39 patients with rare cancers provided relevant information in the majority of cases. Although outcomes data are premature, this approach represents a reasonable standard for patients with rare cancers. The potential discovery of germline associated malignancy identifies the need for genetic consultation.

6541 Poster Session (Board #98), Mon, 1:15 PM-4:45 PM

Precision oncology: molecular testing and targeted treatment beyond indication. *First Author: Josh John Carlson, University of Washington, Seattle, WA*

Background: Advances in cancer research indicate that successful treatment may depend more on genomic alterations in the tumor rather than the organ of origin. However, data on the use of off-label molecular testing and targeted treatment is lacking. Our objective was to evaluate off-label testing and targeted treatment in a commercially insured population. **Methods:** We analyzed data from the MarketScan databases, a large employer-based claims repository, from 2011-2013 on the use of off-label molecular tests and targeted drugs for the top 10 incident cancers. We limited the analysis to the metastatic setting using a previously validated algorithm. We defined off-label use as using the test or agent in a tumor type not included in an FDA-approved medication label. **Results:** Test use was limited overall, but rose considerably in 2013 with the most use in lung, colon, and breast cancers. There was also limited though non-negligible use of targeted agents with the most common being erlotinib, imatinib, trastuzumab, vemerafinib, and dasatinib. Drug use rates remained relatively constant over the three-year period. Off-label treatment was most common in breast, lung, and colon cancers. **Conclusions:** There is limited but non-negligible use of off-label molecular testing and targeted treatment in the top 10 incident cancers. Further work will explore predictors of off-label use and patient outcomes.

	2011		2012		2013	
Tests	**n**	**%**	**n**	**%**	**n**	**%**
EGFR			0	0.00%	213	0.37%
BRAF			12	0.02%	378	0.66%
Bcr-Abl1			0	0.00%	128	0.22%
KRAS			6	0.01%	331	0.58%
Drugs*						
Erlotinib	37	0.06%	34	0.05%	25	0.04%
Afatinib	0	0.00%	0	0.00%	1	0.00%
Dabrafenib	0	0.00%	0	0.00%	5	0.01%
Vemurafenib	18	0.03%	20	0.03%	13	0.02%
Trastuzumab	17	0.03%	20	0.03%	23	0.04%
Lapatinib	6	0.01%	4	0.01%	5	0.01%
Imatinib	27	0.04%	23	0.03%	25	0.04%
Nilotinib	3	0.00%	1	0.00%	2	0.00%
Dasatinib	12	0.02%	18	0.03%	8	0.01%
Crizotinib	1	0.00%	6	0.01%	4	0.01%

*Trametinib, pertuzumab, trastuzumab emtansine, basutinib had no use reported.

6542 Poster Session (Board #99), Mon, 1:15 PM-4:45 PM

Social-ecological perspectives on breast cancer care seeking patterns in Karnataka, India. *First Author: Arun S. Shet, University of Minnesota, Minneapolis, MN*

Background: India bears approximately ten percent of the global burden of breast cancer but has lower survival rates than developed countries possibly due to delays in diagnosis and treatment. Early recognition and diagnosis of breast cancer potentially offers the opportunity for treating the early stage disease and potentially improve treatment outcomes. The underlying factors responsible for delays in access to treatment are not well-defined. There are few published studies that attempt to understand the factors that facilitate or impede care-seeking and timely diagnosis and treatment of breast cancer in the Indian context. **Methods:** Using the social-ecological theory of behaviour, we conducted semi-structured in-depth interviews with 27 breast cancer patients and 22 primary caregivers receiving care at a non-profit tertiary care hospital in Bengaluru, India to understand how care-seeking and the timing of diagnosis and treatment were influenced by multilevel factors, including knowledge and awareness of breast cancer, family and community reactions to symptoms and diagnosis, and availability and access to different types of clinical services. **Results:** Factors that impeded timely diagnosis and treatment were women's lack of awareness about the signs and symptoms and the need for timely care-seeking, competing family/household priorities, fear of a cancer diagnosis, inconsistent pathways through the healthcare system for diagnosis and treatment, financial constraints, and fear and stigma related to cancer.The main facilitators in care seeking included hope of getting cured, financial and social support from the family. **Conclusions:** A range of multilevel factors seem to be associated with women's breast cancer care trajectories. Qualitative findings suggest that multifaceted interventions that address knowledge, fear and stigma among individuals, families and communities and that improve access to health care through financial protection may be needed to downstage breast cancer in India.These emerging findings from our qualitative research are being used to develop a quantitative instrument to further study this issue using a more representative sample.

6543 Poster Session (Board #100), Mon, 1:15 PM-4:45 PM

Medical Oncologists' and Surgeons' approaches to communication of breast cancer recurrence risk. *First Author: Aaron Sabolch, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI*

Background: Risk of breast cancer recurrence can be estimated with tools such as Adjuvant! Online, but little is known about how medical oncologists and surgeons use such tools or communicate risk information to patients. **Methods:** In 2012, we surveyed 750 medical oncologists and 750 surgeons identified using the AMA Physician Masterfile (a comprehensive physician list not limited to AMA members). Using a vignette, we evaluated risk communication practices (discussing risk using descriptive words, discussing risk using numbers, using online calculators, providing copy of risk estimates) and analyzed correlates of specific approaches in a logistic regression model that included physician (e.g., gender, specialty) and practice characteristics (number of breast cancer patients seen in past year, multidisciplinarity [i..e., offering same-day multi-specialty appointments]). **Results:** 498 surgeons and 398 medical oncologists responded (60.5% response rate). We excluded 130 who did not see breast cancer pts. Respondents averaged 19 years in practice, 79% were male, 74% saw > 10 breast cancer pts/yr, and 45% offered same-day multi-specialty appointments. 84% of medical oncologists and 85% of surgeons reported discussing recurrence risk using terms such as "high risk." Medical oncologists were much more likely than surgeons to use an online risk calculator (76 vs 24%, $p < .001$), provide numerical risk estimates (88 vs 47%, $p < .001$), and provide a copy of risk estimates (71 vs 17%, $p < .001$). Specialty ($p < .01$) and multidisciplinarity ($p < .01$) were the only significant independent correlates of communication practices. After controlling for specialty, clinicians offering same-day multi-specialty appointments were more likely to use online calculators (OR 1.6, 95% CI 1.1 - 2.3) and discuss numerical risk estimates (OR 1.8, 95% CI 1.2 - 2.5). **Conclusions:** Most medical oncologists use online calculators and numerical estimates to communicate recurrence risk to breast cancer patients; fewer surgeons do so. Patients who do not see a medical oncologist until after surgery may make critical treatment decisions (including whether to remove the contralateral breast) without full understanding of relevant risk information.

6544 Poster Session (Board #101), Mon, 1:15 PM-4:45 PM

A systematic approach to smoking cessation in Ontario's Regional Cancer Programs. *First Author: William K. Evans, McMaster University, Hamilton, ON, Canada*

Background: Smoking cessation (SC) is rarely undertaken in busy cancer centres but potential health benefits in cancer patients include improved general health, improved all-cause and cancer-specific mortality, reduced toxicity, greater response to treatment, decreased risk of disease recurrence and of second primaries. Based on this evidence, Cancer Care Ontario (CCO) undertook a SC initiative for new ambulatory cancer patients in its Regional Cancer Programs (RCPs). **Methods:** A steering committee recommended a framework for SC in RCPs in 2012, based on the Ottawa Model for Smoking Cessation. The initiative was piloted in all 14 provincial health regions in 2014. Regional SC "champions" participated in monthly web meetings, data calls and in-person meetings led by a secretariat at CCO. Presentations on the health benefits of SC were made to physicians and other health care providers in the RCPs. New ambulatory cancer patients are screened, advised and referred to internal or external SC services dependent on regional resources. CCO's data collection processes capture performance metrics. Patient data are aggregated at the RCP-level and provincial performance indicators reported quarterly. A standardized cancer patient resource on SC will be available in both French and English in a print-ready format and adapted for the Aboriginal population by March 2015. **Results:** During Q1 and Q2 of the 2014/15 fiscal year, 56.0% (Q1) and 51.5% (Q2) of new ambulatory cancer cases were screened for their smoking status: 25% of those screened were current or recent smokers (within last 6 months); 75% of these were advised of the benefits of cessation; nearly 50% were recommended a referral for cessation services, and about 67% of those referred accepted a referral. **Conclusions:** CCO's approach has led to province-wide implementation of a standardized intervention in a relatively short timeframe despite limited financial resources. Despite oncologist resistance and limited regional resources, there has been substantial progress. Framing SC as a quality of care issue has been critical to the success to date. Sustainability of the initiative will be dependent on funding for dedicated SC counselors and evidence of program cost-effectiveness.

6545 Poster Session (Board #102), Mon, 1:15 PM-4:45 PM

The impact of chemotherapy on hospitalizations and emergency care in older adults with advanced cancer. *First Author: Elena B. Elkin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The benefits of systemic chemotherapy for metastatic disease vary by tumor type and must be weighed against potential side effects. In patients receiving chemotherapy for advanced cancer, toxicity-related hospitalizations and emergency room (ER) visits may reduce the quality of an already limited life expectancy, particularly in the face of modest or uncertain expected benefit. **Methods:** In the population-based SEER-Medicare dataset, we identified patients 66 years or older diagnosed in 2001-2009 with metastatic cancer originating in one of 10 disease sites. The cohort was limited to patients who died by December 31, 2010. Chemotherapy recipients were matched to non-recipients by age, sex, race, geographic region, comorbidity and survival duration. The impact of chemotherapy on toxicity-related and any-cause hospitalizations and ER visits were estimated by cancer site in multivariable regression models, controlling for additional demographic characteristics. **Results:** Of 18,486 patients who received systemic chemotherapy for metastatic cancer, 92% had a hospitalization and 83% had an ER visit. Among their matched peers who did not receive chemotherapy, rates of hospitalization and ER visit were 83% and 72%, respectively. Controlling for patient and disease characteristics, chemotherapy was associated with a significantly increased risk of toxicity-related hospitalization in all 10 cancers: bladder, breast, prostate, colorectal, esophageal, pancreatic, stomach, ovarian, small cell and non-small cell lung cancers [adjusted odds ratios from 1.40 (95% CI 1.19-1.65) in prostate cancer to 3.16 (95% CI 2.79-3.57) in small-cell lung cancer] and similarly increased risks of toxicity-related ER visit in all 10 cancers [adjusted odds ratios from 1.26 (95% CI 1.10-1.53) in prostate cancer to 2.84 (95% CI 2.51-3.22) in small-cell lung cancer]. **Conclusions:** Hospitalizations and ER visits are common in patients with incurable advanced malignancies, and more likely among those who receive chemotherapy. Understanding common causes of these events may help reduce adverse effects of chemotherapy for metastatic cancer, and help patients and their families make informed treatment decisions.

6546 Poster Session (Board #103), Mon, 1:15 PM-4:45 PM

Wealth, health expenditure, and cancer: A national perspective. *First Author: Jad Chahoud, The University of Texas Health Science Center, Houston, TX*

Background: The healthcare system in the United States (US) is characterized by high expenditures with penultimate health outcomes. Socioeconomic status is a strong determinant of general population health. Our study evaluates the associations between (1) wealth and cancer outcomes, and (2) health expenditure and cancer outcomes at the State level. **Methods:** We used publicly available data from the Bureau of Economic Analysis, the Centers for Medicare and Medicaid Services and the United States Cancer Statistics. We employed GDP per capita and Health expenditure per capita as indicators for wealth and health expenditure respectively. As for cancer outcomes, we used incidence and mortality rates as well as mortality/incidence (M/I) ratios. We constructed scatter plots to illustrate these associations and used the Spearman's rank correlation coefficient to determine their strength, directionality and significance. **Results:** GDP per capita was significantly correlated with lower M/I ratios for all cancers (rho = -0.4406; p = 0.0017), breast cancer (rho = -0.3605; p = 0.0118) and colorectal cancer (CRC) (rho = -0.3612; p = 0.0117). As for health expenditure per capita, a preliminary descriptive analysis highlighted a rift between the Northeastern and the Southern States. This wide gap in health expenditure translated into worse all-cancer and breast cancer outcomes in Southern states. Further analysis showed that higher health expenditure was significantly correlated with decreased breast cancer M/I ratio (rho = -0.4237; p = 0.0027). However, CRC outcomes were not significantly affected by high health expenditure (rho = -0.1634; p = 0.2670), neither were all-cancer outcomes (rho = -0.2458; p = 0.0922). **Conclusions:** Cancer outcomes are strongly correlated with wealth as both breast cancer and CRC had significantly better outcomes in states with higher GDP per capita. However, only breast cancer outcomes were significantly correlated with higher health expenditure. CRC outcomes were not associated with higher health expenditure. This highlights a need for future research assessing the optimization of resource allocation in the States' efforts against CRC.

6547 Poster Session (Board #104), Mon, 1:15 PM-4:45 PM

How TNM stage affects surveillance intensity after treatment for breast cancer. *First Author: Daniel Wu, Saint Louis University School of Medicine, Saint Louis, MO*

Background: The mean lifetime cost of surveillance for a woman diagnosed with breast cancer at age 45 is estimated to be > $35,000. Based on trials comparing low and high intensity surveillance, ASCO and NCCN have published recommendations encouraging low intensity strategies. We aimed to determine whether ASCO experts carry out surveillance differently for patients with breast cancer of varying TNM stages. **Methods:** We created a web-based survey instrument with 4 idealized patient vignettes depicting patients with TNM stages 0 to IIIA. Respondents were asked how often they would recommend 12 specific diagnostic modalities for each vignette during post-treatment years 1-5. The survey was e-mailed to the 3245 ASCO members who had identified breast cancer as their major clinical focus. We used repeated measures ANOVA for analysis. **Results:** 1,012 (31%) of the 3245 ASCO members surveyed responded. There were 915 (90%) evaluable responses. Office visit was most frequently recommended. Responders also commonly recommended complete blood count (CBC), liver function tests (LFTs), and mammogram. There was statistically significant variation in recommended surveillance intensity for all 12 modalities according to TNM stage. **Conclusions:** We have demonstrated significant variability in surveillance after curative-intent treatment. Modalities not recommended by ASCO guidelines, such as CBC and LFTs, are frequently recommended by physicians. The frequency of recommended modalities varied depending on the TNM stage of the described patients, but ASCO guidelines do not stratify according to TNM stage. Our results suggest both overuse and underuse of surveillance modalities. Innovative solutions to promote physician and patient education can help physicians follow evidence-based surveillance guidelines and help patients to participate in these decisions. There is a need for new randomized controlled trials to evaluate newer surveillance modalities to guide clinical practice.

Frequency of recommended use of office visits: mean ± SD.

Year	TisN0M0	T2N0M0	T1N1M0	T3N2M0
1	2.8 ± 1.2	3.3 ± 1.3	3.3 ± 1.2	4.1 ± 2.2
2	2.5 ± 1.2	3.0 ± 1.1	3.0 ± 1.1	3.3 ± 1.2
3	2.1 ± 1.3	2.4 ± 1.1	2.5 ± 1.2	2.7 ± 1.3
4	2.0 ± 1.4	2.2 ± 1.1	2.3 ± 1.3	2.5 ± 1.3
5	1.9 ± 1.5	2.1 ± 1.3	2.2 ± 1.3	2.4 ± 1.3

6548 Poster Session (Board #105), Mon, 1:15 PM-4:45 PM

Racial differences in 20-year cardiovascular outcomes among childhood and young adult cancer survivors. *First Author: Amy M Berkman, University of Vermont, Burlington, VT*

Background: Individuals diagnosed with childhood (0-14 years) or young adulthood (15-34 years) cancers are at higher risk of cardiovascular disease (CVD) death compared to those without a history of cancer. No study has investigated whether CVD risk differs as a function of race and primary cancer type. **Methods:** Case data from the years 1973-2011 were analyzed using the 2013 Surveillance, Epidemiology and End Reports (SEER) registries. We categorized cases according to ICD-0-3 / WHO 2008 Adolescent and Young Adult classification. CVD death was based on ICD-10 codes for: diseases of the heart, atherosclerosis, cerebrovascular diseases or other diseases of the arteries. Hazard ratios were calculated using Fine & Gray methodology for competing risks (all-cause, cancer and CVD mortality) and relative risk ratios were calculated to compare risk of CVD death by race (black : white). **Results:** A total of 164,316 cases of childhood and young adult primary cancers were identified, of which 16,060 cases were black (10%), 133,932 cases (82%) were white, and 14,314 (8%) were other or unknown. There were a total of 1,584 CVD deaths. Overall, blacks had a higher risk of CVD death compared to whites at 5-years (RR 2.15, 95% CI: 1.65-2.80), 10-years (RR 2.23, 95% CI: 1.80-2.76), and 20-years (RR 1.83, 95% CI: 1.54-2.17) from the date of cancer diagnosis. The relative risk for CVD death between blacks and whites varied by cancer type, with the largest black:white difference among those diagnosed with CNS neoplasms at 10-years (HR 3.02, 95% CI: 1.47-6.18) and melanoma at 5-years (HR 26.9, 95% CI: 3.40-212.08). **Conclusions:** Black individuals diagnosed with cancer in childhood or young adulthood have a higher risk of CVD at 5-, 10-, and 20-years compared to whites. The risk of CVD mortality among blacks and whites varied by cancer type and time from cancer diagnosis. Further study is needed to understand the etiology of racial differences in this population.

6549 Poster Session (Board #106), Mon, 1:15 PM-4:45 PM

Factors associated with the large disparities in *BRCA* testing among high risk Black women. *First Author: Tuya Pal, H Lee Moffitt Cancer Ctr and Rsrch Inst, Tampa, FL*

Background: Concerns about genomic advances to increase health disparities have been raised. We sought to explore factors associated with receipt of *BRCA1* and *BRCA2* (*BRCA)* testing and assess for racial disparities through a population-based sample of young breast cancer survivors. **Methods:** Women diagnosed with invasive breast cancer at or below age 50 in 2009-2012 were recruited through the Florida State Cancer Registry with oversampling of Blacks compared to non-Hispanic Whites (NHW). Participants were asked to complete a baseline questionnaire and a medical records release for verification of genetic test results. Summary statistics, Pearson Chi-square tests and multivariable logistic regression were used to examine associations between dichotomous demographic and clinical variables and access to *BRCA* testing rates prior to enrollment. **Results:** Of the 877 participants included in this analysis, 36.7% (165/450) of Blacks versus 67.7% (289/427) of NHW had *BRCA* testing ($p < 0.001$). Medical record verification of the *BRCA* test result was achieved in over 75% of the sample. In the final logistic regression model, controlling for educational attainment and household income age at breast cancer diagnosis and triple negative status, NHW race remained the strongest predictor for having had *BRCA* testing with an odds ratio (OR) of 4.2 (95% Confidence Interval: 3.0-6.1). Other highly significant predictors of having *BRCA* testing included: 1) breast cancer diagnosis at or below age 40 (OR: 3.4); 2) annual income of $25,000 or greater (OR: 2.6); 3) triple negative disease (OR: 1.9); and 4) college education or higher (OR: 1.7) (all p-values < 0.005). Variables not significantly associated with having *BRCA* testing included having private insurance at the time of diagnosis and having children. **Conclusions:** Our results demonstrate the enormous disparity in *BRCA* testing among high risk Black women compared to NHW, which is not explained by socioeconomic factors. The rapid diffusion of gene-based care to refine cancer prevention and treatment and ultimately improve patient outcomes underscores the need to systematically understand and address these disparities so all populations may benefit from these scientific advances.

6550 Poster Session (Board #107), Mon, 1:15 PM-4:45 PM

Perceptions of clinical trial participation in African American cancer patients. *First Author: Daniel M. Geynisman, Fox Chase Cancer Center, Philadelphia, PA*

Background: African Americans (AA) participate in oncologic clinical trials (CT) at lower rates than Caucasians, despite a disproportionally high rate of cancer. While general barriers to participation in CT among AA have been explored, little is known in regard to specific differences of perspectives in those who do or do not participate. Based on an initial and separate qualitative analysis of 16 patients, a perceptual mapping survey was developed to explore barriers and facilitators to participation in CT amongst AA. **Methods:** We surveyed AA adult cancer patients at two cancer centers about demographics and knowledge, beliefs, attitudes and perceptions in regard to CT. We asked them to report how much they agreed or disagreed on a 0-10 scale (0 = strongly disagree, 10 = strongly agree) with statements regarding clinical trials' helpfulness, benefits, barriers, and value, support from those around them, and beliefs about healthcare providers. We used descriptive statistics and t-tests to assess for differences between those willing to and unwilling to participate in CT. **Results:** Of 41 patients recruited, 54% have not participated in a CT within the last 9 months. Mean age was 60 years (27-78), 51% were female, 39% completed high school and 71% had private insurance. CT participants more strongly agreed that their doctor had given them enough information to make a decision about being part of a CT ($p < 0.001$). Agreement that the benefits of being in a CT outweigh the possible side effects ($p = .016$) and that being in a CT offers the best treatment available for cancer ($p = .015$) were also stronger among CT participants. Non-CT participants more strongly believed that being in a clinical trial would make them sicker ($p = .019$), that important information would be withheld from them if they were in a clinical trial ($p = .008$) and that no one talked to them about being part of a CT ($p < 0.001$). **Conclusions:** Significant perceptual differences between AA cancer patients who have and have not participated in a CT were noted. Greater attention needs to be given to addressing negative perceptions of CT, as well as ensuring that all AA cancer patients receive clear and sufficient information regarding CT participation in order to make an informed decision about their care.

6551 Poster Session (Board #108), Mon, 1:15 PM-4:45 PM

Racial disparities in attrition among oncology clinical trial participants. *First Author: Leo Chen, University of British Columbia, Surrey, BC, Canada*

Background: Studies indicate that racial minorities are underrepresented in clinical trials. The outcomes of these minority groups following study enrollment are less clear. Our aims were to compare outcomes between White and non-White patients (pts) enrolled in oncology clinical trials and to determine if there are persistent racial disparities among study participants. **Methods:** All pts who participated in phase III breast, lung, gastrointestinal (GI) and genitourinary (GU) cancer clinical trials from 1999 to 2013 at any of the regional cancer centers in British Columbia were included. We conducted time-to-event analyses with attrition as the main outcome, defined as the time interval from study randomization to when a participant was removed from study due to 1) a primary disease-related endpoint being reached (e.g. recurrence, progression, or death) or 2) a non-cancer related cause (e.g. treatment toxicity). Multivariate Cox regression models were constructed to examine the impact of race on attrition, while adjusting for age, gender, ECOG, tumor site, and cancer stage. **Results:** We identified 780 pts with known racial status: 564 (72%) White and 216 (28%) non-White. Median age was 58 years, 70% female, 54%/35% ECOG 0/1, 43% stage IV disease, and 55%/20%/15%,10% enrolled in breast, lung, GI and GU trials, respectively. Attrition occurred in 364 (47%) pts of whom 146 (40%) were due to a primary study endpoint and 218 (60%) were attributable to non-cancer related factors, such as toxicity. Compared to White pts, non-White pts experienced higher overall (43% vs 57%, $p = 0.0004$) and cause-specific attrition (18 vs 22% and 25 vs 35% for cancer and non-cancer causes, respectively). Multivariate adjusted analysis continued to show that non-White pts faced greater likelihood of attrition due to cancer (HR 1.45, $p = 0.012$) as well as non-cancer related factors (HR 1.43, $p = 0.050$). Increased age, poor ECOG, and advanced disease were also associated with worse trial outcomes (all $p < 0.05$). **Conclusions:** In addition to underrepresentation in clinical trials, racial minorities were more likely to face attrition during study participation, potentially further hindering the generalizability of study findings in the real world population.

6552 Poster Session (Board #109), Mon, 1:15 PM-4:45 PM

Evaluation of hematology/oncology patient and physician expectations for integrative oncology in an ethnically diverse population. *First Author: Damien Mikael Hansra, Oncology and Radiation Associates, Miami, FL*

Background: Many integrative modalities are recommended in NCCN guidelines & evidence shows increased patient (pt) utilization.We aim to compare how integrative services are valued between hematology/oncology physicians (MD) & pts. **Methods:** Pts & MDs at an academic tertiary care medical center were enrolled to complete a survey. Demographics include: age, gender, race, & ethnicity. Clinical info include: cancer subtype & treating MD. Survey consisted of 7 questions assessing opinions on integrative care asking: "In addition to standard care, it is important to incorporate/provide" nutrition services, exercise therapy, spiritual/religious counseling, supplement/herbal advice, support groups, music therapy, or other complimentary medicine services (acupuncture, massage, relaxation therapy). Answers recorded on a 5 point scale (1 = highly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = highly agree) & converted into 2 categories (1,2,3 = neutral/disagree vs. 4,5 = agree). Fisher's exact test with 2 sided p-value used to compare significance between MD & pt responses. **Results:** 909 pts and 55 MDs enrolled from June 2013 to January 2015. Pt mean age 55, range 18-88 with 47% male & 53% female. 65% of pts were Hispanic vs. 35% not Hispanic. 81% white, 12% black/African American, 2% Asian/Pacific Islander, & 5% other. 15% of pts had hematologic disorders (93% malignant 7% benign) vs. 85% of pts had solid malignancies. Significance disparities were demonstrated: 82% of pts agree that nutritional advice is important vs. 67% of MDs, $p = 0.01$, exercise therapy (86% vs. 73%, $p = 0.02$), spiritual/religious (68% vs. 50%, $p = 0.01$), supplement/herbal therapies (85% vs. 56%, $p < 0.0001$), music (64% vs. 30%, $p < 0.0001$), &"other complementary services" (75% vs. 45%, $p < 0.0001$). Non statistical favoring of support groups by pts observed (71% vs. 68% respectively, $p = 0.64$). **Conclusions:** With with exception of support groups, pts value integrative modalities more than MDs. It is expected that increased availability & utilization of integrative oncology modalities at tertiary hospital sites could improve pt satisfaction, quality of life, & other clinical endpoints.

6553 Poster Session (Board #110), Mon, 1:15 PM-4:45 PM

Genomic landscape of primary breast cancer in black vs. white women and association with tumor recurrence. *First Author: Tanya Keenan, Massachusetts General Hospital, Boston, MA*

Background: Black Americans are much more likely to die from breast cancer (BC) than white Americans. While socioeconomic issues contribute to this disparity, the influence of genomics is unclear. We aimed to determine key genomic traits and their effect on BC recurrence. **Methods**: Whole exome sequencing and gene expression data collected between 2010 and 2014 on primary breast tumors were obtained from The Cancer Genome Atlas. Genomic profiles, including intratumor genetic heterogeneity measured by the mutant-allele tumor heterogeneity (MATH) algorithm, were compared by race with logistic regression models. Cox proportional hazard models evaluated the association of race, triple negative breast cancer (TNBC), mutations, MATH, and PAM50 subtype with risk of tumor recurrence. **Results**: A total of 609 white Americans and 102 black Americans were analyzed. Black Americans had significantly more TNBC than white Americans. Black Americans compared to white Americans had more TP53 mutations (43.1% vs 27.3%, $p = 0.002$) and fewer PIK3CA mutations (20.6% vs 34.0%, $p = 0.01$). MATH was greater (5.3 units, 95% CI 2.6 to 8.0, $p < 0.001$) in black Americans than in white Americans. Black Americans had a greater prevalence of the PAM50 basal subtype (40.2% vs 18.6%, $p < 0.001$) and a lower prevalence of the PAM50 luminal A subtype (10.8% vs 35.0%, $p < 0.001$) than white Americans. By Lehmann TNBC subtype, black Americans had more basal-like 1 tumors (25.9% vs 9.8%, $p < 0.001$). Of the 506 white Americans and 89 black Americans with follow up data, black Americans also had a higher risk of tumor recurrence than white Americans (Table). Separate adjustment for TP53 mutation, PAM50 subtype, and TNBC but not MATH decreased the magnitude and significance of the racial association with tumor recurrence. **Conclusions**: Besides having a higher prevalence of TNBC, BC in black American women had significantly greater TP53 mutations, intratumor genetic heterogeneity, PAM50 basal tumors, and TNBC basal-like 1 tumors, all of which are associated with more aggressive tumor biology. These genomic differences could contribute to racial disparities in BC outcomes.

	Hazard Ratio for Tumor Recurrence	95% CI	p
Black race (adjusted for age, stage)	2.22	(1.05, 4.67)	0.04
Black race additionally adjusted for MATH	2.19	(1.03, 4.64)	0.04
TP53 mutation	1.99	(0.94, 4.21)	0.07
TNBC	1.57	(0.72, 3.44)	0.26
PAM50 subtype	1.41	(0.64, 3.09)	0.39

6554 Poster Session (Board #111), Mon, 1:15 PM-4:45 PM

Treatment and characteristics of stage II colon cancer patients residing in CDC Specialized Registry areas. *First Author: Mary Elizabeth O'Neil, Centers for Disease Control and Prevention, Atlanta, GA*

Background: Some guidelines advise adjuvant chemotherapy be considered after surgical resection for high-risk stage II colon cancer patients; however, high-risk criteria are ill-defined and the long term benefits debated. This study documents patterns of care by selected patient and tumor characteristics using a population-based cohort of stage II colon cancer patients diagnosed in 2011. **Methods:** We used data from 10 CDC Specialized Cancer Registries participating in the National Program for Cancer Registries' (NPCR) Enhancing Cancer Registry Data for Comparative Effectiveness Research (CER) project to describe demographic and clinical characteristics of stage II colon cancer patients treated by surgery and adjuvant chemotherapy. We evaluated factors associated with adjuvant chemotherapy by logistic regression. **Results:** Of a total of 3,999 stage II colon cancer patients, 14.0% were treated with surgery and adjuvant chemotherapy compared to 83.6% by surgery alone. The patients treated with surgery plus adjuvant chemotherapy were more likely to be white (82.3%), non-Hispanic (83.8%), and younger but there were no differences by gender or urban residence. Most patients were insured by Medicare alone (28.2%) or private insurance (includes Medicare with private supplement) (45.9%). Approximately one-third (34.6%) had a T4 extension, 13.4% had < 12 lymph nodes examined, 21.7% had lymphovascular invasion and 21.6% were Grade III. Compared to surgery alone, the four characteristics associated with adjuvant therapy were younger age (median 61 years vs. 71 years; adjusted odds ratio [aOR]: 0.94, $P < .01$); T4 invasion (aOR: 4.38, $P < .01$); lymphovascular invasion (aOR 1.83, $P < .01$) and grade (aOR comparing Grade III to I: 1.78, $P < .01$). **Conclusions:** In this population-based cohort, younger stage II colon cancer patients with T4 lesions, lymphovascular invasion and a poorly differentiated tumor were more likely to receive adjuvant chemotherapy in addition to surgery. Ongoing data collection on outcomes, both recurrence and survival, will help clarify the benefits of adjuvant treatments in stage II colon patients. Better tools for risk stratification and predicting treatment benefits are still needed.

6555 Poster Session (Board #112), Mon, 1:15 PM-4:45 PM

The impact of the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) in reducing outcome disparities based on race. *First Author: Mark A Fiala, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: The NBCCEDP, created in 1990, provides breast and cervical cancer screening and diagnostic services to low-income and uninsured women. The program's effectiveness in reducing racial disparities in outcomes is unclear. Therefore, we examined the incidence of metastatic (distant) disease at diagnosis and the mortality rates of women with metastatic disease by race before and after the advent of the NBCCEDP. **Methods:** Using the SEERStat software, we extracted the case listings of all women diagnosed with breast or cervical cancer from 1981 through 2010 in Surveillance Epidemiology and End Results (SEER)-9 registries database based on the November 2013 submission. Autopsy or death certificate only cases were excluded. As the targeted ages for breast cancer screening is 50-69 years old and 16-69 years old for cervical, only cancers diagnosed during those respective ages were included. The women were divided into three cohorts based on the year of diagnosis [1981-1990; 1991-2000; 2001-2010]. Socioeconomic status was approximated by median household income of county of residence from the 2000 US census. Incidence rates of metastatic disease were compared using χ^2, and mortality rates were compared using multivariate cox regression. **Results:** 224,183 women with breast cancer and 28,532 with cervical cancer were analyzed. Black women represented 15% of the breast cancers and 9% of the cervical. The proportion of women with metastatic disease was consistently higher for black women than white women. The mortality rate of those with metastatic disease, adjusted for year of diagnosis, age, and SES, was also consistently higher for black women than white women (Table 1); neither improved during the two most recent decades. **Conclusions:** Racial disparities persist between black and white women with breast or cervical cancer despite the screening efforts of the NBCCEDP.

	Breast			Cervical		
	White		Black	White		Black
	Distant	Distant	aHR (95% CI)	Distant	Distant	aHR (95% CI)
1981-1990	7%	11%	1.5(1.4-1.6)	8%	10%	1.4(1.3-1.5)
1991-2000	6%	9%	1.8(1.7-1.8)	7%	9%	1.5(1.4-1.6)
2001-2010	6%	11%	2.2(2.1-2.3)	11%	13%	1.5(1.3-1.6)

aHR, adjusted Hazard Ratio.

6556 Poster Session (Board #113), Mon, 1:15 PM-4:45 PM

Religious beliefs and stage at diagnosis in a biracial sample of newly diagnosed colon cancer patients. *First Author: Blase N. Polite, The University of Chicago, Chicago, IL*

Background: Blacks are more likely to present with advanced stage colon cancer and more likely to die from this disease than Whites. Blacks are also more likely to place God in control of their health care decision-making. Limited evidence in breast cancer suggests stronger religious beliefs may lead to more delayed care and more advanced stage at diagnosis especially among Blacks. **Methods:** Newly diagnosed patients with colon cancer were recruited at 9 facilities in metropolitan Chicago (2 public and 4 private non-academic, and 3 academic institutions). Eligible patients had a diagnosis of a first primary invasive colon cancer between the ages of 30 and 79 years, and were non-Hispanic White or non-Hispanic Black. Patients were interviewed on their prior screening and the process of their diagnosis, which was augmented with detailed chart abstraction. A broad range of social and attitudinal constructs were measured including 3 well validated religiosity scales: God Locus of Health Control (GLHC), Religious Problem Solving (RPS), and Religious Coping (Brief RCOPE). The final response rate was 54% and includes 407 patients. **Results:** Median age of the sample was 60, 52% were Black, 33% had income $<$ 20K, and 13% had $<$ HS education. Cancer stage was available on 372 (91%), and 62% were late stage (stage III, IV). Blacks had significantly higher levels of GLHC than whites (mean 22 vs. 13, on a scale of 6-30, $p < 0.001$). Univariate logistic regression models for age, race, sex, income, education, and religiosity items showed that only younger age ($p = 0.01$) and higher levels of GLHC ($p = 0.016$) were associated with late stage at diagnosis. These significant associations held in the multivariate model when both were adjusted for. There was no significant interaction between race and GLHC ($p = 0.238$). **Conclusions:** In a large bi-racial sample across diverse health care systems, younger age and higher scores on the GLHC predicted late stage at diagnosis. While Blacks had significantly higher GLHC scores, race was not associated with stage at presentation. The relationship between GLHC and advanced disease stage was not limited to Blacks. Further work is ongoing to characterize the relationship between religious beliefs and health outcomes.

6557 Poster Session (Board #114), Mon, 1:15 PM-4:45 PM

Impact of racial residential segregation (RRS) on stage at diagnosis and survival after diffuse large B-cell lymphoma (DLBCL). *First Author: Loretta J. Nastoupil, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Racial disparities in disease presentation and survival have been reported for DLCBL, which may arise from biological or socioeconomic status (SES) differences that influence treatment and outcomes. We examined the associations between RRS, stage at diagnosis, overall survival (OS) and lymphoma-related survival (LRS) for non-Hispanic Black and White patients (pts), hypothesizing that RRS is associated with advanced stage disease and inferior survival for Black pts with DLBCL. **Methods:** We merged data from the population-based California Cancer Registry for new cases of DLBCL diagnosed during 1996-2007 with 5 Census indices of segregation among Blacks relative to Whites: dissimilarity, exposure, isolation, relative centralization, and spatial proximity. We included a measure of the % of black individuals per neighborhood (%B). Controlling for demographic and clinical factors, we used multivariable logistic regression and Cox regression to examine each RRS measure, modified by %B, on stage and survival, respectively, for Blacks and Whites separately. **Results:** Among 10,505 White and 749 Black DLBCL pts, Blacks more commonly had advanced stage disease (52 vs 45%) and resided in the lowest SES neighborhoods (28 vs 7%). Among Black pts, medium to high segregation as measured by dissimilarity (HR 2.1; 95% CI 1.1-4.1) and isolation (HR 2.2; 95% CI 1.0-5.0) were associated with advanced stage; however, there were no significant association between any RRS measure and survival. Among White pts, there was no significant associations between RRS and stage; whereas low segregation measured by spatial proximity (LRS HR 1.2; 95% CI 1.2-1.1; OS HR 1.2; 95% CI 1.1-1.4), isolation (LRS HR 1.3; 95% CI 1.1-1.5; OS HR 1.3; 95% CI 1.1-1.4), and dissimilarity (LRS HR 1.2; 95% CI 1.0-1.4; OS HR 1.3; 95% CI 1.1-1.4) in neighborhoods with high %B were associated with worse OS and LRS. **Conclusions:** Despite association with stage at diagnosis for Black pts, neighborhood composition and segregation had minimal impact for White pts and no impact for Black pts on survival, suggesting that other sociological/biological factors influence racial differences in DLBCL survival.

6558 Poster Session (Board #115), Mon, 1:15 PM-4:45 PM

Effect of demographic factors and histology on stage IV non-small cell lung cancer (NSCLC): A National Cancer Database review. *First Author: Brody Slostad, Creighton University School of Medicine, Omaha, NE*

Background: Demographic characteristics, especially race and insurance status, affect the incidence of lung cancer diagnosed at Stage IV[1]. This is the largest epidemiological study to determine patient features associated with the development of Stage IV NSCLC. **Methods:** A population-based study using the National Cancer Database (2000-2012), which contains 70% of all cancer diagnoses in the U.S. from 1658 ACS Accredited-Hospitals. Demographic groups of NSCLC presenting with Stage IV were compared to the entire cohort of NSCLC patients using the Chi square test. **Results:** Of all NSCLC patients (N=2,956,237), 36% were Stage IV at presentation. Uninsured (52%), aged 40-49 (47%), Medicaid recipients (46%), aged 50-59 (42%), Hispanic (41%) and Black (41%) patients presented with more Stage IV at diagnosis. Medicare recipients (34%) presented with less Stage IV. Adenocarcinoma (AC) and Squamous Cell (SQ) presented with 43% and 25% Stage IV disease at diagnosis, respectively. Uninsured AC (60%) patients had the most frequent Stage IV disease at diagnosis. **Conclusions:** AC presents much more frequently than SQ as Stage IV. In particular, uninsured AC patients have the most frequent Stage IV presentation. Similar to a previous NCDB study, this study, which includes 5 times as many lung cancer patients as the previous study, shows uninsured, Medicaid, Hispanic and Black NSCLC patients present with more Stage IV disease (Halpern MT, et al. (2008) Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. Lancet Oncol 9:222-232.). Conversely, Medicare patients present with less Stage IV disease.

Stage IV NSCLC * = p<.001.

		% Stage IV
Race/ Ethnicity*		
	Hispanic	41
	Black	41
	White	35
Gender*		
	Male	38
	Female	35
Distance Traveled (miles)*		
	<5	39
	5 to 9	37
	10 to 24	36
	25 to 49	34
	50 to 99	32
	>=100	32
Insurance*		
	None	52
	AC	60
	SQ	38
	Medicaid	46
	Private	38
	Other Gov't	37
	Medicare	34
% Without HS Degree*		
	>23%	38
	15-22.9%	37
	11-14.9%	36
	6-10.9%	35
	<6%	35
Household Income*(per year)		
	<$36,000	37
	$36,000 - 43,999	36
	$44,000 - 52,999	36
	$53,000 - 68,999	36
	>$69,000	36
Comorbidity*		
	None	39
	One	33
	2+	34
Age*		
	40-49	47
	50-59	42
	60-69	37
	70-79	33
	80-89	33
Overall % Stage IV		36

6559 Poster Session (Board #116), Mon, 1:15 PM-4:45 PM

Patient navigation as a model to increase minority participation in cancer clinical trials. *First Author: Mona Fouad, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

Background: For ethical, social, and scientific reasons, cancer clinical trials require participation of patients from diverse population groups. Less than 10% of all patients enrolled in clinical trials are minorities. The patient navigation model has been used to assist under-resourced cancer patients to access medical care. However, the model has not been evaluated as a tool for increasing the participation of minorities in clinical trials. The project "Increasing Minority Participation in Clinical Trials" (IMPaCT) utilized patient navigation (PN) to enhance the recruitment and retention of African Americans (AA) in therapeutic cancer clinical trials in an NCI-designated comprehensive cancer center. **Methods:** Lay individuals were recruited and trained to serve as PNs for clinical trials. The training curriculum included content related to clinical trials, the navigation process, interaction with patients, the clinical environment, and case management. The training sessions were co-led by clinical research nurses, physicians, and health educators. AA patients potentially eligible for clinical trials were identified through chart review or referrals by clinic nurses, physicians, and social workers. PNs provided two levels of services to AA cancer patients who consented to receive PN support: 1) Clinic-based education about clinical trials; and 2) Tailored supportive services for patients who enrolled in clinical trials. **Results:** Two lay individuals matching the demographic characteristics of the patients were trained and hired as PNs. Between 2007 and 2014, 424 AA cancer patients were referred to IMPaCT. Of the patients eligible for a clinical trial ($N = 378$), 302 (79.9%) enrolled in a trial and 270 (71.4%) consented to receive PN support during the trial. Of those receiving PN support, 74.5% completed the trial, compared to 37.5% of those who chose not to receive PN support. The difference in the clinical trial completion rates between participants who received PN support vs. those who did not was statistically significant ($P < 0.001$; Chi-Square test). **Conclusions:** This study indicates that PN could address barriers to clinical trial participation in AA cancer patients and improve retention in clinical trials.

6560 Poster Session (Board #117), Mon, 1:15 PM-4:45 PM

Endocrine therapy adherence, side effects, and risk perception among racially diverse breast cancer patients. *First Author: Stephanie B. Wheeler, UNC Chapel Hill, Chapel Hill, NC*

Background: Differential endocrine therapy (ET) use by race may contribute to disparities in breast cancer outcomes. The goal of this study was to examine racial variation in ET adherence, side effect experiences and perceptions about recurrence risk. **Methods:** We surveyed 1,507 stage I-III breast cancer patients using a mailed, self-administered questionnaire at 18-months post-diagnosis as part of the Carolina Breast Cancer Study Phase III (CBCS-III), a population-based, prospective cohort study that recruited participants via rapid case ascertainment in 2008-2013. Non-adherence was defined as not taking ET pills every day as prescribed, discontinuing ET pills, or missing > = 3 pills in the past 14 days. Bivariable analyses identified differences in adherence, side effect experiences and risk perceptions by race. **Results:** Overall, 994 women in our sample were prescribed ET; of these, 43% were African American (AA). The mean age at diagnosis was 54, and the majority were diagnosed with stage 1 (50%) or 2 (37%) disease. Overall, 19% were classified as non-adherent; 22% of AA women were non-adherent (vs.16% of white women, p = 0.014). Compared to white women, AA women more often forgot to take ET when traveling away from home (25% vs. 16%, p = 0.035); felt sticking to their ET treatment plan was difficult (25% vs. 14%, p < 0.0001), had trouble remembering to take their ET pills (24% vs. 13%, p = 0.0001), reported cost-related non-adherence (16% vs. 7%, p = 0.0001), and experienced bothersome side effects (25% vs. 18%, p = 0.0033). AA women more often than white women reported experiencing the following side effects frequently in the past 7 days: hot flashes (55% vs. 45%, p = 0.0017), night sweats (41% vs. 30%, p = 0.0002), breast sensitivity (24% vs. 16%, p = 0.0015), and joint pain (46% vs. 38%, p = 0.011). More AA women reported believing there would be no change in their recurrence risk if they stopped ET (20% vs. 8%, p < 0.0001). **Conclusions:** These data highlight important racial differences in adherence behaviors, side effect experiences and perceptions of recurrence risk. Culturally-tailored interventions that can help women taking ET to better manage side effects and reframe risk perceptions may better motivate adherence.

6561 Poster Session (Board #118), Mon, 1:15 PM-4:45 PM

Disparities in hospice use among patients with cancer in the Deep South. *First Author: Bradford E. Jackson, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

Background: Higher rates of hospice use are an indicator for high-quality end-of-life care for cancer patients, however disparities have been reported. Known racial disparities in hospice utilization may be explained by hospital characteristics that would affect the likelihood of referral to hospice. The purpose of this study was to explore variations in hospice use at both the patient and hospital level. **Methods:** Administrative claims were obtained forMedicare patients ≥ 65 years old diagnosed with cancer within the UAB Health System Cancer Community Network (UAB CCN) from 2008-2014. Enrollment in hospice was assessed for all deceased patients in the 90 days before death. Using logistic regressions we assessed the association between hospice use and patient-level factors (race, gender, and cancer type), as well as hospital-level factors (presence of a board certified palliative care physician and ownership of a hospice facility). Results are presented as frequencies and percentages as well as odds ratios (OR) and their corresponding 95 % confidence limits (95%CL). **Results:** Sixty-eight percent (n = 7,186) of patients enrolled on hospice in the 90 days before death. In the unadjusted analysis, females were more likely to be enrolled on hospice than males (70% vs 66%; p = 0.002), blacks less likely than whites (62% vs 69%; p = 0.002). Hospice use varied by cancer type (77% for pancreatic cancer patients and 60% for hematologic malignancies). Hospice use was not significantly different for hospitals with board certified palliative care physicians (67% vs 69%; p = 0.178) or those certified to provide (home or inpatient) hospice care (69% vs 67%; p = 0.130). In the multivariable model adjusting for patient- and hospital-level characteristics, we observed lower odds of hospice use for blacks (OR 0.67; 95%CL: 0.57, 0.80); higher odds for hospitals certified to provide hospice care (OR = 1.41; 95%CL: 1.16, 1.71) and no difference for hospitals with palliative care physicians (OR = 0.9; 95%CL: 0.79, 1.04). **Conclusions:** Disparities in hospice enrollment exist in this hospital network of the rural Deep South. Although patient characteristics may help explain variation in hospice use, our findings show mixed associations with palliative care services.

6562 Poster Session (Board #119), Mon, 1:15 PM-4:45 PM

Utility of surveillance following curative intent resection of metastases. *First Author: Richard M. Lee-Ying, BC Cancer Agency, Vancouver, BC, Canada*

Background: Surveillance is frequently conducted after the completion of curative treatment in early stage cancers to detect resectable recurrences. As more stage IV patients undergo curative resection of metastases (CRM), surveillance of such cases is increasingly performed, but its utility is unclear. Using a cohort of metastatic colorectal cancer (mCRC) patients, we aimed to 1) characterize surveillance patterns in a population-based setting and 2) examine if surveillance contributed to improved outcomes. **Methods:** Patients diagnosed with mCRC from 1995 to 2010 and referred to any 1 of 5 cancer centers in British Columbia were reviewed. Using Cox regression models that adjusted for confounders, we identified predictors of overall survival (OS) in patients who underwent CRM. Recurrences were categorized into those detected by surveillance vs symptoms and whether further attempts at CRM were feasible. **Results:** We identified 2082 mCRC patients of whom 254 proceeded to CRM. Median age was 63, 52% were men, 44% had de novo stage IV disease, 56% received perioperative chemotherapy, and 17%/66% had lung/liver metastases, respectively. Surveillance practices after CRM varied widely, but included clinical examination (85%), CEA (86%), imaging (89%) and endoscopy (28%) in the first 5 years. The median OS of CRM cases was 40.9 months, including 191 (75%) recurrences. The median time to recurrence was 10.2 months. Recurrences were detected by surveillance in 152 (80%) cases, and proceeded to a second CRM in 41 (21%). Compared to recurrences detected by symptoms, those based on surveillance were more likely to proceed to another CRM (25% vs. 11%, p < 0.001). Adjusting for confounders, surveillance (HR 0.61 95% CI 0.39-0.94, p = 0.026) and a second CRM (HR 0.53, 95% CI 0.34-0.82, p = 0.004) were independently correlated with improved OS. **Conclusions:** In this population-based cohort of mCRC patients, the majority recurred after the initial CRM, but recurrences detected by surveillance were more amenable to a subsequent CRM. While surveillance was performed in most cases, significant variations in practice were observed, underscoring the need for wider dissemination of evidence-based guidelines for the surveillance of selected metastatic disease.

6563 Poster Session (Board #120), Mon, 1:15 PM-4:45 PM

Trends in use of PET imaging in surveillance of lung and colorectal cancer. *First Author: Christine Marie Veenstra, University of Michigan, Ann Arbor, MI*

Background: Surveillance PET imaging following curative intent treatment of non-small cell lung cancer (NSCLC) or colorectal cancer (CRC) is not supported by available evidence. ASCO and ABIM's joint Choosing Wisely campaign recommends against surveillance PET, yet the frequency with which PET imaging is performed during surveillance care is unknown. **Methods:** 65,748 patients age 66+, diagnosed with stage I-IIIA NSCLC or Stage I-III CRC in 2001-2009, who underwent surgical resection were identified in SEER-Medicare data. Eligibility for surveillance started 180 days post-operatively. Use of imaging was assessed during the first year of surveillance and classified as 1) Any PET: receipt of PET or PET/CT regardless of other imaging, or 2) PET-only: receipt of PET or integrated PET/CT only, in patients who did not undergo separate dedicated CT imaging. Unadjusted proportions of patients receiving each category of surveillance were calculated by cancer type, diagnosis year, and stage. Equality of proportions was assessed between diagnosis years with ANOVA tests. **Results:** 7,393 NSCLC patients and 35,050 CRC patients met inclusion criteria. PET use more than doubled over the study period in both cohorts. 11% of all NSCLC patients diagnosed in 2001 received any PET vs. 25% diagnosed in 2009 (P < 0.001). Similarly, 4% of all CRC patients diagnosed in 2001 received any PET vs. 12% diagnosed in 2009 (P < 0.001). PET utilization was more common in higher stage NSCLC and CRC patients, and increased significantly between 2001 and 2009. In Stage IIIA NSCLC patients diagnosed in 2001, 15% received any PET compared to 42% diagnosed in 2009 (P = 0.015). In this same group of patients, 1.5% diagnosed in 2001 received PET-only, compared to 15% diagnosed in 2009. Among Stage III CRC patients any PET use increased from 9% for those diagnosed in 2001 to 27% for those diagnosed in 2009 (P < 0.001), while use of PET-only increased from 1% to 8% over the same period (P < 0.001). **Conclusions:** Although not indicated in surveillance, PET utilization has more than doubled among NSCLC and CRC survivors over the study period. While surveillance rates may be increasing generally, increased rates of PET-only imaging suggest PET is inappropriately replacing existing surveillance protocols.

6564 Poster Session (Board #121), Mon, 1:15 PM-4:45 PM

Young adult cancer survivors' expectations of physicians for follow-up and general health care: Implications for health services delivery. *First Author: Pierre Camateros, University of British Columbia, Vancouver, BC, Canada*

Background: As patients transition from cancer treatment to survivorship, the involvement of multiple physicians may lead to confusion as to who is primarily responsible for the patients' ongoing care. This is particularly concerning for young adult cancer survivors who may have specific survivorship care needs. In this study, we examined survivors' expectations of their physicians regarding cancer follow-up and general healthcare, and identified factors associated with these expectations. **Methods**: We surveyed patients aged 20 to 39 years who were diagnosed with solid tumors, evaluated at any 1 of 5 regional cancer centers in British Columbia, and alive at 2 or more years after their original diagnosis. Using multivariate regression models, we explored the relationships between patient expectations of their care and the factors associated with these expectations, while controlling for potential confounders. **Results:** With a survey response rate of 57%, a total of 447 patients were analyzed: median age was 35 years (IQR 31-38), 30% were men, 89% had ECOG 0. Tumor sites included breast (222; 50%), testicular (126; 28%), gynecological (76; 17%), and colorectal (23; 5%). For the entire cohort, the majority (67%) viewed their cancer specialist (CS) as being chiefly responsible for their care during the first 10 years of their diagnosis, but most (64%) shifted this expectation towards their primary care provider (PCP) after 10 years of follow-up ($p < 0.001$). PCPs were also viewed as more responsible for providing preventive care than CS (85% vs. 35%, $p < 0.001$). Active contact with the CS in the past year was significantly associated with higher expectations of their CS being engaged in the ongoing care of their most recent malignancy ($p < 0.001$), treatment of side effects ($p = 0.03$), and screening of future cancers ($p < 0.001$). **Conclusions:** Young patients expect involvement from their CS even years after their original cancer diagnosis. Early integration of PCPs in the cancer care trajectory may better foster a shared-care model of health services delivery and facilitate the transition of many young cancer survivors as they complete cancer treatment and enter follow-up care.

6565 Poster Session (Board #122), Mon, 1:15 PM-4:45 PM

Effect of improving guideline-based prophylactic growth factor (pGCSF) use with chemotherapy (CT) on the risk of febrile neutropenia (FN) in non-small cell lung cancer (NSCLC) patients (pts): A Cleveland Clinic Taussig Cancer Institute (TCI) Quality Improvement (QI) Project. *First Author: Lindsey Martin Goodman, Cleveland Clinic, Cleveland Heights, OH*

Background: Per accepted guidelines, pGCSF is not recommended for pts receiving CT regimens with low risk ($< 10\%$) for FN. Factors contributing to inappropriate pGCSF use include lack of provider familiarity with national guidelines as well as the presence of standing pGCSF orders in EMR CT templates. Inappropriate use of pGCSF increases pt morbidity and healthcare costs. **Methods:** A multidisciplinary team performed a QI project through the ASCO Quality Training Program. All NSCLC pts at TCI who initiated a new CT regimen from April 2013 to October 2014 were reviewed. First-cycle pGCSF use was deemed appropriate if prescribed for CT associated with high risk of FN ($> 20\%$) or intermediate risk (10-20%) if other risk factors for FN were present. Use with low-risk CT was considered inappropriate. We implemented three QI strategies: education of NSCLC providers, development of TCI Consensus Guidelines for the use of pGCSF in NSCLC, and EMR modification: labeling of CT regimens by FN risk and removal of standing pGCSF orders from low-risk CT. Follow up data were collected from January to October 2014. FN rates before and after the QI interventions were documented. **Results:** 300 NSCLC pts received a new CT regimen during the specified time period. Prior to the interventions, 34/118 pts (29%) treated with low-risk CT received pGCSF (average 2.6 doses/pt). In all other instances pGCSF use was in accordance with guidelines. Following QI interventions, 8/126 (6%) treated with low-risk CT received pGCSF. No patient treated with low-risk CT required inpatient admission for FN during post-intervention follow up. Cost analyses indicate a potential reduction of $1.9 million in charges over 1 year with guideline-based pGCSF usage with low-risk CT. **Conclusions:** Excessive pGCSF use can be improved with focused provider education and EMR modification. The lack of FN admissions in the post-intervention period validates current guidelines. Appropriate pGCSF administration in NSCLC leads to significant cost savings without increasing neutropenic complications.

6566 Poster Session (Board #123), Mon, 1:15 PM-4:45 PM

Utility of pre-operative PET/CT staging in sentinel lymph node-positive melanoma. *First Author: Benjamin Scheier, University of Michigain Health System, Ann Arbor, MI*

Background: Sentinel lymph node (SLN) mapping is an integral part of melanoma staging. If regional metastases are identified, patients often undergo lymph node dissection (LND) as definitive treatment. The National Comprehensive Cancer Network (NCCN) makes a category 2B recommendation- based on "low-level evidence" and a non-uniform consensus- that prior to LND, patients may be considered for staging by positron emission tomography with a computed tomography scan (PET/CT). PET/CT, however, lacks data supporting this use, may inconsistently impact treatment decisions and carries a risk of false positives that may detract from clinical utility. **Methods:** A retrospective evaluation of patients seen at the University of Michigan with melanoma and clinically silent regional lymph nodes between July 2013 and September 2014 was performed.We identified78 patients with positive SLN mapping, 46 of which underwent PET/CT prior to LND. Remaining patients either underwent no staging or CT with brain MRI. Outcomes measured include changes in clinical management and incidence of false positives, defined as biopsy-evaluated PET/CT findings non-diagnostic for melanoma. **Results:** Of the 46 patients who underwent PET/CT, 15 (33%) had abnormal findings distant from the primary tumor and local lymph node basin. 9 of those 15 patients (60%) had abnormalities biopsied prior to LND. Of the 46 patients assessed, only 3 (6.5%) had PET/CT findings that ultimately identified metastatic melanoma and precluded LND. This yields a false positive rate of 67% in screening for distant metastases. There was not a statistically significant association between T and N stage and whether or not patients underwent PET/CT imaging (Fisher's exact test, $p = 0.12$ and 0.85, respectively). There was a statistical association between undergoing PET/CT and ulceration status ($p = .004$). **Conclusions:** The utility of PET/CT staging following SLN mapping in melanoma is unknown, despite its recommended use by the NCCN. In our retrospective review, we found that PET/CT has a high false positive rate and a minimal effect on patient management. PET/CT staging should be reevaluated as a category 2B recommendation by the NCCN and its utility evaluated prospectively in a clinical trial.

6567 Poster Session (Board #124), Mon, 1:15 PM-4:45 PM

Developing oncology goals and objectives for medical students: A national Delphi process. *First Author: Vincent Channing Tam, Tom Baker Cancer Centre, Calgary, AB, Canada*

Background: Our previous study showed that oncology education in medical schools is currently inadequate. The purpose of this process was to develop oncology goals and objectives for medical students based on a national consensus by oncology educators. **Methods:** A comprehensive list of oncology objectives was created using existing resources. Experts in oncology education and undergraduate medical education (UME) from all 17 medical schools in Canada were asked to participate in a 3-round Delphi consensus process. For round 1, experts scored objectives on a 9-point scale according to the degree with which they agreed an objective should be taught in UME. Objectives with a mean score of ≥ 7.0 were included. Round 2 was a web meeting where objectives with a mean score of 4.0 to 6.9 were discussed. In round 3, experts voted on inclusion and exclusion of round 2 objectives. **Results:** 34 of 37 (92%) invited experts from 14 medical schools participated. Experts consisted of oncologists (medical, radiation, pediatric, surgical, gynecologic), family physicians, UME curriculum committee members, and oncology residency program directors. The comprehensive list reviewed in round 1 contained 214 objectives. 146 received a mean score ≥ 7.0 and 68 scored 4.0 to 6.9. Nine new objectives were suggested. Main themes of expert comments were to reduce the number of objectives and to aim objectives at the general knowledge level of a family physician. In round 2, 77 objectives were discussed. In round 3, $> 75\%$ of experts agreed to include 7 (9%) objectives. The final 153 objectives were divided into the following categories: Basic Science of Oncology, Public Health, Diagnosis, Treatment, Prognosis, Knowledge of Common Cancers, Psychosocial Issues, Ethics and Professionalism, Communication, and Essential Oncology Experiences. **Conclusions:** Through a systematic process we have created a comprehensive and consensus-based set of oncology goals and objectives which may be used in UME curriculum design and also by educators and medical students. The objectives will be made available online to be shared with educators and learners globally, which will hopefully facilitate improvements in oncology education and patient care.

6568 Poster Session (Board #125), Mon, 1:15 PM-4:45 PM

Quality of life EQ-5D results from the AETHERA trial: A phase III study of brentuximab vedotin consolidation following autologous stem cell transplant for HL. *First Author: Scott David Ramsey, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The AETHERA trial demonstrated that early consolidation treatment with brentuximab vedotin (BV) post-ASCT significantly improved PFS in pts with HL. Peripheral neuropathy (PN) was the most common adverse event. Here, we report the results of the Quality of Life (QoL) component of the trial. **Methods:** After ASCT, 329 pts were randomized to BV 1.8 mg/kg q3wk or placebo for up to 16 cycles. The EQ-5D questionnaire, including the descriptive system and visual analog scale (VAS), was administered at each cycle, end of treatment (EOT), and q3 mos during follow up until 24 mos from Day 1. Utility index value scores were calculated using the time trade-off (TTO) method for US- and UK-based value sets. Differences between arms were compared to the lower bound of an estimated minimally important difference (MID) in cancer pts (Pickard et al 2007). **Results:** In both arms, EQ-5D scores declined from baseline to 24 mos. Slightly lower scores were seen with BV vs placebo from mos 9-18, but this resolved by end of follow up. In the analysis as randomized (US TTO), the difference between arms was <0.06 (MID) at all timepoints except for mos 15 and 18. Scores by cycle were similar in the 2 arms; mean differences did not reach the MID threshold. In both arms, scores for pts with PD per investigator were lower over time vs. pts with no PD. In the BV arm, scores for pts reporting PN were similar to those who did not. Similar results were obtained with US- or UK-based value sets. EQ VAS scores did not show an important difference between arms at any timepoint. **Conclusions:** As assessed using the EQ-5D questionnaire, treatment with BV did not have a sustained impact on QoL in HL pts. In both arms, decreased QoL was observed after progression. Clinical trial information: NCT01100502.

US-indexed EQ-5D TTO scores.

	BV N=165	Placebo N=164	BV-placebo
	Mean	Mean	Mean Difference (95% CI)
Baseline	0.897	0.907	-0.010 (-0.035, 0.014)
3 mos	0.869	0.884	-0.014 (-0.048, 0.019)
6 mos	0.868	0.872	-0.004 (-0.041, 0.032)
9 mos	0.816	0.860	-0.043 (-0.087, 0.001)
12 mos	0.799	0.859	-0.059 (-0.109, -0.010)
15 mos	0.782	0.852	-0.071 (-0.126, -0.015)
18 mos	0.776	0.837	-0.061 (-0.121, 0.000)
21 mos	0.783	0.814	-0.029 (-0.094, 0.037)
24 mos	0.757	0.787	-0.030 (-0.102, 0.042)

6569 Poster Session (Board #126), Mon, 1:15 PM-4:45 PM

Evaluation of a pharmacist-driven oral chemotherapy adherence program. *First Author: Iris Chen Zhao, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Oral anticancer drug therapy has increased: about 1/3 of new oncology drugs in development are for oral administration. The question of adherence may complicate interpretation of response and adverse events. In a study of adjuvant tamoxifen in women with breast cancer, Partridge showed a progressive decrease in adherence from 83% in the 1st year to 50% by the 4thyear of therapy. Strategies to improve adherence should optimize efficacy and minimize toxicity. We created an Oral Chemotherapy Adherence Program (OCAP), which provides education, adherence and toxicity monitoring, coverage verification, co-pay assistance, and delivery services. The purpose of this study was to assess the effect of OCAP on adherence to oral anticancer drugs. **Methods:** Patients enrolled in OCAP from October 2013 to October 2014 were ascertained. Adherence analysis was conducted for those on oral anticancer agents for 2 or more cycles both pre- and post-enrollment. Adherence rates for these patients were measured by medication possession ratio (MPR). MPR was calculated by dividing total days of drug supply by expected duration of therapy. MPR ranged from 0-1(1 = 100% adherence). High adherence was 80-100%. Pre- and post-enrollment MPR were compared using the paired t-test. **Results:** A total of 148 patients were enrolled in OCAP. Of these, 40 patients had received 2 or more cycles of therapy pre- and post-enrollment. Prior to enrollment, the mean (SD) adherence rate was 90.3% (19.9%) with 20% of patients falling into the 65-85% adherence range. 7.5% of patients fell below 40% adherence. After enrollment, the mean (SD) adherence rate was 99.3% (8.7%) with 97.5% of patients at 85% adherence or above. The lowest adherence rate post-enrollment was 68.5% in a patient with unreliable means of contact. The mean increase in adherence was 9.08% (23.2%), which was statistically significant (P = 0.02). **Conclusions:** Higher adherence rates were observed after enrollment into our oncology pharmacist-driven oral chemotherapy adherence program. Enrollment of patients into OCAP at the time of initiation of oral anticancer therapy would likely result in increased overall adherence rates. Effects of OCAP on other important outcomes, such as adverse events and costs, are ongoing.

6571 Poster Session (Board #128), Mon, 1:15 PM-4:45 PM

Impact of enhanced reimbursement on provider participation a cancer care quality program and adherence to cancer treatment pathways in a commercial health plan. *First Author: Jennifer Malin, Anthem, Inc., Woodland Hills, CA*

Background: Payment for treatment planning and care coordination for cancer care in the U.S. has been largely funded through the margin between the acquisition cost and reimbursement of cancer drugs. The Institute of Medicine has called for new payment models to align reimbursement to support patient-centered, high-quality affordable cancer care. **Methods:** In July 2014, 6 commercial HPs in the Midwest and Georgia implemented a cancer care quality program that included additional reimbursement for treatment planning and care coordination when oncologists selected regimens that were on a pathway. Cancer treatment pathways were developed using an evidence-based process with expert advisors from academic centers and community practices for breast, lung and colorectal cancer (available at www.cancercarequalityprogram.com). Practices provided clinical data on HP members starting systemic therapy through a web portal, including tumor type, stage, line of therapy, biomarkers, performance status, and planned treatment. Using program data linked with HP data, rates of participation and pathway adherence for the initial 6 months of the program were estimated. **Results:** Between July and December, 616 practices registered 5538 patients in the program, with a mean of 8.7 patients per practice (SD 23.8, range 1 to 275). The most commonly cancer types were breast and lung cancer (29% and 15%, respectively, of all registered regimens) followed by colorectal cancer (13%) and lymphoma (10%). Based on chemotherapy claims for members incurred in September and October, 64% (95% CI, 62%-65%) of members (n = 2,989) were registered with the program, ranging from 8% to 100% patients within participating practices. Among registered patients, pathway adherence was 43% for breast cancer, 65% for colorectal cancer, and 51% for non-small cell lung cancer. **Conclusions:** A new payment model that supports quality affordable cancer care through enhanced reimbursement for treatment planning and care coordination when treatment adheres to a cancer treatment pathway is feasible. Additional interventions may be needed to increase program participation and pathway adherence.

6572 Poster Session (Board #129), Mon, 1:15 PM-4:45 PM

Avoiding overtreatment in rectal cancer when the benefit of adjuvant chemotherapy is unclear. *First Author: Jonathan M. Loree, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: Adjuvant chemotherapy (AC) is intended for early stage cancers that pose a high risk of recurrence, but its use is frequently generalized to cases in which the probability of recurrence is low and absolute benefit is small. Using a cohort of stage II rectal cancer (RCa)patients (pts), we aimed to examine population-based outcomes stratified by receipt of AC and to characterize pts in whom AC provides benefit. **Methods:** Prospectively collected data from pts referred to 5 cancer centers in British Columbia for pathologic stage II RCa from 1998 to 2009 were reviewed. Overall (OS), disease-specific (DSS) and relapse-free (RFS) survival were assessed with Kaplan-Meier methods. Cox regression models that adjusted for age, ECOG, gender and high risk features were constructed. **Results:** Of 851 pts reviewed, 469 who received neoadjuvant radiotherapy were analyzed. Median age was 67, 63% were men, 73% were ECOG 0/1, 70% underwent short course radiotherapy and 43% received AC. Those treated with AC were younger ($P<0.001$), had better ECOG ($P<0.001$) and had more high risk features ($P<0.001$). In univariate analyses, AC contributed to superior OS (HR 0.46 95%CI 0.35-0.62, $P<0.001$), DSS (HR 0.63 95% CI 0.43-0.92, $P=0.02$), and a trend to improved RFS (HR 0.70 95%CI 0.49-1.01, $P=0.055$). In multivariate analyses, however, AC correlated with better OS (HR 0.61 95%CI 0.42-0.90, $P<0.001$), but not DSS ($P=0.25$) or RFS ($P=0.46$). Subgroup analysis revealed that AC correlated with improved OS (HR 0.22 95%CI 0.07-0.70, $P=0.011$), DSS (HR 0.25 95%CI 0.07-0.89, $P=0.033$) and RFS (HR 0.24 95%CI 0.07-0.85, $P=0.03$) only in selected pts who received short course radiotherapy and had ≥ 2 high risk features (n = 49, 12% of pts), such as T4 lesion, poor differentiation, inadequate lymph node sampling or obstruction/perforation. Outcomes in other subgroups were similar regardless of receipt of AC. **Conclusions:** In this population-based cohort of stage II RCa pts, the majority do not appear to benefit from AC. Risk factors conventionally used to guide AC decisions in early colon cancer should be considered in early RCa. Incorporating molecular tests into future risk stratification may further minimize unnecessary use of AC and potential over-treatment of pts.

6573 Poster Session (Board #130), Mon, 1:15 PM-4:45 PM

Can oncology readmissions be reduced? The Cleveland Clinic experience. *First Author: Alberto J. Montero, Cleveland Clinic, Cleveland, OH*

Background: Reducing 30-day readmissions is a national policy priority. Readmissions in medical oncology patients have not been extensively evaluated, and may not be reasonably preventable. We examined the impact of interventions focused on reducing oncology readmissions in the palliative medicine (PM) and general medical oncology (GMO) units. **Methods:** Baseline rates of readmissions were gathered in the period January 2013 to March 2014. Interventions were initiated in the period leading to April 1, 2014 including: (i) provider education, (ii) within 48 hours post-discharge nursing phone calls, and (iii) within-5-day post-discharge provider follow-up appointments. Calling nurses performed symptom management, education and encouraged prescription/appointment compliance. **Results:** There were a total of 3,729 combined admissions and 1,003 readmissions in the baseline period, for a readmission rate of 26% for PM and 27% for GMO units. In the 8-month intervention period (May-Dec 2014), there were 1,694 admissions, and 396 readmissions. Callbacks and 5-day appointments were monitored with a mean compliance of 77% and 70%, respectively, improving during the study period. PM readmission rates declined by 5% to 21% ($p = 0.01$, relative risk reduction 19%). GMO readmissions also decreased by 3% to 24% ($p = 0.02$, relative risk reduction 11%). The mean total cost of one readmission was $18,365, suggesting an annual potential cost savings of $2.91 million with the observed reduction in readmissions. **Conclusions:** Readmission reductions in both units were achieved through better systematic transitions to outpatient care, including follow-up calls and early provider visits; thereby leading to a reduction in utilization of inpatient resources. These data suggest that efforts focused on improving outpatient care transition are effective in reducing oncology readmissions. This is particularly relevant in the transition towards novel bundled payment models in oncology. The observed feasibility and patient/provider acceptance of these interventions suggests sustainability, and will be validated over longer time periods.

6574 Poster Session (Board #131), Mon, 1:15 PM-4:45 PM

How well do surrogate endpoints and overall survival endpoints in clinical trials predict real-world survival? *First Author: Jason Shafrin, Precision Health Economics, Los Angeles, CA*

Background: The survival of cancer patients in the real world often differs from that measured in randomized controlled trials (RCT) for reasons including differences between trial participants and real-world patients, and crossover contamination. We compare the ability of RCT overall survival (OS) and RCT surrogate endpoints -- progression-free survival (PFS) and time-to-progression (TTP) -- to predict real-world OS prognosis across five cancers. **Methods:** Using NCCN guidelines, we identified 30 drug treatments for breast, colorectal, lung, ovarian, or pancreatic cancer approved before 2009 with Phase III RCTs reporting both OS and either PFS or TTP. Median RCT survival (i.e., PFS or TTP, and OS) and inclusion criteria were identified within each treatment's relevant pivotal trial publication. We measured median real-world OS for each treatment using a Kaplan-Meier estimator applied to SEER-Medicare data (1991-2010). Accuracy of trial PFS/TTP and OS in predicting real-world OS was measured using median absolute prediction error and $R^2$from linear regressions. **Results:** Among the 49,827 patients qualifying for inclusion in the relevant RCT study population, median survival across the 30 treatments was 6.0 months for trial surrogates (i.e., PFS/TTP), 14.8 for trial OS, and 13.5 months for real-world OS. Median error from predictive models using trial surrogates was 3.55 months compared to 1.80 months for trial OS (p= 0.156; R^2: PFS/TTP = 0.382 vs. OS = 0.613). Among all patients receiving a relevant treatment (240,852 individuals), prediction error was 5.32 months for models using trial surrogate endpoints and 5.34 months for models using trial OS (p= 0.802; R^2: PFS/TTP = 0.113 vs. OS = 0.167). **Conclusions:** RCT OS tended to outperform PFS/TTP in predicting real-world OS prognosis for patients similar to trial participants. However, in the broader real-world population of treated patients, RCT PFS/TTP and OS performed similarly. Among the five cancer sites studied, trial PFS and trial OS may be equally valuable to payers and providers seeking to predict survival in broad real-world populations.

6575 Poster Session (Board #132), Mon, 1:15 PM-4:45 PM

Time to treatment (TTT) and breast cancer survival in the United States. *First Author: Richard J. Bleicher, Fox Chase Cancer Center, Philadelphia, PA*

Background: Time to initiate breast cancer treatment is increasing in the United States, but controversy surrounds the impact of TTT on survival. The impact of the interval between diagnosis and treatment is a source of concern to patients and clinicians. We investigated the relationship using separate analyses of two of the largest cancer databases in the United States. **Methods:** Patients had noninflammatory, nonmetastatic, invasive breast cancer, with surgery as initial treatment. The first study used the SEER-Medicare database (SMDB), and second, the National Cancer Database (NCDB). Each analysis assessed survival as a function of time between diagnosis and operation (≤ 30, 31-60, 61-90, 91-120, and 121-180 days [d] from diagnosis), adjusting for demographics, comorbidities, tumor-related factors, and treatment. **Results:** The SMDB cohort had 94,544 patients ≥ 66 years old, diagnosed between 1992 and 2009. With each interval delay increase, adjusted overall survival (OS) was lower for all patients (hazard ratio [HR] 1.09, $p< 0.001$), and for those having stage I (hazard ratio [HR] 1.13, $p< 0.001$) and stage II (HR 1.06, $p= 0.010$) disease. Breast cancer-specific mortality increased with each 60-d interval (subhazard ratio 1.26, $p= 0.03$). The NCDB study evaluated 115,790 patients ≥ 18 years old, diagnosed between 2003 and 2005. The adjusted overall mortality HR was 1.10 ($p< 0.001$) for each increasing interval, significant in stages I (HR 1.16, $p< 0.001$) and II (1.09, $p< 0.001$) disease. Five-year OS adjusted for demographics, comorbidities, tumor-related factors and treatment in the SMDB progressively declined from 78.1% for ≤ 30 d to 60.9% for 121-180 d and in the NCDB from 88.0% for ≤ 30 d to 80.4% for 121-180 d. **Conclusions:** Independent analyses of two national cohorts demonstrate that an increased time to initiate surgical treatment confers lower overall and disease-specific survival for patients with early stage breast cancer. A shortened delay is associated with an outcome benefit comparable in magnitude to the addition of some standard therapies. Although time is required for preoperative evaluation and consideration of options such as reconstruction, efforts to reduce TTT should be pursued where possible to enhance survival.

6576 Poster Session (Board #133), Mon, 1:15 PM-4:45 PM

Are conflict of interest (COI) slides displayed long enough to comprehend? *First Author: James Austin Talcott, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Conflicts of Interest (COI) are displayed to alert the scientific audiences to potential financial biases. At scientific meetings, COI of oral presenters are visually displayed. COI slides increase in complexity with disclosed COI categories (CC) and relationships (R), requiring more time for audience members to process the information. We reviewed the COI slides displayed at the 2014 ASCO Annual Meeting in video presentations archived for the Virtual Meeting to assess the relationship between display time (DT) and the information they contained. **Methods:** Two reviewers (AD and JS) reported the following information for each oral scientific presentation: session, role (presenter, discussant), disclosed CG and R, and COI slide display time. To estimate the required time (RT) to process the information, we measured the required time to process the content of a sample of COI slides and created a predictive model, assuming that 1 second is required to focus on COI, and CC items require more process time than R items. **Results:** Of 485 presenters, over half reported 0 (43.1%), 1 (12.8%) or 2 (10.7%) R, but up to 29 R were reported. COI slides were visible for 1-65 seconds. However, we observed no relationship between R and COI slide display time (slope: = -.055, p = 0.39). RT (in seconds) = 1 + (1 x CC) + (0.85 x R) fit the observed RT data. We found DT ^{3} calculated RT for three-fourths of presenters when reported R was 1 or 2, but < 50% if reported R^{3}3 ($P < 0.001$). **Conclusions:** At a major cancer scientific meeting, measured DT of presenter COI slides did not increase with disclosed R. Based on estimated RT to process the COI information, DT was inadequate for comprehension for most presentations if reported R exceeded 2.

R (number)	0	1	2	3-4	5-7	8-10	> 10	Total
Presentations (%)	209 (43)	62 (13)	52 (11)	42 (9)	45 (9)	31 (6)	44 (9)	455 (100)
DT adequate, %	100	77	73	33	24	10	2	67

6577 Poster Session (Board #134), Mon, 1:15 PM-4:45 PM

An analysis of corrective action plans to address slow accruing NCI-held IND early phase trials. *First Author: Holly A Massett, National Cancer Institute, Bethesda, MD*

Background: In 2011, NCI began requesting Corrective Action Plans (CAP) for early phase trials accruing < 50% of their projected accrual rate after Qtr 2 for Phase 1 (Ph1) or Qtr 3 for Phase 2 (Ph2). Study PIs of low accruing trials are asked to complete and return a CAP within 2 weeks and identify reasons and possible actions to address accrual. We report findings from an analysis of CAPs received on all NCI Cancer Therapy Evaluation Program (CTEP) held IND studies active between Aug 2011 and Feb 2013 (N = 327). **Methods:** Three methods were employed: 1) content analysis of CAPs to categorize slow accrual reasons and proposed actions (3 coders, intercoder reliability = 78%; 100% after post-coding deliberation); 2) analysis of CAP trial timelines and accrual data; 3) assessment of whether closed CAP trials met their primary scientific objectives. **Results:** CTEP requested CAPs for 150 (46%) of the 327 trials; 135 were eligible for analysis with 51% Ph1 (n = 69) and 49% Ph2 trials, and 88% adult trials (n = 119). CAP trials were open a median of 30 months (14 mo pre- and 16 mo post-CAP), and 70% (n = 94) were closed to accrual at analysis. Of closed CAP trials: 68% (n = 64) met their primary objective but took 3x longer than projected; those not meeting their objective(s) were open 6x longer before closing; and 27% (n = 25) had an accrual rate increase, post-CAP, associated with a greater likelihood of meeting the objective(s). For Ph1 trials, safety delays dominated slow accrual reasons while institutional/administrative reasons were common for Ph2. Site activation delays and access to patients ranked high for both. Only 54% of proposed corrective actions matched the reasons given for slow accrual. **Conclusions:** CAP requests had a positive impact on accrual for over one-quarter of the trials analyzed; however, most trials receiving a CAP took substantially longer to complete than projected. CTEP's new Experimental Therapeutics Clinical Trial Network (ETCTN) is poised to address many concerns identified in this analysis. CAPs should be implemented prior to Q2/Q3 to identify and address slow accruing trials earlier. CTEP is standardizing the CAP data collection to develop statistical algorithms to aid decisions related to trial closure for slow accrual.

6578 Poster Session (Board #135), Mon, 1:15 PM-4:45 PM

Prevalence and prognostic impact of prior cancer in locally advanced lung cancer. *First Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Locally advanced lung cancer patients with prior cancer diagnoses are generally excluded from clinical trials. Although the impact of prior cancer on outcomes has been described for early-stage and metastatic disease, it remains largely unknown for locally advanced lung cancer. To inform future decisions about this widespread clinical trial exclusion policy, we determined the characteristics and prognostic impact of prior cancer diagnoses among patients with locally advanced lung cancer. **Methods:** We identified patients > 65 years of age with locally advanced lung cancer in the Surveillance, Epidemiology, and End Results-Medicare linked registry. Prior cancer was characterized by prevalence, type, stage, and timing. All-cause and lung cancer-specific mortality were compared between patients with and without prior cancer using propensity score-adjusted Cox regression. **Results:** Of 50,715 locally advanced lung cancer patients, 16.4% had a history of prior cancer. Prostate (24%), gastrointestinal (17%), breast (16%), and other genitourinary cancers (15%) were the most common cancer types; 69% of prior cancers were localized or in situ. The majority (57%) of prior cancers were diagnosed within 5 years of the index lung cancer diagnosis. Prior cancer did not adversely impact all-cause (HR 0.97; 95% CI, 0.95-1.00; P= 0.03) or lung cancer-specific (HR 0.84; 95% CI, 0.82-0.87; P< 0.001) mortality compared to patients with no prior cancer. Similar outcomes were seen in a simulated clinical trial eligible population (age < 75 years, no recorded co-morbidities, and received surgery and/or radiation for the locally advanced lung cancer diagnosis; N = 3,601): overall survival HR 1.07; 95% CI, 0.97-1.19; P= 0.19; lung cancer-specific survival HR 0.85; 95% CI, 0.75-0.97; P= 0.02). **Conclusions:** For locally advanced lung cancer, prior cancer does not negatively impact outcomes. Given the ongoing need for new and better treatments for this disease, locally advanced lung cancer patients with history of prior cancer should not be excluded from clinical trials. Modifying this longstanding and widespread eligibility criterion will increase trial accrual rates and improve generalizability of study results.

6579 Poster Session (Board #136), Mon, 1:15 PM-4:45 PM

Outcomes and predictors of life sustaining treatments in patients with metastatic cancer. *First Author: Kah Poh Loh, Baystate Medcl Ctr, Springfield, MA*

Background: Patients with metastatic cancer admitted to the ICU or requiring invasive mechanical ventilation (IMV) have historically had high mortality rates. However, little is known about how frequently these patients receive life-sustaining treatments (LSTs) or which characteristics are associated with receipt of LSTs. *Methods*: We used the 2010 California Healthcare Cost and Utilization Project - State Inpatient Database to identify metastatic cancer patients (≥ 18 years), focusing on patients with a medical DRGs. Using ICD-9-CM procedure codes, we examined use of LSTs. We stratified patients by the use of LSTs and cancer types and compared patient characteristics and outcomes via chi-square or Wilcoxon tests. We used multivariate logistic regression models to identify predictors for potential use of LSTs and IMV while accounting for the clustering of patients within hospitals. **Results:** We identified 68,890 admissions among metastatic cancer patients. Mean age was 65 years and 48% were male. Cancer types were divided into lung (18%), breast (8%), colorectal (8%), GU (11%) and others (29%). Approximately 8% of these received at least one LSTs, including IMV (4%), PEG (1%), acute dialysis (1%), and TPN (3%). Receipt of LSTs varied by cancer types. Compared to patients who did not receive these treatments, length of stay (LOS) was longer in patients receiving LSTs [11.0 days vs. 5.5 days; p-value < 0.001] and in-hospital mortality rate was higher (41% vs. 10%, p-value < 0.001). In multivariable models, predictors of receipt of LST included older age, non-white race and greater burden of comorbidities. Compared to lung cancer, breast (OR 0.82, 95% CI 0.71-0.88) and GU cancer (OR 0.75, 95% CI 0.66-0.80) were less likely to receive LSTs. DNR status were marginally associated with the receipt of LSTs (OR 0.95, 95% CI 0.88-0.99) and not associated with the receipt of IMV (OR 1.04, 95% CI 0.94-1.09). **Conclusions:** Nearly 8% of hospitalized metastatic cancer patients received LSTs. Patients receiving LSTs had a longer LOS and higher in-hospital mortality rates than all hospitalized metastatic cancer patients. Lung or colorectal cancers were associated with the patients receiving LSTs. DNR status was not associated with receiving IMV.

6580 Poster Session (Board #137), Mon, 1:15 PM-4:45 PM

Determinants of early mortality in 37,568 colon cancer patients participating in 25 clinical trials of the ACCENT database. *First Author: Winson Y. Cheung, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: Clinical trials are the gold standard for evaluating novel therapeutics. Accrual of patients (pts) at substantial risk of significant treatment toxicity or early mortality compromises trial integrity, may pose greater harm than benefit, and can complicate trial interpretation. We aimed to define prognostic factors that may be used to guide risk-benefit assessments among pts being considered for phase III adjuvant colon cancer (CC) studies. **Methods:** A pooled, retrospective analysis of individual level data from CC pts enrolled in randomized trials of adjuvant systemic therapy was conducted. Separate multivariate logistic regression models with different definitions of early mortality (30, 60, 90 days, and 6 months from trial randomization) as outcome variables were constructed, adjusting for clinically and statistically significant variables from univariate and interaction tests. **Results:** We included 37,568 pts from 25 trials. Median age 61 years (IQR 53-68), 54% men, 90% White, 29% and 71% stage II and III disease, and 79%, 20%, and 1% ECOG performance status (PS) 0, 1, and 2+, respectively. Rates of early mortality were low: 109 (0.3%) at 30 days, 215 (0.6%) at 60 days, 281 (0.8%) at 90 days, and 540 (1.4%) at 6 months in the pooled cohort. On univariate analyses, increasing age, male gender, poorer PS, and stage III vs. stage II disease predicted for higher likelihood of early mortality. Race, body mass index, lymph node ratio, micro-satellite status as well as study time era were not associated with worse outcomes. In multivariate models, increased age and poorer PS were associated with early mortality at all time-points (age: p < 0.0001 and PS: p = 0.05 at 6 months), with pts aged > / = 80 years having a 6 month death rate of 4.6% as compared to < 1% for the youngest and pts with PS 2+ having a 6 month death rate of 4.4% as compared to 1.7% and 1.1% for PS 1 and 0, respectively. **Conclusions:** Early mortality in adjuvant trials of CC was infrequent. However, it was more prevalent in the elderly and among individuals with PS 2+, underscoring the need for specific trial designs that can accommodate the vulnerabilities of these underrepresented subsets of the population.

6581 Poster Session (Board #138), Mon, 1:15 PM-4:45 PM

Hospital treatment patterns and survival for metastatic colorectal cancer. *First Author: Robert Wallace Krell, University of Michigain Health System, Ann Arbor, MI*

Background: Despite evidence that multimodality therapy (surgery and multi-agent chemotherapy) improves survival for patients with metastatic colorectal cancer (CRC), there is broad variation in its use across hospitals. It is unclear whether survival differences across hospitals reflect differences in hospital quality or their treatment choices. We assessed survival for patients with metastatic CRC based upon their treatment and the hospitals treating them. **Methods:** We assessed patients with metastatic CRC in the 2003-06 National Cancer Data Base (N = 53,884 patients in 1019 hospitals). We compared survival across hospitals based on their adjusted relative utilization of cancer treatments (primary and distant site surgery, chemotherapy, or palliative care). Then, to assess the influence of different treatment patterns on survival, we compared outcomes for patients who received similar treatments across hospitals. **Results:** Compared to hospitals with low multimodality treatment utilization, patients in hospitals with high utilization were more likely to receive multi-agent chemotherapy (51.0% vs 32.1%, $p < 0.001$), primary site resection (66.3% vs 62.3%, $p < 0.001$), metastatic site resection (32.0% vs 10.0%, $p < 0.001$), or palliative care (9.1% vs 6.9%, $p = 0.014$), and had longer median survival (15.2 vs 12.4 months, $p < 0.001$). The observed survival differences across hospitals were eliminated once patients were stratified by treatment modality (adjusted HR for treatment in a high-utilization hospital 1.02 [0.98-1.07]). For example, there were minimal differences in median survival between high and low utilization hospitals for patients treated with multimodality therapy (30.7 vs 29.1 months, $p = 0.31$), chemotherapy only (12.1 vs 12.6 months, $p = 0.04$) or palliative care (7.8 vs 7.8 months $p = 0.24$). **Conclusions:** There is broad variation in hospital treatment utilization for patients with metastatic CRC. Survival differences across hospitals are minimal, however, when patients receive similar treatments. Higher survival in hospitals with high treatment utilization likely reflects their willingness to utilize cancer treatments, include palliative care, rather than other features of their overall quality of care.

6582 Poster Session (Board #139), Mon, 1:15 PM-4:45 PM

Association between Oncologic Drugs Advisory Committee (ODAC) members' financial conflicts of interest (FCOIs) and recommendations for drug approval by the U.S. Food and Drug Administration (FDA). *First Author: Ariadna Tibau Martorell, Hospital de la Santa Creu i Sant Pau, Barcelona, YT, Spain*

Background: FDA advisory committees influence decisions relating to the regulatory approval of drugs in the United States. Little is known about whether ODAC members' FCOIs affect the FDA's oncologic drug approval process. **Methods:** We consulted the FDA website for transcripts from ODAC meetings between January 2000 and December 2014. We included all meetings at which drugs used for prevention, treatment, or palliation of cancer were discussed. We restricted our analysis to meetings at which yes/no votes were cast for at least one question relating to an oncologic drug. We collected data on drug name, prevalence of self-reported FCOIs of voting members, type of FCOIs (with sponsor or competitor) and the number of members recused or with waivers allowing discussion but no voting. Association between votes favoring a drug, final drug approval and FCOIs of ODAC members were explored using logistic regression. **Results:** Eighty transcripts were available for analysis. ODAC voted favouring the drug in 50% of cases. In 6% of cases, ODAC voted against a drug, but it was subsequently approved. At least one FCOI was declared for at least one voting committee member in 59% of votes. At least one member was recused or given a waiver in 14% and 6% of votes, respectively. There has been a significant reduction in the proportion of voting members with FCOIs over time (41% in 2000 vs. 0% in 2014, trend $p < 0.001$). Voting members with any FCOIs were more likely to vote in favor of a drug (OR 1.34, $p = 0.04$). There was a near-significant interaction between the presence and type of FCOIs; FCOIs with the sponsor were associated with higher odds of voting in favor of a drug compared to FCOIs with a competitor (OR 1.89 vs. 0.97, interaction $p = 0.052$). Similar results were seen for the association of ODAC members' FCOIs and final FDA approval (OR 1.42, $p = 0.03$). **Conclusions:** FCOIs among voting members of ODAC are common, but have decreased significantly over time. FCOIs, especially with the sponsor, are associated with higher odds of ODAC recommendation and of final FDA approval of oncologic drugs.

6583 Poster Session (Board #140), Mon, 1:15 PM-4:45 PM

Frequency and predictors of hospitalization during chemotherapy: a systematic review. *First Author: Rebecca M. Prince, Princess Margaret Hospital, Toronto, ON, Canada*

Background: Hospitalization during chemotherapy is a significant event from both the patient and healthcare system perspectives but little is known about how often it occurs and in which settings. We conducted a systematic review to define the frequency of and factors associated with treatment-related hospitalization among cancer patients (pts) undergoing chemotherapy. **Methods:** A systematic search of Medline and EMBASE databases, from 1946 to September 2013, was undertaken to identify articles reporting rates of hospitalization in pts with cancer undergoing chemotherapy. Observational studies and clinical trials were eligible but results were analysed separately for each group. Summary statistics were used to describe the results and the Chi-square test was used to compare the groups. **Results:** Sixty articles met inclusion criteria: 44 observational studies comprising 189,342 pts and 16 randomized controlled trials comprising 13,086 pts. The majority of articles (80%) focused on chemotherapy given with palliative intent most commonly in breast, lung and colorectal cancers. The proportion of pts hospitalized at least once was significantly higher in observational studies at 32% (range 27-38%) compared with 21% (range 15-27%) in randomized trials (OR 2.13, 95%CI 2.03-2.23, $p < 0.0001$). A significant difference was seen in both the adjuvant and palliative settings between real life and trial pts with 42 vs 16% (OR 2.94, 95%CI 2.72-3.18, $p < 0.0001$) of adjuvant and 33 vs 23% (OR 3.24, 95%CI 3.03-3.48, $p < 0.0001$) of palliative pts being hospitalized, respectively. Factors associated with hospitalization in observational studies included higher comorbidity, type of chemotherapy and geographic location, while performance status and type of chemotherapy were significant predictors in clinical trials. Age was not a risk factor in either population. A number of methodological issues regarding reporting of hospitalization parameters were identified such as poor definitions of the at-risk period and attribution of hospitalization as treatment-related. **Conclusions:** Hospitalization during chemotherapy is common especially in unselected patient populations. However, few articles report this and often do so poorly.

6584 Poster Session (Board #141), Mon, 1:15 PM-4:45 PM

Choosing wisely: Treatment recommendations from 36 Michigan Oncology Clinical Treatment Pathways practices. *First Author: Amy Hatfield Seung, CARET, Ann Arbor, MI*

Background: ASCO identified ten low value, commonly used practices (Schnipper et al JCO 14:1715, 2012 and JCO 31:4362, 2013) as part of the "Choosing Wisely" (CW) campaign. Pathways is a statewide quality improvement program sponsored by Michigan BlueCross BlueShield. It measures and incentivizes adherence to locally defined treatment pathways (Fineberg et al JOP 8e32s, 2012). CARET^{SM}, a web-based patient registry was developed to support this program. CARET allows providers to enter treatment data and patient characteristics, and to demonstrate pathway compliance. We report preliminary data for three CW items. **Methods:** CARET includes records entered by participating providers for medical anticancer treatment regimens. Provider-reported data is matched to insurance claims data. Three CW items were easily available for analysis, avoiding: 1) chemotherapy for patients with advanced incurable cancer, 2) unnecessary myeloid growth factors, and 3) unnecessary antiemetic drugs for chemotherapy with low or moderate risk of nausea or vomiting. **Results:** A total of 1060 anticancer regimens representing 937 unique patients were initiated in 2014. 114 physicians from 36 practices were included. 690 (65.1%) regimens required prophylactic myeloid growth factor and antiemetic pathways. Results by tumor type and by CW item are shown in the table. **Conclusions:** Pathways practices appear to CW for these three treatment measures. From our initial data, we cannot discern the role of incentives for pathway adherence; the effect of real-time, registry-based, decision support tools (CARET); support from payors; or other factors in CW. We plan to explore these reasons and analyze cost savings from CW.

	Regimens (n)	Advanced disease with PS 3-4 receiving chemotherapy n (%)	Regimens with supportive care (n)	Antiemetic nonadherence n (%)	Growth factor nonadherence n (%)
Breast	442	7 (1.58%)	306	49 (16.1%)	38 (12.4%)
Colon	133	1 (0.75%)	110	17 (15.5%)	4 (3.6%)
Lung	201	6 (2.99%)	119	23 (19.3%)	15 (12.6%)
Lymphoma	116	2 (1.72%)	87	16 (18.4%)	4 (4.6%)
Multiple Myeloma	59	0	41	3 (7.3%)	2 (4.9%)
Ovarian	46	0	16	3 (18.8%)	6 (37.5%)
Prostate	59	1 (1.7%)	11	3 (27.3%)	2 (18.2%)
Renal	4	0	0	-	-
Total	1060	17 (1.6%)	690	114 (16.5%)	71 (10.3%)

6585 Poster Session (Board #142), Mon, 1:15 PM-4:45 PM

Prospective clinical study of precision oncology in solid tumors. *First Author: Davendra Sohal, Cleveland Clinic, Cleveland, OH*

Background: Advances in tumor genomic profiling offer the promise of precision oncology but a systematic prospective evaluation is lacking. We conducted a prospective cohort study of tumor genomic testing to identify prevalence of actionable alterations and their impact on management decisions. **Methods:** Patients provided written informed consent for this prospective cohort study approved by the Cleveland Clinic Institutional Review Board. Eligibility requirements included pathologic diagnosis of select solid tumor malignancies without a known curative option, age ≥ 18 years, and ECOG PS 0-2. Tumor samples were sequenced for up to 315 candidate genes using FoundationOne (Cambridge, MA). Results were reviewed at the Cleveland Clinic Genomics Tumor Board (GTB) for biologically actionable alterations, defined as those linked to an approved therapy in the solid tumor under study or another solid tumor, a clinical trial, or a contraindication to a targeted therapy. Sample size was 250 patients. Outcomes were feasibility and clinical impact of tumor sequencing. **Results:** From Aug 2013 to Oct 2014, all 250 patients were enrolled. Median age was 60 years; 128 (51%) were female; 220 (88%) were white. Colorectal (25%), breast (18%), lung (13%), pancreatobiliary (12%), and head and neck (10%) cancers were common diagnoses. Median time from consent to genomic test result was 25 days (range, 3-140), with 27 (11%) samples having insufficient tissue for analysis. Of 223 resulted samples, an alteration was found in 96% (n = 214), with a median of 4 (0-20) alterations per sample. At GTB review, a biologically actionable alteration was declared in 63% (n = 141) of cases. However, only 10% (n = 22) of patients received tumor genomics-driven targeted therapies: 12 went on clinical trials, 3 received on-label drugs, and 7 received off-label drugs. Lack of clinical trial access was the most common reason for non-recommendation/receipt of genomics-driven therapy. **Conclusions:** This prospective study shows that routine tumor genomic profiling is feasible, with almost two-thirds of resulted samples having a biologically actionable alteration, but paucity of genomics-driven clinical trials of targeted therapies is a barrier to the success of precision oncology.

6586 Poster Session (Board #143), Mon, 1:15 PM-4:45 PM

Breast cancer progression and workplace productivity. *First Author: Wesley Yin, UCLA, Los Angeles, CA*

Background: A significant fraction of women with breast cancer leave employment due to their disease. However, little is known about the effects of breast cancer progression on productivity among those who remain employed **Methods:** Linking commercial health claims to employer records on workplace productivity, we created a cohort of employed U.S. women ages 18-64 who were treated for breast cancer between 2005 and 2012. Disease stage was measured through diagnosis codes and treatments observed, to classify women into the following breast cancer groups in each 90-day quarter: local; locally advanced; other non-metastatic; metastatic, 1st line therapy; metastatic, 2nd line therapy; metastatic, ≥ 3rd line therapy; metastatic, end-of-life care. Productivity was defined as work hours missed per quarter. We performed linear regression analysis to predict hours missed as a function of disease stage, age, comorbidities, industry of occupation, region and a time trend. To explore possible selection bias, we used a Cox survival model to test whether women whose cancer progressed were more likely to exit our employment-based dataset, controlling for age, comorbidities, industry and region. **Results:** In our cohort of 19,496 women with breast cancer,stage varied as follows:23% local; 1% locally advanced; 69% other non-metastatic; 5% metastatic 1st line; 1% metastatic 2nd line; < 1% metastatic ≥ 3rd line; 1% metastatic, end-of-life care. Women treated for breast cancer missed an average of 79 hours (about 10 days) per quarter. Disease progression was associated with greater work hours missed. In adjusted analysis, hours missed varied by stage as follows: other non-metastatic, 77h; local, 81h; locally advanced, 83h; metastatic 1st line, 87h; metastatic 2nd line, 112h; metastatic ≥ 3rdline, 106h; metastatic end-of-life care, 126h. Women whose cancer progressed were more likely to exit our employment-based dataset. Thus our estimated productivity effects are likely conservative. **Conclusions:** Breast cancer progression is associated with impaired workplace productivity, with greater impairment among those with more advanced disease. Avoiding or delaying disease progression could bring productivity gains to the workplace in addition to the benefits to the patient.

6587 Poster Session (Board #144), Mon, 1:15 PM-4:45 PM

Uncontrolled chronic conditions prior to cancer diagnosis in older adults as a predictor of unplanned hospitalizations during cancer care: A Medicare claims analysis. *First Author: Noam Avraham VanderWalde, University of Tennessee West Cancer Ctr, Memphis, TN*

Background: Unplanned hospitalizations (UH) during cancer care have been identified as a poor outcome that may significantly increase costs of care. We hypothesized that poor quality of care prior to cancer diagnosis, as defined by preventable hospitalizations for Ambulatory Care Sensitive Conditions (ACSCs), predicts for UH during cancer care. **Methods:** A retrospective claims study was conducted among Medicare fee-for-service enrollees with a first time diagnosis of one of seven cancers (breast, lung, colorectal, lymphoma, melanoma, pancreatic, or thyroid) from 6 different states (TX, OH, ME, NM, GA, and FL) between 2011 and 2012. Date of diagnosis was defined as the first cancer diagnosis claim from inpatient or outpatient claims. At least nine months of pre-diagnosis claims was required to identify pre-cancer Charlson comorbidity (CCI) and ACSC hospitalizations as measured by ER and hospitalization diagnosis codes. UHs were defined as hospitalization, with admission type of urgent or emergent within 1 year from diagnosis, excluding those for cancer treatment. Multivariate logistic regression analysis was used to model UH using known patient and county level socio-demographic variables. **Results:** A total of 21,735 cancer patients were identified. The majority of patients had breast (n = 7,548), lung (n = 5,841) or colorectal cancer (n = 3,904). Median age at diagnosis was 74. Thirty four percent of patients were male. UHs were experienced by 33% of all patients during their cancer care, while 8% had pre-diagnosis ACSC hospitalizations. ACSC hospitalizations were strongly associated with UH during cancer care (OR: 1.49, 95% CI: 1.34 – 1.66, p-value: < .001). Other variables associated with higher likelihood of UH include CCI (OR: 1.22, p-value < .001) AA race (OR: 1.30 p-value < .001), and cancer type compared to breast (lung cancer OR 3.30, p-value < .001). **Conclusions:** There is a strong association between pre-diagnosis ACSC preventable hospitalizations and UHs during cancer care, even after controlling for comorbidity. Interventions that identify vulnerable older adults at diagnosis may help improve outcomes and costs of cancer related care.

6588 Poster Session (Board #145), Mon, 1:15 PM-4:45 PM

Potentially inappropriate medication use in elderly breast cancer patients. *First Author: Meghan Sri Karuturi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Screening for potentially inappropriate medication (PIM) use is recommended in elderly cancer patients receiving chemotherapy. However, few studies have examined the patterns and impact of PIM use in this population. Our objective was to determine predictors of PIM use and impact on outcomes in breast cancer patients receiving chemotherapy. **Methods:** We used data from the Surveillance, Epidemiology, and End Results database linked to Medicare claims. Our cohort included women 66 years and older with a diagnosis of Stage II/III breast cancer receiving adjuvant chemotherapy between 7/1/2007 and 12/31/2009. We used the National Center for Quality Assurance Drugs to Avoid in the Elderly list to define baseline PIM use as a dichotomous variable in the 4 months prior to diagnosis. Outcome measures included ER visits, hospitalization, or death within 6 months of diagnosis. We included age, race, stage, Charlson comorbidity, poverty level, and number of providers as covariates. We used Chi-square or Fisher's exact test to determine associations of PIMs with covariates and outcomes, and multivariable logistic regression to determine the association of PIMs with outcomes. **Results:** 1595 patients met our criteria, of whom 339 (21.3%) had PIM use at baseline. In multivariate analysis, baseline PIM was associated with higher comorbidity (OR 1.33, 95% CI 1.0-1.76 for 1; OR 1.51, 1.07-2.13, for 2+), higher poverty level (OR 2.03, 1.43-2.88 for third quartile; OR 1.44, 1. -2.07, for highest quartile), and higher number of providers (OR 1.70, 1.18-2.44 for 4+ providers). 669 (41.9%) had an ER visit, unplanned hospitalization or died within 6 months after diagnosis. Baseline PIM was not significantly associated with the composite outcome in univariate analysis (OR 1.23, 95% CI, 0.97-1.57). Associations with outcome in the multivariate analysis included advanced stage (OR 1.48, 95% CI 1.19-1.82), higher comorbidity index (OR 1.67, 95% CI 1.23-1.26 for 2+ vs. 0) and baseline ER visits/hospitalizations (OR 1.82, 95% CI 1.33-2.49). **Conclusions:** We found no significant association between overall baseline PIM use and adverse outcomes. Ongoing analyses are evaluating the association between PIM use during chemotherapy and adverse outcomes.

6589 Poster Session (Board #146), Mon, 1:15 PM-4:45 PM

Creating a national collaborative strategy to enhance trial accrual in NCI's National Clinical Trials Network (NCTN) in the era of precision medicine. *First Author: Andrea Denicoff, National Cancer Institute, Bethesda, MD*

Background: NCI launched the NCTN on March 1, 2014 to reinvigorate the publically funded cancer trials system. As precision medicine (PM) trials increasingly require screening large numbers of patients to identify a subset of patients whose tumors contain specific molecular targets, national accrual strategies are needed. We report findings from a Network-wide interactive meeting held in Dec, 2014 to explore accrual to PM and adolescent and young adult (AYA) trials. **Methods:** NCI convened a 2-day meeting of NCTN grantees and NCI staff, with 75 representatives from Groups, Patient Advocates & Lead Academic Participating Sites (LAPS), to discuss accrual in the era of PM. Accrual challenges and strategies were identified via a mixed method approach: pre-meeting worksheets, trial case studies, group and breakout sessions and a priority ranking activity. Findings were triangulated to determine next steps to maximize future accrual. **Results:** Key themes identified included the need to streamline trial communication and promotion, emphasize accrual feasibility during trial design and review, better address minority and underserved populations, increase the efficiency and clarity of regulatory processes, and incentivize and enhance participation in trials by investigators and sites. Consensus was reached on the need for a cross-NCTN forum to collaborate on accrual for specific challenging trials and address broader accrual issues. Key themes and recommendations for the forum will be elaborated on in light of PM and AYA trials. **Conclusions:** A new NCTN Accrual Core Team (ACT) will be formed to collaboratively address identified cross-cutting themes that have implications for accrual to trials. Next steps that may be addressed by ACT include identifying ways to target messaging to promote trials to key groups (including investigators, research teams, and patients), developing templates for trial education, facilitating the pooling of resources currently replicated by sites such as Medicare Coverage Analyses, standardizing trial tools and processes, and developing metrics to monitor accrual enhancement efforts.

6590 Poster Session (Board #147), Mon, 1:15 PM-4:45 PM

Does paid sick leave affect the unmeasured costs of colorectal cancer treatment? *First Author: Christine Marie Veenstra, University of Michigan, Ann Arbor, MI*

Background: For working patients, the financial impact of colorectal cancer (CRC) diagnosis and treatment can be substantial. Unmeasured costs can include unpaid time away from work and job loss. Although not a provision of the Affordable Care Act or FMLA, paid sick leave may help CRC patients retain their jobs and alleviate some financial burden. **Methods:** In 2011-13, we surveyed Stage III colorectal cancer patients from Detroit and Georgia SEER registries 4-12 months after diagnosis. The analytic sample was restricted to respondents who were working at the time of diagnosis. We assessed two outcomes, job retention and personal financial burden. We measured personal financial burden using a validated 6-item scale and categorized it as a binary measure indicating low vs. high burden. We assessed associations between 1) paid sick leave and job retention and 2) job retention and personal financial burden in separate models, using logistic regression to control for age, sex, race, education, and income. **Results:** Among 1469 patients who returned surveys (RR 68%), 38% were working for pay at the time of CRC diagnosis. Overall, 46% of patients did not retain their jobs and 32% reported high financial burden during CRC treatment. In adjusted analyses, availability of paid sick leave was significantly associated with job retention (OR 2.59, 95% CI 1.68–3.98). After adjustment, job retention was inversely associated with high personal financial burden (OR 0.25, 95% CI 0.160.38). Compared with respondents who had paid sick leave available, those without paid sick leave were more likely to be older, have a high school education or less, and have an income of under $50,000 (all $p < 0.001$). **Conclusions:** In a robust, population-based study, we found that the availability of paid sick leave during CRC treatment was positively associated with job retention. Furthermore, personal financial burden was reduced when working patients were able to retain their jobs throughout CRC treatment. Millions of working Americans do not have access to paid sick leave, but our results indicate that an investment in paid sick leave by employers and government may provide long-term societal dividends.

6591 Poster Session (Board #148), Mon, 1:15 PM-4:45 PM

Impact of maternal death from female cancers on child mortality. *First Author: Raymond Mailhot Vega, New York University School of Medicine, New York, NY*

Background: Cervical and breast cancers are the most common causes of cancer mortality in women of childbearing age. The impact of maternal mortality on child mortality remains an under-investigated area. Elevated mortality rates in offspring are significantly associated with maternal death in both Bangladeshi and Scandinavian cohorts (Ronsmans 2010, Li 2014). This effect is contextual: when a mother dies, a child in Bangladesh is 10 times more likely to die before 10, versus 1.5 times more for a Scandinavian child. By ignoring this impact disease mortality rates underrepresent life lost, and this underestimation affects appropriate resource allocation. We propose a country-specific model to allow for estimates of offspring death rates attributable to breast and cervical cancers in women of childbearing age. **Methods:** A Monte Carlo simulation model (TreeAge) analyzed a sample population of 1 million 15yo fertile girls of a specific nationality and at risk of dying from cervical and breast cancer. Information was obtained from Globocan and UN World Population Prospects. Criteria included: 1) country-specific life tables for baseline child mortality 2) child risk of dying due to maternal loss until 10 years of age; and 3) definition of a coefficient "Q" = the multiplicative contextual increase in all cause mortality. Bangladesh and Denmark served as two benchmark populations, and coefficient Q was varied. Sensitivity analyses were performed in five nations with the highest breast or cervical mortality. The outcome measurement is relative mortality increase (RMI), such that a value of 2% denotes for every 100 women succumbing to disease, 2 children die in association. **Results:** Benchmark cases illustrate RMIs of 0.83% in Bangladesh and 0.01% and in Denmark. For 19,012 estimated maternal deaths, Bangladeshi absolute mortality increase equals 154 child deaths. Sensitivity analyses in nations with high burden of disease illustrate RMIs as high as 7.2% in Nigeria and 5.6% in Malawi. **Conclusions:** Current cause-specific mortality rates ignore child deaths in association with maternal deaths and under-allocate resources due to underestimation of effect. This model serves as a means to accurately reflect disease burden and as a guide for policymakers.

6592 Poster Session (Board #149), Mon, 1:15 PM-4:45 PM

Nationwide utilization of cardiac imaging in patients undergoing cardiotoxic chemotherapy. *First Author: Michaela Ann Dinan, Duke Clinical Rsrch Inst, Durham, NC*

Background: Current guidelines recommend cardiac evaluation in patients undergoing selected cardiotoxic regimens. However, utilization of cardiac imaging and adherence to guidelines have not been previously examined in a nationally representative cancer patient population. **Methods:** Retrospective SEER-Medicare analysis of patients with incident cancer of the breast, lung, colon, prostate (metastatic), leukemia (acute) or lymphoma between 2000 and 2009. We examined claims-based receipt of chemotherapy, cardiotoxic chemotherapy (anthracycline, trastuzumab, or bevacizumab) and their association with cardiac evaluation in the year following diagnosis. **Results:** A total of 346,903 patients met study criteria (Table). Receipt of cardiotoxic chemotherapy ranged from 1% in prostate cancer to 35% in lymphoma. Overall, 43% of patients underwent cardiac evaluation (84% echo, 30% exercise EKG, 9% MUGA, 1% nuclear imaging, 0.2% cardiac PET). Among patients receiving cardiotoxic chemotherapy, 80-90% of breast, leukemia, and lymphoma patients underwent one or more cardiac studies compared to only 40-60% of patients with colorectal, lung, or prostate cancer. **Conclusions:** Cardiac evaluation appears more common in cancer populations more frequently treated with cardiotoxic chemotherapy than in cancer populations with less exposure to these agents. Increased awareness of cardio-oncologic principles may be warranted among oncologists treating cancer types for which cardiotoxicity has not historically been a concern.

Cardiac imaging utilization by receipt of systemic and cardiotoxic therapy, 2000-2009.

		Systemic Chemotherapy		Cardiac Imaging		
Cohort	Total Patients (N = 346,903)	Any†	Cardiotoxic Chemotherapy	No Chemotherapy	Any Noncardiotoxic Chemotherapy	Cardiotoxic Chemotherapy
Acute Leukemia	9,621	13%	2%	51%	73%	85%
Breast						
Curative	86,261	20%	12%	27%	68%	84%
Palliative	6,882	37%	23%	36%	72%	83%
Colorectal						
Curative	84,504	25%	2%	46%	41%	48%
Palliative	20,277	41%	14%	37%	39%	42%
Lung						
Curative	29,715	25%	1%	57%	61%	62%
Palliative	78,509	40%	3%	34%	43%	48%
Lymphoma						
Early Stage	10,902	56%	36%	41%	76%	89%
Late Stage	12,835	64%	35%	51%	75%	91%
Metastatic Prostate	7,397	8%	1%	33%	38%	61%

6593 Poster Session (Board #150), Mon, 1:15 PM-4:45 PM

A prospective evaluation of radiotherapy (RT) related skin reactions in a multi-racial/ethnic population of women with newly diagnosed breast cancer (BC). *First Author: James John Urbanic, UC San Diego, Encinitas, CA*

Background: RT-related early adverse skin reactions (EASR) are common in BC patients. EASR occur during/within 2 months post-RT. Predictive biomarkers for EASR are under active investigation. Previous studies have limited sample size/lack racial/ethnic diversity. This study designed to evaluate disparities in EASR of a multi-racial/ethnic BC population. **Methods:** Stage 0-III BC patients. Inclusion criteria: RT dose $>$ 40 Gy and daily RT 1.8 to 2.7 Gy/fx. Regional nodal irradiation, mastectomy/lumpectopmy, concur/sequent boost, chemotherapy, hormonal therapy allowed. Exclusion criteria: immediate reconstruction, partial breast RT. Primary outcome: EASR (Oncology Nursing Society (ONS) acute skin toxicity (0-6 scale)) assessed during/2 months post-RT. Mixed effects repeated measures analysis of variance used to assess race/ethnicity and mastectomy/lumpectomy differences in EASR over time. **Results:** 10/2011-6/2013, 1000 patients accrued (405 non-Hispanic white (NHW), 277 non-Hispanic black (NHB), 241 Hispanic, 62 Asian/Pacific Islanders, 15 other). Both time by race/ethnicity and time by mastectomy interactions statistically significant ($p < 0.001$ & $p = 0.008$, respectively). Based on race/ethnic cohorts, significant differences in patient characteristics ($p < 0.05$) existed for age, BMI, marital status, education, health insurance, cancer stage, and medical comorbidities. Mean ONS peaked at last day of RT (2.23), higher: mastectomy vs lumpectomy (2.66 vs 2.19) not different between race/ethnic groups. NHW women greater mean ONS score at 3 weeks into RT than other groups; however, NHW had lower mean ONS at 1 and 2 months post-RT ($p < 0.01$). ONS grade 4+ skin toxicities occurred: 15% of women at the end of RT, but no difference by race/ethnic cohorts. **Conclusions:** EASR peaks at end of RT with variation in time course by race/ethnicity. High grade toxicity uncommon and not different by race/ethnicity. This is first large study of RT EASR in a multi-racial/ethnic BC population. Additional analyses: RT dosimetry, genomics, DNA damage/repair biomarkers, and late effects are forthcoming. Clinical trial information: NCT01407770.

6594 Poster Session (Board #151), Mon, 1:15 PM-4:45 PM

PROSPECT eligibility and clinical outcomes: Results from the pan-Canadian rectal cancer consortium. *First Author: Dominick Bosse, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

Background: The current standard for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiation therapy (nCRT) followed by surgery. The PROSPECT trial (N1048) is investigating neoadjuvant FOLFOX with selective use of nCRT in patients (pts) with LARC undergoing low anterior resection (LAR). We evaluated outcomes of PROSPECT eligible and ineligible pts from a retrospective multi-institution database. **Methods:** Data from pts with LARC who received nCRT and had curative intent surgery from 2005 to 2014 were collected from 5 Canadian cancer centres. PROSPECT eligible pts included: cT3N0, cT2N1 and cT3N1 rectal adenocarcinoma, ECOG performance status (PS) $\leq$ 2, hemoglobin $>$ 80 g/L, age $>$ 18 years and receipt of LAR. Overall survival (OS), disease free survival (DFS), recurrence free survival (RFS), and time to local recurrence (TLR) were estimated using Kaplan-Meier method. Cox proportional hazards regression (MVA) was used to adjust for prognostic factors including circumferential resection margin (CRM), PS, clinical stage, pathological stage (ystg) and adjuvant chemotherapy (aCT), sex, age and RT dosage. **Results:** 1531 pts were included of whom 566 (37%) were considered eligible for PROSPECT. Eligible pts were more likely to have better PS ($p = 0.0003$), RT $\geq$ 45Gy ($p = 0.001$), negative CRM ($p < 0.0001$) and distance $\geq$ 5cm from anal verge ($p < 0.0001$). PROSPECT eligibility was associated with improved DFS (HR 0.75, 95% CI: 0.61-0.91), OS (HR 0.73, 95% CI: 0.57-0.95) and RFS (HR 0.68, 95% CI: 0.54-0.86) in univariate analyses. In MVA, RFS was improved for PROSPECT eligible pts (HR 0.75, 95% CI: 0.57 – 1.00, $p = 0.0499$), but not for OS and DFS. TLR was also similar (HR 0.95, 95% CI: 0.31-3.0) adjusting for CRM, ystg and aCT. The 3-year DFS for PROSPECT eligible pts was 79.1% compared with 71.1% for ineligible pts and the rate of freedom from local recurrence at 3 years was 97.4 v 96.8%, respectively. In comparison, the PROSPECT trial has estimated a 3-year DFS of 69-74% and a 3-year freedom from local recurrence of 96%. **Conclusions:** Real world data corroborate the eligibility criteria used in the PROSPECT study, identifying a subgroup of patients in whom recurrence risk is lower and where selective use of CRT should be actively examined.

6595 Poster Session (Board #152), Mon, 1:15 PM-4:45 PM

Conflicts of interest in pharmaceutical sponsored economic studies of breast cancer therapies: An empirical study. *First Author: Jordan D. Lane, jordan_lane@hms.harvard.edu, Boston, MA*

Background: Cost-effectiveness studies are increasingly included in the regulatory decisions of many countries and in formulary decisions worldwide. In 1999, we reported that pharmaceutical company sponsorship of economic analyses of three oncology drugs (anti-emetics, granulocyte colony stimulating factors, and taxanes) was associated with reduced likelihood of reporting unfavorable results. We re-evaluate this hypothesis 15 years later, focusing only on a single diagnosis (breast cancer) and an updated review of the economic literature. **Methods:** Breast cancer was selected for analysis since it is the cancer with the largest number of cost effectiveness studies and the cost of recent drugs has caused questioning of their incremental cost effectiveness. Search of the Tufts Medical Center Cost Effectiveness Analysis Registry resulted in 105 studies published between 1991-2012 that evaluated the cost effectiveness of drugs used to prevent or treat breast cancer. Overall study conclusions regarding cost-effectiveness of the investigated drugs were evaluated using three thresholds: $50,000 per quality adjusted life-year (QALY), $100,000 per QALY, and $150,000 per QALY. A logistical regression was performed to determine how study characteristics including funding source were associated with study findings. **Results:** Overall, 65 studies were funded by industry (62%). Studies with pharmaceutical company funding were more likely than studies with other funding to report favorable cost-effectiveness estimates (75.4% vs 40.0%, OR = 4.01 CI = 1.55-10.92 at the $50,000 threshold; 80.0% vs 57.5%, OR = 3.14, CI = 1.14-9.08 at the $100,000 threshold; and 87.7% vs 67.5%, OR = 3.27, CI = 1.05-11.08 at the $150,000 threshold). **Conclusions:** Industry sponsorship continues to be associated with a higher likelihood of reporting favorable results. These findings suggest that steps are necessary to ensure that the cancer cost effectiveness literature is not biased by sponsorship. Expanding funding sources other than pharmaceutical companies for these studies or pre-registering cost effectiveness studies may help mitigate this potential source of bias.

6596 Poster Session (Board #153), Mon, 1:15 PM-4:45 PM

Cancer mortality and published research output: Is there any relationship? *First Author: Francis Patafio, Division of Cancer Care & Epidemiology, Cancer Research Institute, Queen's University, Kingston, ON, Canada*

Background: The relative distribution of cancer research output across disease sites is not well described. Here we evaluate whether the volume of published research and clinical trials is proportional to mortality by cancer site. We also explore whether research output is proportional to research funding by cancer site. **Methods:** Statistics from the American and Canadian Cancer Societies were used to identify the top ten causes of cancer death in 2013. The OVID MEDLINE database identified all journal articles and clinical trials published in 2013 by US/Canadian authors for these cancer sites. Total research funding in Canada by cancer site was obtained from the 2011 report by Canadian Cancer Research Alliance. Descriptive statistics and Pearson correlation coefficient (r) were used to describe the relationship between research output (volume of publications and clinical trials), cancer mortality, and research funding. **Results:** We identified 19,361 publications and 2,661 clinical trials. The proportion of publications and clinical trials were substantially lower than the proportion of deaths for lung (41% deaths, 15% publications, 16% clinical trials), colorectal (14%, 7%, 6%), pancreas (10%, 7%, 5%), and gastroesophageal (7%, 5%, 3%) cancers. Conversely, research output was substantially greater than the proportional death for breast cancer (10% deaths, 29% publications, 30% clinical trials) and prostate cancer (8%, 15%, 17%). There was substantial variation in total research investment across cancer sites that was not due to differences in relative mortality. Total investment in 2013 in Canada per cancer death was $599 for bladder cancer, $1039 for lung cancer, $2197 for colorectal cancer, $9212 for prostate cancer, and $14,329 for breast cancer. There was stronger correlation between research output and funding (all publications $r = 0.8942$ $p < 0.001$; clinical trials $r = 0.9258$, $p < 0.001$), than there was between research output and cancer mortality ($r = 0.3625$, $p = 0.3033$ and $r = 0.3395$, $p = 0.3372$). **Conclusions:** Research output is not well correlated to cancer mortality but is correlated to relative level of research funding.

6597 Poster Session (Board #154), Mon, 1:15 PM-4:45 PM

Trends in the costs and utilization of targeted cancer therapies for the privately insured non-elderly: 2001-2011. *First Author: Fabrice Smieliauskas, University of Chicago, Chicago, IL*

Background: Studies documenting high costs of cancer drugs often focus on targeted therapies as a whole without differentiating between oral and intravenous agents; such distinction is important because they differ in insurance design. Our study examined recent trends on targeted oral anticancer medications (tOAMs), and targeted IV anticancer medications (tIVAMs) and explored the cost drivers. **Methods:** We classified cancer drugs as tOAMs, tIVAMs, and non-targeted agents. Using the 2002-2011 LifeLink Health Plan Claims Database, we described trends in utilization and in insurance payments and out-of-pocket (OOP) costs per patient per month (PPPM) and during the first year of systemic therapy among privately insured non-elderly cancer patients. We performed Cochran-Armitage tests and generalized linear models to test the statistical significance of utilization and cost trends, respectively, and conducted decomposition analysis to disaggregate the cost trend into the increase driven by therapeutic substitution to more expensive classes of drugs vs. increases in drug prices over time. **Results:** Targeted therapies accounted for 11% of all systemic therapy utilization and 22% of systemic therapy expenditures in 2001, increasing to 42% (28% tIVAMs and 14% tOAMs) of utilization but 63% (38% tIVAMs, 25% tOAMs) of expenditures in 2011. Insurance payments PPPM for tOAMs more than doubled in ten years, growing from $3,381 PPPM in 2001 to $7,370 in 2011 ($P < 0.001$), whereas PPPM for tIVAMs remained fairly constant (around $7,000) throughout. Decomposition analyses of two time periods (2001-2005 and 2005-2010) showed that switching to more expensive classes of drugs accounted for the large majority of cost increase. Post-launch price increases contributed a 10-11% of spend increases during the two periods, while the increase in launch price accounted for 6% and 15% of spending growth, respectively, for each period. **Conclusions:** Payers should consider more aggressive management of pharmacy benefits for tOAMs and payment reforms for injectable drugs to contain the rising costs of cancer care.

6598 Poster Session (Board #155), Mon, 1:15 PM-4:45 PM

Target wise and pound foolish: A simple technique to evaluate the trade-off between economic burden and clinical benefit of monoclonal antibodies. *First Author: Matt Christopher Brennan, Penn State Milton S. Hershey Medical Center, Hershey, PA*

Background: Monoclonal antibodies (mabs) have great clinical potential for individual patients, but also substantial cost to society. We propose a very simple, transparent calculation to frame this debate in objective terms for practicing oncologists and policy makers. We then apply this strategy to all mabs currently approved for hematology/oncology indications. **Methods:** Mabs were identified from the FDA's approved drug products list. Approved indications for each mab in the clinical practice of hematology/oncology were extracted from section 14 of the approved prescribing information. All comparative studies used to support each drug's approval for each indication were analyzed. Cost data was obtained from publically available sources. Using this data, we calculated the cost to achieve one additional good outcome as defined by each study. Overall survival was our preferred outcome measure. If not explicitly stated, OS was calculated from the Kaplan-Meier curves using pixel coordinates. If OS data was not collected, the primary endpoint used in the trial was substituted. Total cost to achieve one additional good outcome was calculated as: cost = (cost per dose)*(median number of doses)*NNT. **Results:** Forty-four mabs were identified; 19 have hematology-oncology-relevant indications. Of 66 studies listed in the prescribing information leading to FDA approval, 47 were comparative and were included. The costs for each mab to achieve one improved outcome at the study-specified time were calculated. An abbreviated table is shown in the table below. **Conclusions**: NNT provides a simple, clinically relevant, robust way of framing the critical debate between individual benefit and public health priorities. Some monoclonal antibodies for some hematology/oncology indications may not meet reasonable thresholds for widespread use.

Drug	Indication	Trial	mOS (exp/control) in months	Endpoint	NNT	Cost ($)
Ramucirumab	Gastric Cancer	RAINBOW	9.6/7.4	6 mo OS	7	1,079,568
12 mo OS	10	1,542,240				
Bevacizumab	mCRC	ECOG E3200	12.9/10.8	12mo OS	8	254,880
24mo OS	16	509,760				
Rituximab	DLBCL	GELA	Not reached	24 mo OS	8	433,126
60 mo OS	9	487,267				
Trastuzumab	Adj HER2 + breast	HERA	Not reached	24 mo OS	12	1,785,028

6599 Poster Session (Board #156), Mon, 1:15 PM-4:45 PM

Serum tumor marker utilization in patients with advanced solid tumors. *First Author: Melissa Kate Accordino, New York Presbyterian Columbia, New York, NY*

Background: Despite data on the sensitivity and specificity of serum tumor marker tests, there is no evidence to suggest that early changes in therapy related to rising tumor markers have an effect on survival. Studies have failed to show benefit of surveillance testing in patients with limited disease. We performed a retrospective analysis in patients with advanced cancer to evaluate trends in utilization of tumor marker testing and the associated costs. **Methods:** Patients at Columbia University Medical Center with advanced or metastatic cancer were identified by ICD9 codes and confirmed with tumor registry and medical record review. Between 7/1/2013-6/30/2014 for each patient, the dates each of the following tumor markers were recorded: alpha fetoprotein (AFP), CA 125, CA 15-3, CA 19-9, CA 27-29 and carcinoembryonic antigen (CEA). Subjects who had $>$ 1 of any single tumor marker over the time-frame were included. We evaluated the maximum number of tests per month and the average number of tests per-month the patient was alive. Costs of each tumor marker were determined using 60% Medicare reimbursement rates. **Results:** Over the 12 month time frame 996 patients were included in the analysis. The mean number of any individual test per-patient was 7 and the maximum was 35; and the mean number of total tests per-patient was 12 and the maximum was 70. CEA and CA-19-9 were the most commonly ordered tests with an average of 1.94 and 2.18 times per-month, per-patient. On average the number of patients that had $>$ 1 of any individual test per month was 33%. The most common tests were CA-125, CEA and CA-19-9 (25.3%, 38.2% and 45.6% respectively). Overall 21.9% of patient had $\geq$ 3 of any individual marker per-month (38% CA19-9 and 25.6% CEA). The mean per-patient annual cost of testing was $421, with a maximum $2,567. Costs per-patient were highest for those with breast cancer (mean $755, max $1,787) and pancreatic cancer (mean $643, max $2,567). **Conclusions:** Tumor marker testing is frequent, with a large number of patients being tested multiple times per month, every month. Given the rising costs of cancer care, the large number of serum tests, and the frequency of use, efforts should be made to determine the clinical utility of tumor marker testing in metastatic cancer patients.

6600 Poster Session (Board #157), Mon, 1:15 PM-4:45 PM

Assessing financial toxicity in insured patients with multiple myeloma. *First Author: Scott F. Huntington, Abramson Cancer Center, Hosp of the Univ of Pennsylvania, Philadelphia, PA*

Background: Financial toxicity is increasingly recognized for its potential to adversely impact the quality of life and health outcomes of patients undergoing treatment for cancer. Patients with multiple myeloma (MM) may be particularly vulnerable due to high utilization of novel therapeutics and extended treatment duration. **Methods:** Patients with at least 3 months of ongoing treatment for MM were invited to participate in a survey during follow up visits at our institution. The survey was derived from published instruments and included the recently developed 11-item COST measure (financial toxicity score 0 – 44). Electronic health records informed insurance and treatment data. **Results:** Of 111 patients approached for the study, 100 individuals completed the survey. The median reported annual household income was between $60,000-79,999 and all participants were insured (43% private, 49% Medicare, 8% Medicaid/dual). Median time from diagnosis was 31 months, 75% had exposure to both lenalidomide and bortezomib, and 58% had undergone autologous transplantation. The majority (59%) labelled treatment costs as higher than expected and 70% endorsed at least minor financial burden. Thirty-six patients reported applying for financial assistance, including 18% of individuals with income over $100,000. Use of savings to pay for MM treatment was common (46%), 21% borrowed money to pay for medications, and 17% reported delays in their MM treatment due to cost. COST scores were normally distributed (median 20.5, range 0-43) and correlated with patient reported incomes, use of savings, borrowing of money, and treatment delays ($p < 0.001$). After controlling for potential confounders on linear regression, time since diagnosis was directly related ($p < 0.03$), while age and income were inversely related with COST scores ($p < 0.03$; $p < 0.001$). **Conclusions:** Financial burden and request for financial assistance were common in our insured population with MM. Younger age, lower household income, and time since diagnosis were associated with higher financial toxicity as measured by the COST score. Additional attention to rising treatment costs and cost-sharing is needed to address the growing evidence of financial toxicity impacting patients with cancer.

6601 Poster Session (Board #158), Mon, 1:15 PM-4:45 PM

Impact of site of service on chemotherapy costs: Influence of geographic location and diagnosis. *First Author: Michael A. Kolodziej, Aetna, Hartford, CT*

Background: Site of service strongly influences the cost of cancer treatment. The migration of community oncology practices to the hospital based practice setting has generated considerable discussion about the cost differential between these sites. **Methods**: We examined claims paid for chemotherapy by Aetna from August 2013 through July 2014 for all malignancies as well as breast/colon/lung cancer (BCL). **Results**: Over this period of time, Aetna paid chemotherapy claims for 46,000 unique members, including 17,000 members with breast, colon and lung cancer (BCL). For all members receiving chemotherapy as well as for members with BCL, 69% received chemotherapy in the office setting (O) and 31% received chemotherapy in the hospital outpatient setting (H). Despite this patient distribution, chemotherapy allowable reimbursement share was 42% for H and 58% for O, indicating a disproportionate share of chemotherapy reimbursement to H. When considering average chemotherapy allowed per member, patients treated in H for all cancers were 59% more costly per member, while patients treated for BCL were 40% more costly per member. When examining site of service by state, considering only states with more than 100 members treated in H, there was great variation in site distribution, from a high of 79% (Massachusetts) to a low of 15% (Florida). The allowed chemotherapy costs per unique member were 229% for all malignancies and 190% for BCL in the most costly H state compared to the most costly O state. Paying H the average O allowable would generate $100 million savings. **Conclusions**: The impact of site of service on chemotherapy costs is complex. Only 30% of patients treated with chemotherapy receive treatment in H but H received a disproportionate share of reimbursement for all malignancies as well as the most common malignancies (BCL). These differences are remarkably variable from state to state both with respect to the distribution of patients by site of service as well as the cost of care by site of service. For a large commercial payer, the site of service differential increases cost of care substantially. Given the geographic variability, a simple solution is not likely.

6602 Poster Session (Board #159), Mon, 1:15 PM-4:45 PM

Quantifying the relative value of drug therapy options in HER2+, ER-/PR- breast cancer. *First Author: John Whang, Real Endpoints, LLC, Westport, CT*

Background: US health care spending continues to exceed that of other industrialized countries, in part because there is insufficient transparency as to the relative value (benefit-cost) of different treatment options. Comparing drug regimens based on their overall value would help create a common set of metrics to enable better drug therapy decision-making and help improve quality and reduce costs of care. **Methods:** We developed a methodology to review, synthesize and assess the evidence of a drug's performance across three major domains of clinical efficacy, safety & use and economics, and to combine those assessments to determine overall value of a drug regimen. We then incorporated multi-attribute decision analysis and our evidence methodology into an interactive web-based tool to compare the relative value of all relevant drug regimens in an indication. The tool uses an explicit and transparent methodology and uses a total of 30 elements within the three domains. **Results:** Using the interactive web-based tool, we compared 3 adjuvant chemotherapy regimens in HER2+, ER-/ PR- breast cancer: 1) doxorubicin + cyclophosphamide then paclitaxel (AC-T), 2) doxorubicin + cyclophosphamide then paclitaxel + trastuzumab (AC-TH), and 3) carboplatin + docetaxel + trastuzumab (TCH). We assessed the relative value of the regimens based on weighted scores within the 3 domains. Higher scores are better. In this case study, AC-TH and TCH had similar efficacy and safety scores; AC-TH scored highest overall because of better economics. (See table.) Scores can be modified by the end user to reflect patient-specific factors such as unique toxicity concerns (e.g., history of heart failure). **Conclusions:** A transparent, personalizable interactive tool created to compare the relative value of drug regimens can be used to support treatment decisions for HER2+, ER-/PR- breast cancer incorporating clinical and economic considerations. Next steps will include validation using network meta-analysis and extension to other related areas of cancer care.

Weighted domain scores by drug regimen.

DOMAIN (Weighting)	AC-T	AC-TH	TCH
Efficacy (70%)	189	320	320
Safety & Use (20%)	58.1	56.6	58.6
Economic (10%)	70.5	63.2	45.7
TOTAL SCORE	318	440	424

6603 Poster Session (Board #160), Mon, 1:15 PM-4:45 PM

Real-world treatment patterns, healthcare resource utilization (HRU), and costs of initial line of therapy (LOT1) in multiple myeloma (MM). *First Author: Stacey DaCosta Byfield, OptumInsight, Eden Prairie, MN*

Background: MM is the second most common hematologic malignancy in adults. Few studies have evaluated the economic impact associated with MM treatment. **Methods:** This retrospective study identified patients (pts) aged ≥ 18 yrs with ≥ 2 claims for MM (ICD-9 203.00) and ≥ 1 claim for anti-cancer systemic therapy (A-CST) in a large national US claims database between Jan 2008 and Aug 2013; first MM claim date was the index date. Pts required continuous enrollment (CE) in the health plan for 6 mos pre- and ≥ 6 mos post-index date (< 6 mos if due to death), and no evidence of any cancers or A-CST in the pre-index period. Treatment patterns, HRU (inpatient, office, outpatient, and ER visits), and costs (drug and medical costs) during LOT1 were examined. LOT1 started with first A-CST; regimens included all agents received in the first 30 d. LOT1 ended at the earliest of: start of a new drug, ≥ 60-d gap after run-out of initial regimen drugs, death, or end of CE/study period (these censored LOTs were included). **Results:** Of 2053 pts, median age was 67 yrs (42% ≥ 70 yrs), 55% were male, and 638 (31%) had hematopoietic cell transplant (HCT) after LOT1 start. Median length of LOT1 was 4.3 mos (mean 6 mos). During LOT1, 96%, 90%, 43%, and 38% pts had ≥ 1 office, hospital outpatient, ER visit, and inpatient stay, respectively. Most common regimens were bortezomib ± dexamethasone (V±d, 25%), lenalidomide ±d (R±d, 17%), and VR±d (14%); in HCT pts, most common regimens were VR±d (25%), V±d (25%), and R±d (16%). Unadjusted per-pt per-month (PPPM) costs in HCT pts were $24,290 (SD $16,619; range $16,401–30,929 depending on initial regimen) and in non-HCT pts were $14,610 (SD $24,875; range $10,214–24,492). Drug and administration costs accounted for 37% of LOT1 costs and varied by initial regimen. 1-year costs after LOT1 initiation were $171,513 (SD $142,511; range $97,076–259,531). Adjusted (by initial regimen, pt characteristics, HCT, and baseline comorbidities) LOT1 costs were not significantly different with V±d and R±d; VR±d costs were higher vs V±d. **Conclusions:** HRU and costs were high during LOT1. Overall healthcare costs for LOT1 ranged from $10,214 to $30,909 PPPM depending on initial regimen and receipt of HCT.

6604 Poster Session (Board #161), Mon, 1:15 PM-4:45 PM

H-TArget model: Early technology assessment for ext generation sequencing in oncology. *First Author: Valesca Retel, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Next Generation Sequencing (NGS) promises to find mutations (targets) in individual cancer patients, to subsequently prescribe targeted therapy. Currently, NGS is in development, the effects on choice of therapy and prognosis are still unclear, and the costs for targeted therapies are high. To accelerate the reimbursement process of NGS and potential new targeted therapies, and have a NGS-panel available for patients in the earliest possible stage, early Technology Assessment (TA) is performed to inform policy making around NGS in the Netherlands. One of the aims of the TA was to conduct a cost-effectiveness analysis. **Methods:** We constructed a target-based decision model (H-TArget) to estimate the cost-effectiveness of NGS versus single- and no testing. Standard- and targeted therapies in first and second line for 9 targets (BRAF, KRAS, NRAS, EGFR, ERBB/HER, MET, ROS, ALK, RET) over 3 tumor types (melanoma, non-small-cell lung cancer (NSCLC), colorectal cancer (CRC)) were incorporated. A Dutch healthcare perspective and a 5-year time horizon were adopted. Outcomes were incremental cost-effectiveness ratios (ICER) expressed in €/quality adjusted life year (QALY). The threshold for cost-effectiveness is 80k in the Netherlands, which means that the concerning technology is cost-effective if the ICER is below this threshold. Expected Value of Partial Perfect Information (EVP(P)I) was calculated to quantify the value of further research into particular subsets of uncertain parameters. **Results:** The expected ICER was €65k/QALY for melanoma, €188k/QALY for NSCLC, and €103k/QALY for CRC. As a weighted average to the three populations, the overall ICER yielded €160k/QALY. The EVPI was €25M for melanoma, the subsets of parameters to focus on in future research were: €2M together for failures, prevalence, survival, and €23M for costs. **Conclusions:** At the moment, using NGS is only cost-effective for melanoma. This is mostly due to the high costs of targeted therapies and the fact that the effects are still small. Based on our findings, industry should strive for a significant cost reduction of targeted therapies or achieve a spectacular improvement in effectiveness, which could improve the cost-effectiveness.

6605 Poster Session (Board #162), Mon, 1:15 PM-4:45 PM

Economic evaluation for the United States (US) of gemcitabine (GEM), nab-paclitaxel plus gemcitabine (NAB-P+GEM), and FOLFIRINOX as first-line treatment for metastatic pancreatic cancer (MPC). *First Author: Mahdi Gharaibeh, Center for Health Outcomes & PharmacoEconomic Research, Tucson, AZ*

Background: Both NAB-P+GEM and FOLFIRINOX have shown superior survival efficacy over GEM alone as first-line treatment for MPC. Independent cost effectiveness/utility analyses for the US of NAB-P+GEM and FOLFIRINOX have not been performed. **Methods:** AMarkov model of outcomes and total costs estimated the life years (LY) and quality-adjusted life years (QALY) gained and incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR) for patients with MPC using probabilistic sensitivity analyses, discounted at 3%/year, with full lifetime horizon, from a payer perspective, and expressed in 2015 US$. Lacking 3-way head-to-head trial results, comparative efficacy and safety of NAB-P+GEM and FOLFIRINOX were estimated using Bucher indirect comparisons. Total costs included chemotherapy, administration, disease monitoring, adverse reactions and supportive care measures. **Results:** In direct comparison, NAB-P+GEM was associated with differentials of +0.27 LY and +0.16 QALY gained over GEM at an incremental total cost of $23,031; yielding ICER of $80,562/LY and ICUR of $141,338/QALY. In direct comparison, FOLFIRINOX was associated with differentials of +0.50 LY and +0.26 QALY gained over GEM at an incremental total cost of $42,846; yielding ICER of $83,978/LY and ICUR of $164,495/QALY. In indirect comparison, FOLFIRINOX was associated with differentials of +0.23 LY and +0.16 QALY gained over NAB-P+GEM at an incremental total cost of $19,815; yielding ICER of $88,031/LY and ICUR of $202,187/QALY. HR for NAB-P+GEM vs. FOLFIRINOX was 1.26 (95%CI = 0.95-1.67, p = ns) indicating no superiority in survival outcome of either regimen. **Conclusions:** In this independent economic analysis, the superior survival efficacy of both NAB-P+GEM and FOLFIRINOX over GEM in the management of MPC is associated with positive cost-effectiveness and cost-utility. With NAB-P+GEM and FOLFIRINOX not differing statistically in survival benefit, the cost differential of $-4053/LY and $-37,692/QALY gained associated with NAB-P+GEM over FOLFIRINOX renders NAB-P+GEM the most economical of both regimens as first-line treatment for MPC.

6606 Poster Session (Board #163), Mon, 1:15 PM-4:45 PM

Price migration of oncology drugs launched in the United States between 2010 and 2015. *First Author: Alex Bastian, GfK Market Access, San Francisco, CA*

Background: As discussions of value increasingly enter the oncology arena, the price, or cost, of drugs is becoming increasingly relevant. Here, we have reviewed new cancer drugs launches in the USA to characterize the level, nature, and extent of price migrations taken by manufacturers **Methods:** FDA approvals (N = 158) between 2010 and 2015 were obtained from the FDA website, from which all non-oncology drugs (n = 119) were excluded. The remaining list (n = 39) included only oncology drugs. The Wholesale Acquisition Cost (WAC) prices at launch, and subsequent price increases, for these products were then extracted from AnalySource, a web-based analytical drug pricing database. We evaluated compound annual growth rate (CAGR), interval periods, and frequency of price increases of these agents. Further analysis identified potential distinctions across tumor types, route of administration (ROA), and other related features **Results:** The mean CAGR was 5.9%, ranging from 0% to 33.7%. Price increases occurred an average of 2.3 times at a mean interval of 11.1 months, ranging from 7 to 27 months. Notably, twelve of drugs did not increase in price. Only three drugs increased their price within 6 months of market entry, and 50% did so by month 23. Solid tumor price migration was higher than for hematologic malignancies (6.6% vs. 4.7%, respectively). The highest increase was seen within lung cancer (13.3%), with gastric and ovarian cancer showing no increase. ROA also had an important impact, with oral drugs demonstrating higher price migrations than injectable drugs (8.3% vs. 3.4%) **Conclusions:** The results of our analysis show important differences in the magnitude and frequency of price increases taken by oncology drug manufacturers. Differences are seen by tumor type and by ROA. Further inquiry may be useful to determine the structural and strategic factors driving these differences.

CAGR (%)	Injectable	Oral	All
Solid Tumors	4.4%	8.5%	6.6%
Lung		13.3%	13.3%
Prostate	12.4%	7.8%	10.6%
Thyroid		7.5%	7.5%
Colorectal	5.1%		5.1%
Skin	0.6%	6.8%	4.2%
Breast	1.1%		1.1%
Other	0.0%	3.6%	2.4%
Hematological	1.7%	8.1%	4.7%
CLL	0.0%	17.6%	8.8%
Lymphoma	3.3%	5.6%	4.1%
CML	0.0%	6.1%	4.0%
MM	1.7%	4.5%	3.1%
Other	1.9%	8.7%	4.1%
All	3.4%	8.3%	5.9%

6607 Poster Session (Board #164), Mon, 1:15 PM-4:45 PM

Patient-reported symptoms and Canadian Health Utility scores in esophageal cancer patients. *First Author: Mark Doherty, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Health utility scores (HUS) are an increasingly important tool to help determine the cost-effectiveness of therapies worldwide. The EQ-5D-3L is a validated tool for deriving HUS, with reference data in numerous populations, but there is limited information on the role that individual symptom complexes (SC) play in determining HUS in Esophageal cancer (EC) patients. **Methods:** A cross-sectional survey of EC patients at Princess Margaret Cancer Centre (2012-2014) assessed EQ-5D-3L and FACT-E. EQ-5D scores were converted to HUS using Canadian references. SC were developed: domains from FACT-E were identified and grouped to represent symptoms such as pain, dysphagia, fatigue, dyspnea, nausea and loss of appetite. Multivariable regression analysis was performed to assess associations between SC and HUS, adjusting for age, sex, and stage of disease. **Results:** Of 197 patients, median age was 67 (range 32-93) years, 76% were male, with stage I/II-IVA/IVB (6%/66%/28%) disease. Mean (SE) HUS were 0.90(0.05), 0.82(0.01), and 0.73(0.03) for stage I/II-IVA/IVB disease. Correlations between HUS and symptom scores are summarised in the table below. SC constructed for appetite, pain, nausea and fatigue showed significant association with HUS. **Conclusions:** A number of prevalent and important symptoms and SC correlated well with EQ5D-derived HUS, particularly appetite, pain, nausea, and fatigue. The strongest association was seen with pain. These relationships provide additional support for using these HUS in health-economic models.

Mutivariable regression model results.

Parameter	β	Standard Error	p
Appetite	-0.012	0.004	0.0013
Dysphagia	0.005	0.003	0.11
Pain	-0.023	0.005	<.0001
Nausea	-0.022	0.007	0.0036
Fatigue	0.088	0.026	0.0008
Dyspnea	0.034	0.042	0.43
Age	-0.002	0.001	0.0219
Sex (F vs M)	-0.006	0.022	0.81
Stage (early vs late)	0.072	0.022	0.0011

6608 Poster Session (Board #165), Mon, 1:15 PM-4:45 PM

Financial hardship associated with cancer in the United States. *First Author: K Robin Yabroff, National Cancer Institute, Rockville, MD*

Background: Expenditures associated with cancer, its treatment, and lasting effects of treatment are increasing in the US. The purpose of this study is to estimate the prevalence of financial hardship associated with cancer and identify characteristics of cancer survivors associated with financial hardship. **Methods:** We identified 1,202 cancer survivors ages ≥ 18 years from the 2011 Medical Expenditure Panel Survey (MEPS) *Experiences with Cancer* survey. Material financial hardship was measured by ever 1) borrowing money or going into debt, 2) filing for bankruptcy, 3) being unable to cover their share of medical care costs, or 4) making other financial sacrifices due to cancer, its treatment or lasting effects of treatment. Psychological financial hardship was measured as worry about paying large medical bills. We examined factors associated with any material or psychological financial hardship using separate multivariable logistic regression models stratified by age group (18-64 and ≥ 65 years). **Results:** Cancer survivors ages 18-64 years were more likely to report any material financial hardship than those ages ≥ 65 years (28.4% vs 13.8%; $p < 0.05$). Worry about paying large medical bills was also more common among cancer survivors ages 18-64 years than those ages ≥ 65 years (31.9% vs 14.7%, $p < 0.05$). In adjusted analyses, cancer survivors ages 18-64 years who were younger, female, non-white, and treated more recently were significantly more likely to report any material financial hardship associated with cancer compared to those who were older, male, non-Hispanic white, and treated less recently. Those who were female, had lower family income, and treated more recently were more likely to report psychological financial hardship. Among cancer survivors ages ≥ 65 years, those who were younger and non-white were more likely to report any financial hardship (all $p < 0.05$). **Conclusions:** Cancer survivors commonly experience material and psychological financial hardship. The working age population is especially vulnerable. Efforts to characterize cancer survivors likely to experience financial hardship and improve patient-provider communication about affordability are crucial, especially with ongoing implementation of the Affordable Care Act.

6609 Poster Session (Board #166), Mon, 1:15 PM-4:45 PM

Impact of a Stage IV NSCLC care pathway on front-line (FL) and maintenance (M) chemotherapy use at the Cleveland Clinic Taussig Cancer Institute (TCI). *First Author: Marc A. Shapiro, Cleveland Clinic, Cleveland, OH*

Background: Care pathways can reduce cancer care costs and variability in NSCLC. Effective implementation requires measurable outcomes and available data in near real-time. **Methods:** Between 10/1/13 and 7/7/14, TCI developed an evidence and value-based Stage IV NSCLC pathway. For patients with non-squamous EGFR WT/ALK neg NSCLC, ECOG PS 0-2 and sufficient renal function, FL carboplatin/pemetrexed (pem) followed by M pem is recommended standard care while bevacizumab (bev) is not. The pathway recommends best supportive care for pts with ECOG PS $\geq$ 3. To test feasibility, 4 academic thoracic and 12 community oncologists implemented the pathway into their practices starting 7/7/14. This analysis studies pathway impact on FL and M treatment decisions and charges in patients with metastatic non-squamous EGFR WT/ALK negative NSCLC. 57 pts meeting pathway criteria initiated care with these oncologists from 7/7/14 to 12/31/14 (Cohort A). A retrospective cohort (Cohort B) of 181 pts meeting similar criteria initiated care from 1/1/12 to 7/1/13. Care patterns were defined by manual chart review through 1/8/15. As only 1 Cohort A pt has progressed on M therapy, charge results assume pts who have initiated M pem will receive the same average of 5.11 doses seen in Cohort B. For Cohort B, actual FL and M therapy charges are reported. 3 Cohort B pts remain on M therapy. **Results:** Care patterns in Cohorts A and B were compared. 53 (93%) vs 128 (71%) ($p = 0.0003$) pts received pathway recommended FL care respectively. 42 (74%) vs 110 (61%) received chemotherapy ($p = 0.0839$). In pts receiving FL platinum-based regimens, 2 (6%) vs 35 (39%) received bev ($p < 0.0001$) outside of pathway recommendations. In Cohort A, 6 (32%) completing FL therapy initiated M therapy vs 36 (40%) in Cohort B. In pts completing FL therapy, FL and M drug charges per pt were an estimated $107,258 vs $205,431 (48% decrease). **Conclusions:** Implementation and measurement of adherence to a stage IV NSCLC pathway is feasible at an academic oncology practice with a regional network. This implementation led to a significant improvement in care variation and nearly 50% reduction in chemotherapy charges primarily through decreased bev use.

6610 Poster Session (Board #167), Mon, 1:15 PM-4:45 PM

Cost-effectiveness of trastuzumab emtansine (T-DM1) for HER2-positive advanced breast cancer (ABC). *First Author: Quang Anh Le, Western Univ of Health Sci, Pomona, CA*

Background: The EMILIA trial demonstrated T-DM1 significantly increased in median profession-free (3.2 months) and overall (5.8 months) survival relative to combination therapy with lapatinib plus capecitabine (LC) in patients with HER2-positive ABC previously treated with trastuzumab and a taxane. We performed an economic analysis of T-DM1 compared to LC and monotherapy with capecitabine (C) from both US payer and societal perspectives. **Methods:** We developed 4 possible Markov models to compare the projected lifetime costs and outcomes of T-DM1 and LC, and C. Markov models 1 and 2 have four health states (progression-free, response to therapy, disease-progression, and death), and Markov models 3 and 4 have three health states (progression-free, disease-progression, and death). In models 1 and 3, the possibility of death can occur in any health state; while in models 2 and 4, death can only occur in disease-progressing health state. Transition probabilities were estimated from published relevant trials. Six-week cycle time was modeled to follow the assessment time interval in the trials. Direct costs of the therapies, major adverse events, laboratory tests, and disease progression, indirect costs (productivity losses due to morbidity and mortality), and health utilities were obtained from published sources. The models used 3% discount rate and reported in 2014 US dollars. One-way and probabilistic sensitivity analyses were performed in the study. **Results:** When incorporating both model structural and parameter uncertainty, the resulting incremental cost-effectiveness ratios (ICER) comparing T-DM1 to LC and T-DM1 to C were $172,152 per quality-adjusted life year (QALY) and $126,251/QALY from the US societal perspective, respectively. From the US payer perspective, the ICERs were $205,598/QALY (T-DM1 vs. LC) and $164,628/QALY (T-DM1 vs. C). (See Table) **Conclusions:** From the US societal perspective, T-DM1 may be cost-effective relative to C. However, T-DM1 is not clearly cost-effective when comparing to LC from both perspectives.

Treatment Regimen	Lifetime Direct Cost ($)	Lifetime Indirect Cost ($)	QALYs
T-DM1	270,630	27,335	2.04
LC	180,202	42,046	1.60
C	101,966	66,653	1.01

6611 Poster Session (Board #168), Mon, 1:15 PM-4:45 PM

A network meta-analysis-based cost-effectiveness analysis of systematic therapies in advanced pancreatic cancer. *First Author: Kelvin K. Chan, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: For advanced pancreatic cancer, there are new treatment options that are more effective than gemcitabine alone (G). In this analysis we utilized data from a recently published Bayesian network meta-analysis (NMA) to assess the cost effectiveness of G, G+5-fluorouracil (GF), G+capecitabine (GCap), G+cisplatin (GCisp), G+oxaliplatin, G+erlotinib, G+nab-paclitaxel (GnP) and FOLFIRINOX from a Canadian health care perspective. **Methods:** Analysis was conducted through a three-state Markov model which follows a cohort of patients with advanced pancreatic cancer until death. Analysis used data on the progression of disease with treatment from the G arms of RCTs combined with estimates from the NMA of the effect of the newer regimens on disease progression and adverse events. Estimates of heath care costs were obtained from local providers and utilities were derived from the literature. The Markov model estimated the effect of treatment regimens on costs and quality adjusted life years (QALYs) discounted at 5% per annum. Detailed sensitivity analyses were conducted. **Results:** If a decision maker was willing to pay between $15,259 and $182,723 for a QALY, GF would be the optimal treatment regimen. For a willingness to pay of greater than $182,723, FOLFIRINOX would be optimal. Based on a willingness to pay for a QALY of $50,000, the price of oxaliplatin would need to be reduced by 83.4% for FOLFIRINOX to be optimal, whilst the price of nab-paclitaxel would need to be reduced by 93.1% for GnP to be optimal. At this threshold, the probability that GF is optimal is 52.7%, compared to 26.8% for GCisp, 19.0% for GCap and 1.6% for G and 0% for all other treatment regimens. **Conclusions:** At the current time with current drug prices and from the Canadian health care perspective, GF is the optimal treatment regimen based on the criteria of cost effectiveness. The acquisition costs of oxaliplatin is expected to decrease significantly once generic, and may make FOLFIRINOX more cost effective in advanced pancreatic cancer. GnP does not appear to be cost-effective regardless of willingness to pay threshold with its current pricing.

6612 Poster Session (Board #169), Mon, 1:15 PM-4:45 PM

Costs and resource utilization associated with skeletal related events in Medicare patients with prostate cancer metastatic to bones. *First Author: Jean A. McDougall, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Approximately 40% of men diagnosed with metastatic prostate cancer will experience $\geq$ 1 skeletal related events (SREs), defined as a pathological fracture, spinal cord compression, or the need for surgery or radiotherapy to the bone. To understand the potential value of recently approved agents for prostate cancer, that may delay or prevent SREs, accurate assessment of their costs and resource utilization is needed. **Methods**: Men $>$ 65years of age, diagnosed with prostate cancer and bone metastasis between 2004 - 2009 were identified from the Surveillance Epidemiology and End Results (SEER) registries and linked to Medicare Parts A and B claims. Propensity score matching was used to establish a cohort of SRE exposed and unexposed patients. Direct medical costs and resource utilization were estimated from Medicare claims records. Kaplan Meier Sample Average (KMSA) estimates were calculated to estimate the cost attributable to an SRE, taking into account censoring. Poisson regressions were used to estimate the incidence rate ratio comparing resource utilization by type and number of SRE to those with no SREs. **Results**: 891 patients with SREs were matched to patients without SREs. The KMSA cost of patients with SREs was $21,191 (USD 2013) higher than the costs of those patients without an SRE. Costs continued to increase linearly with cumulative numbers of SREs, with patients experiencing only one SRE accruing a total of $85,625 in direct medical costs, compared to $115,603 in patients experiencing 2 SREs and $142,547 for patients experiencing $\geq$ 3 SREs. Resource use was substantially higher in patients experiencing at least one SRE than in matched unexposed patients. Compared to unexposed patients, those with 1 or more SREs had twice as many emergency room visits and nearly 4-times as many hospitalizations. **Conclusions**: Among men with metastatic prostate cancer, experiencing an SRE may increase the cost of care by over $20,000 and is associated with substantially higher resource utilization. This cost continues to rise with recurring SREs, emphasizing the importance of therapies to prevent or treat SREs in patients with prostate cancer metastatic to the bones.

6613 Poster Session (Board #170), Mon, 1:15 PM-4:45 PM

Cost-effectiveness analysis of regorafenib for metastatic colorectal cancer. *First Author: Daniel A. Goldstein, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Regorafenib was approved by the FDA in 2012 for the management of previously treated metastatic colorectal cancer (mCRC). It is now the standard of care in the third-line setting. Compared to placebo it improves median overall survival by 1.4 months but is associated with adverse effects and additional cost. The objective of this study was to examine the cost-effectiveness of regorafenib compared to best supportive care for patients receiving 3rd-line treatment for mCRC. **Methods:** We developed a Markov model to compare the cost and effectiveness of regorafenib compared to best supportive care in the 3rd-line treatment of mCRC based on randomized data from the CORRECT trial. Weibull models were fitted to the published overall and progression-free survival curves, and were used to extrapolate the cause-specific mortality and progression risks. Costs for administration and management of adverse events were based on Medicare reimbursement rates for hospital and physician services, and drug costs based on the Medicare average wholesale prices (all in 2014 US $). Health outcomes were measured in life years (LYs) and quality-adjusted life years (QALYs). Quality of life adjustments were calculated based on health utility values in the CORRECT trial and toxicity disutilities and durations were included for the most common toxicities: hand/foot syndrome, diarrhea, and hypertension. Model robustness was addressed by univariate and probabilistic sensitivity analyses (PSA). **Results:** In the model, regorafenib provided an additional 0.04 QALYs (0.13 LYs) at a cost of $39,391. The incremental cost-effectiveness ratio (ICER) was $897,411/QALY. In all one-way sensitivity analyses, the ICER of regorafenib was > $700,000/QALY. The ICER of regorafenib was greater than $200,000/QALY in > 99% of PSAs. **Conclusions:** This is the first US-based cost-effectiveness analysis of regorafenib in mCRC and our findings show that regorafenib provides minimal incremental benefit at high incremental cost per QALY. The ICER of regorafenib could be improved by use of an effective biomarker to select patients most likely to benefit, or by a lower price for payers.

6614 Poster Session (Board #171), Mon, 1:15 PM-4:45 PM

Stage specific health utility index scores of Canadian cancer patients. *First Author: Hiten Naik, University of Toronto, Toronto, ON, Canada*

Background: In order to improve the precision of health economics analyses in oncology, reference datasets of health utility index (HUI) scores are needed from cancer patients. These data are particularly sparse among Canadian patients. Using EQ5D we generated stage-specific HUI scores for lung, breast, colorectal, prostate, head/ neck and ovarian cancer, and all-stage reference values for 21 additional cancer sites. **Methods:** 1,760 ambulatory cancer patients at the Princess Margaret completed the EQ5D instrument. HUI scores were calculated using Canadian valuations. Clinical information was abstracted from patient charts and data was analyzed using descriptive statistics and multiple regression. **Results:** Among all patients, the mean±SEM HUI score was 0.81±0.004 (Canadian algorithm). The cancer sites with the lowest mean HUI scores were acute lymphoblastic leukemia (0.70±0.03) and pancreatic (0.76±0.03); testicular (0.89±0.02) and chronic lymphocytic leukemia (0.90±0.05) had the highest scores. Scores varied by stage among lung, breast, colorectal, prostate, head and neck and ovarian cancer patients (see Table). After adjusting for age and cancer site, HUI scores were significantly higher amongst patients with a university/ college education ($p = 0.002$), those married or living with a partner ($p < 0.001$), employed ($p < 0.001$), and those with local/regional vs. distant metastatic disease ($p = 0.001$). **Conclusions:** This work represents the first reference set of stage specific HUI scores for several cancers derived using Canadian valuations. Mean HUI scores varied by basic socio-demographic and clinical parameters, including stage. Future research will incorporate these data into the economic analyses required for policy and clinical decision-making.

	Lung		Breast		Colorectal		Prostate		Head/Neck		Ovarian	
Stage	N	HUI ±SEM	N	HUI± SEM	N	HUI ±SEM	N	HUI ±SEM	N	HUI ±SEM	N	HUI ±SEM
0	---	---	19	0.91±0.02	---	---	---	---	5	0.90±0.06	---	---
1	43	0.81± 0.03	97	0.82±0.02	4	0.80±0.07	26	0.92±0.02	36	0.86±0.02	13	0.82±0.04
2	16	0.77± 0.03	102	0.79±0.02	26	0.87±0.02	60	0.92±0.01	20	0.83±0.04	10	0.81±0.06
3	32	0.76±0.03	34	0.74±0.04	48	0.83±0.02	19	0.83±0.05	19	0.78±0.05	49	0.77±0.02
4	37	0.76±0.03	16	0.81±0.04	34	0.81±0.02	10	0.78±0.04	61	0.81±0.01	6	0.77±0.04

6615 Poster Session (Board #172), Mon, 1:15 PM-4:45 PM

Disclosure of industry payments to oncologists: Early open payments data. *First Author: Deborah Catherine Marshall, UC San Diego, Department of Radiation Medicine and Applied Sciences, La Jolla, CA*

Background: The Open Payments program discloses industry payments to identified physicians ('physician payments'). We characterize these payments by oncology specialty. **Methods:** We analyzed the December 2014 release of Open Payments data on physician payments made from August-December 2013. We characterized physician payments by type (general or research). We also evaluate physician ownership interests in reporting manufacturers. Data were aggregated by physician and oncology specialty [medical oncology (hematology/oncology, medical oncology, pediatric hematology/oncology); radiation oncology; and surgical oncology (surgical oncology, gynecologic oncology)]. We compared the number of physicians receiving payments to the total number of active physicians in each specialty in 2012 (AMA. Physician Characteristics and Distribution in the US. Chicago: AMA; 2014). **Results:** There were 82,213 payments to 9,893 oncology physicians (50% vs. 46% for all medical specialties) totaling $31 million ('M'), Table. Payments for food/beverage were most common (79%) but represent only 10% of the total value. The most common nature of payment by total value was compensation for services (excluding consulting and CME) in medical oncology (38%), consulting fees in radiation oncology (30%), and education in surgical oncology (27%). Ownership interests totaled $8M in amount invested and $12M in total value of interest. Medical oncology had the highest proportion of physicians with ownership interest (1.7%) of oncology specialties. **Conclusions:** These data can inform policy-making and advocacy efforts for oncology specialties. Partially supported by the NIH (Grant TL1TR00098).

Industry payments to oncology physicians, August-December 2013.

Specialty	Number of payments	% of physicians receiving payments	Total value: all payments	Total value: general payments	%	Total value: research payments	%
Medical oncology	74,107	54%	$26,317,128	$14,900,718	57%	$11,416,410	43%
Radiation oncology	4,612	31%	$ 3,440,178	$ 1,048,742	30%	$ 2,391,436	70%
Surgical oncology	3,494	86%	$ 1,108,222	$ 1,082,796	98%	$ 25,426	2%
All oncology	82,213	50%	$30,865,528	$17,032,256	55%	$13,833,272	45%

6616 Poster Session (Board #173), Mon, 1:15 PM-4:45 PM

Improving the value of PSA prostate cancer screening with "smarter" strategies and increased use of active surveillance. *First Author: Joshua A. Roth, Fred Hutchinson Cancer Rsrch Ctr, Seattle, WA*

Background: Prostate-specific antigen (PSA) screening for prostate cancer is controversial. Epidemiological researchers and guideline groups have suggested many personalized and conservative strategies to improve benefit-risk tradeoffs.The goal of this study is to identify strategies most likely to be cost-effective, and to examine the added value of increased active surveillance (AS) for low-risk cases. **Methods:** We extended an established CISNET microsimulation model to project life years (LY), quality-adjusted life years (QALYs), and costs for cohorts of U.S. men from age 40 to death in 15 screening strategies with fixed or personalized screening ages, intervals, and PSA biopsy thresholds. We calculated the incremental cost-effectiveness ratio (ICER) for each vs. no screening under "contemporary" or "increased AS" treatment practices. "Contemporary" practices were based on age, stage, and grade-specific initial treatments in the SEER program. "Increased AS" practices immediately treated cases if Gleason sum ≥ 7 or clinical T-stage ≥ T2a and monitored all others. Analyses used a 3% annual discount rate and a willingness to pay of $150,000/QALY. **Results:** All PSA screening strategies increased LYs (range = 0.014-0.021) and costs (range = $100-900) vs. no screening and were highly cost-effective (ICER range = $25,000-43,000/LY). With "contemporary" treatments, only strategies with biopsy threshold at PSA ≥ 10 mg/L increased QALYs (range = 0.001-0.002), and only quadrennial screening of ages 50-74 was cost-effective ($150,000/QALY). With "increased AS," all strategies with biopsy threshold at PSA ≥ 10 mg/L increased QALYs (range = 0.003-0.005) and were cost-effective (ICER range = $45,000-95,000/QALY), as was quadrennial screening of ages 55-69 with biopsy threshold at PSA ≥ 3 mg/L (Inc QALYs = 0.002, Inc Cost = $130, ICER = $65,000/QALY). **Conclusions:** Personalized PSA screening strategies with conservative screening frequency and/or PSA biopsy threshold appear to be cost-effective vs. no screening, particularly when combined with increased AS for low-risk cases.

6617 Poster Session (Board #174), Mon, 1:15 PM-4:45 PM

Hepatitis B virus screening before adjuvant chemotherapy in patients with early stage breast cancer: A cost-effectiveness analysis. *First Author: William W. L. Wong, University of Toronto, Toronto, ON, Canada*

Background: The seroprevalence of Hepatitis B virus (HBV) infection among Canadian was 0.4%, and 1.6% among immigrants. Most infected individuals have clinically silent disease. Cytotoxic chemotherapy causes reactivation in 30% of the HBV infected patients. This can be severe and fatal, may also lead to interruption of chemotherapy. HBV screening before adjuvant chemotherapy (ADJ) for breast cancer (BC) seems to be a plausible strategy. Our objective is to estimate the health and economic effects of HBV screening strategies. **Methods:** We developed a state transition microsimulation model to examine the cost effectiveness of 3 strategies for 55 year old BC patients undergoing ADJ: (1) *No screen*; (2) *Screen Imm*: Screen immigrant only and treat; (3) *Screen all*: Screen all and treat; with antiviral therapies. In the model, health states were constructed to reflect the natural history of BC and HBV. Model data were obtained from published literature. We used a payer perspective, a lifetime time horizon, and used a 5% discount rate. **Results:** *Screen all* would prevent 38 severe reactivations (SR), 9 deaths from reactivation (DR), 21 chemotherapy interruptions (CI), 32 decompensated cirrhosis (DC), 38 HCCs, and 56 HBV deaths per 100,000 persons screened over the lifetime of the cohort. *Screen Imm* would prevent 29 SR, 7 DR, 16 CI, 23 DC, 27 HCCs, and 41 HBV deaths. *Screen all* was associated with an increase of at least 0.0034 quality adjusted life years (QALY) and cost C$164 more per person, translating to an incremental cost effectiveness ratio (ICER) of C$47,808-76,527/QALY gained compared with *No screen*, depends on different antiviral therapies. *Screen all* was the most cost effective, while *Screen Imm* was ruled out due to extended dominance (ED) by *No Screen* and *Screen all*. **Conclusions:** HBV screening before ADJ for BC patients would prevent a significant number of reactivations, and is likely be cost effective.

Strategy	Cost($)	QALYs	VS no screen			Sequential ICER($)
			DCost($)	DQALYs	ICER($)	
No screen	53,986	10.4345	-	-	-	-
Screen Imm	54,120-54,203	10.4361-10.4361	134-217	0.0016-0.0017	82,188-130,084	ED
Screen all	54,150-54,252	10.4379-10.4379	164-266	0.0034-0.0035	47,808-76,527	

6618 Poster Session (Board #175), Mon, 1:15 PM-4:45 PM

Grading financial toxicity based upon its impact on health-related quality of life (HRQol). *First Author: Jonas A. De Souza, University of Chicago Medicine, Chicago, IL*

Background: Financial toxicity (FT) is an important patient-centered outcome. The impact of this toxicity on patients' HRQoL is not well known. We hypothesized that FT can be graded based on statistically significant and clinically meaningful decreases in HRQoL. **Methods:** FT was assessed by the quantitative COST (COmprehensive Score for financial Toxicity). Gradations of FT's impact on HRQoL were based on established conventions for clinically meaningful small, medium and large effect sizes (e.s.) for the FACT-G HRQoL instrument. The optimal COST cutoff scores for FT grades were determined by ROC curve analyses maximizing the sum of the sensitivity and specificity in comparison with normative FACT-G values for the general adult population. Following FACIT standards, higher FT was represented by lower COST values. Demographics, tumor type, length of disease, chemotherapy use, resource utilization, HRQoL, and symptoms (EORTC QLQ-C30 symptom scales) were collected. Data were analyzed using Pearson correlations, linear regression, and chi-square tests. **Results:** A total of 233 patients who had completed at least 3 months of chemotherapy were assessed. The correlation between the COST and FACT-G was $r = 0.42$, $p < .001$. ROC curve analyses produced optimal COST FT grades (G) as follows: G0 $\geq$ 26 (n = 99 patients, 42%), G1: $\geq$ 14-25 (n = 71, 31%) and G2: $>$ 0-14 (n = 58, 25%). Five patients (2%) had scores of 0 (G3). On multivariate analyses, pts with G0 had no impact of FT in their HRQoL; G1 had a statistically significant small and meaningful e.s. difference compared to G0 (0.26, $p < .05$); G2 had a statistically significant and medium e.s. (0.47, $p < .001$); G3 had a significant and clinically meaningful large e.s. (0.99, $p < .005$). There was a significant relationship between FT (grades 1-3) and younger age ($p <$ .01), non-Caucasians ($<$ .05), less than a college degree ($<$ .01), unemployment (.001), Medicaid ($<$ .05), and lower income ($<$ .001). **Conclusions:** We developed a FT grading system based on clinically meaningful changes in HRQoL. There were 134 (58%) patients with Grades 1-3 FT. Financial distress as it relates to HRQoL is a meaningful event that can be objectively measured, and should be included in the assessment of patient-centered outcomes.

6619 Poster Session (Board #176), Mon, 1:15 PM-4:45 PM

Medical expenditures and productivity loss among colorectal, breast, and prostate cancer survivors in the US. *First Author: Zhiyuan Zheng, American Cancer Society, Atlanta, GA*

Background: We examined the economic burden among survivors of the three most prevalent cancers (colorectal, female breast, and prostate) in nonelderly and elderly populations in the US. **Methods:** The 2008 to 2012 Medical Expenditure Panel Survey data was used to identity colorectal (n = 540), breast (n = 1,568), and prostate (n = 1,170) cancer survivors, and individuals without a cancer history (n = 109,423). Total economic burden was defined as the sum of medical expenditures and productivity loss (i.e. employment disability, productivity loss at work measured by missed work days, and productivity loss at home measured by additional days stayed in bed). Excess burden was measured as the difference in economic burden between cancer survivors and individuals without a cancer history. All analyses were conducted by cancer site and stratified by age (nonelderly: 18-64 vs elderly: 65+). Multivariable analyses controlled for age, sex, race/ethnicity, marital status, education, comorbidities, health insurance, and geographic region. **Results:** The total annual economic burden per nonelderly cancer survivor was $20,238 for colorectal, $14,202 for breast, and $9,278 for prostate. When compared to individuals without a cancer history, excess medical expenditures among nonelderly cancer survivors was $8,647 for colorectal, $5,119 for breast, and $3,586 for prostate (all $p < 0.01$). Moreover, nonelderly colorectal and breast cancer survivors experienced significantly greater excess employment disability (colorectal: 14%; breast: 5%) and productivity loss at work (colorectal: 7 days; breast: 3 days) and at home (colorectal: 5 days; breast: 3 days; all $p < 0.01$). Elderly cancer survivors also bear significant total economic burden (colorectal: $18,860; breast: $14,351; prostate: $16,851). However, their excess medical expenditure is much lower than nonelderly cancer survivors. Excess productivity loss among elderly cancer survivors was not significantly different from elderly individuals without a cancer history. **Conclusions:** The economic burden of cancer varies by cancer site and age group. Nonelderly cancer survivors experience greater excess economic burden than elderly cancer survivors.

6620 Poster Session (Board #177), Mon, 1:15 PM-4:45 PM

Contribution of cancer care to total spending among high-cost Medicare beneficiaries. *First Author: Miranda Kim, Harvard Rad Onc Prog, Boston, MA*

Background: Medicare spending is highly concentrated, with the top decile of Medicare patients accounting for more than half of total Medicare expenditures. Understanding the patterns of spending that contribute to these high costs may lead to important policy changes and innovative programs aimed at successfully reducing spending and potentially improving outcomes. We know little about the contribution of cancer as a diagnosis and types of cancers present among high cost Medicare beneficiaries. **Methods:** We used 20% of the 2012 Medicare data to identify fee-for-service (FFS) beneficiaries who were continuously enrolled for the year and were age 65 or older. High cost patients were defined as those in the top decile of spending in 2012 and non-high cost patients were the remaining patients. To identify patients with a cancer diagnosis, we used ICD-9 codes for the top 10 cancer killers. **Results:** Among all Medicare fee-for-service beneficiaries, 18% carried a cancer diagnosis. A cancer diagnosis was far more likely to be present among high-cost patients compared to non-high-costs patients: 26.2% versus 17.1% ($p < .001$). Cancer diagnoses found more frequently in the high-cost group as compared to the rest of Medicare beneficiaries included colorectal (32.7% vs. 24.8%, $p < .001$), head and neck (3.2% vs. 0%, $p < .001$), lymphoma (1.0 vs. 0%, $p < .001$), pancreatic (9.9 vs. 6.8%, $p < .001$) and esophageal cancer (2.7% vs. 0.8%, $p < .001$). There were significantly fewer breast (3.6% vs. 9.2%, $p = < .001$) and prostate (2.4% vs. 12.3%, $p < .001$) patients in the high-cost group. **Conclusions:** Among elderly Medicare recipients, high-cost patients are significantly more likely to carry a cancer diagnosis, suggesting that interventions aimed reducing cancer costs may be highly effective in reducing overall healthcare spending. Certain cancer diagnoses are particularly overrepresented in this cohort, pointing to a need for further studies aimed at understanding specific components driving cancer costs in this population.

6621 Poster Session (Board #178), Mon, 1:15 PM-4:45 PM

A framework to assess the cost effectiveness of predictive biomarkers in oncology: Test Incremental Cost Effectiveness Ratio (TICER). *First Author: Anton Safonov, Yale School of Medicine, New Haven, CT*

Background: Cost effectiveness of predictive biomarkers is currently assessed by Markov Chain (MC) simulations, requiring resources and expertise. Our goal was to develop a practical index to aid clinicians in biomarker cost utility estimation at an early stage of development. **Methods**: We used decision trees to derive a test incremental cost-effectiveness ratio (TICER) index that combines six parameters including biomarker prevalence, progression free survival (PFS), health-related quality of life (HRQoL), cost of testing, cost of treatment, and cost of progression. We assessed the model on existing (HER2, ALK, OncotypeDx) and emerging (PDL1 expression) predictive biomarkers. We conducted one-way and multivariate probabilistic sensitivity analyses (PSA) and generated cost-effectiveness acceptability curves (CEAC). Benefit was expressed as quality-adjusted progression-free years (QAPFY). **Results**: We used literature reported values for base case and varied the parameters over a broad range to estimate the contribution of each variable to TICER. TICER was calculated by one-way PSA for each variable as the median CEAC (cost at 50% probability of acceptance), while sampling the remaining variables from their respective distributions. The table shows the base case and range of TICER compared to literature values and the acceptance probability considering a cutoff of $200K/QAPFY, providing a relative ranking in terms of cost effectiveness. The TICER model is driven primarily by PFS and HRQoL while biomarker prevalence and test costs have a lesser effect. **Conclusions**: TICER is flexible to a variety of clinical scenarios and does not require assumptions about health states up to death like MC-based methods do. The cost effectiveness of a predictive test is driven by the efficacy and QOL associated with biomarker-directed therapy rather than marker prevalence or assay cost.

Biomarker	Base Case TICER ($K/QAPFY)	Range of TICER by PSA ($K/QAPFY)	Acceptance Probability of $200K/QAPFY	Literature Value ($K/QALY)
HER2	155.2	113 to 235	74.9%	145
ALK	258.3	206 to 433.2	18.4%	256
PD-L1	280.7	227 to 482	12.8%	N/A
OncotypeDx	-5.1 (negative indicate cost saving)	-13.2 to – 2.8	99.5%	-6.7

6622 Poster Session (Board #179), Mon, 1:15 PM-4:45 PM

Cost-sharing and financial burden for Medicare patients with newly diagnosed cancer. *First Author: Amol Narang, Department of Radiation Oncology and Molecular Sciences, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Proposals for reducing Medicare spending include measures that increase beneficiary cost-sharing by regulating the extent of supplemental insurance. However, the financial burden on patients of such policies is unclear, particularly for health shocks such as cancer. To address this question, we used the Health and Retirement Study (HRS) to characterize the out-of-pocket (OOP) cost burden of newly diagnosed cancer and its relation with supplemental insurance. **Methods:** Medicare-eligible, community-dwelling HRS participants who did (N = 1409) or did not (N = 16,757) report a new cancer diagnosis from 2002-2012 were identified. Supplemental insurance was classified in order of increased cost-sharing as public (dual-eligible/VA), private (employer-sponsored/Medigap), or none (Medicare alone). OOP costs included hospital stays, doctor visits, outpatient surgery, prescription drugs, home health, dental, and special facilities. Financial burden was defined as OOP costs over per-capita household income. Multivariable quantile regression was used to assess the median and 90thpercentile (p90) of OOP costs and financial burden. **Results:** Newly diagnosed cancer patients experienced increased annual OOP costs (median: $2222 vs. $1791, $p < 0.001$; p90: $10,420 vs. $7807, $p < 0.001$) and financial burden (median: 9.0% of household income vs. 7.4%, $p < 0.001$; p90: 51.0% vs. 42.4%, $p < 0.001$). Supplemental insurance significantly affected cancer patients' median financial burden (public: 3.3%, private: 9.9%, none: 16.6%, $p < 0.001$), which was magnified at the 90th percentile (public: 31.8%, private: 48.3%, none: 106.2%, $p < 0.001$). Importantly, financial burden at the 90thpercentile did not increase following a new cancer diagnosis for patients with public or private supplemental insurance, but significantly increased for patients with Medicare alone (p90: 106.2% vs. 58.1%, $p < 0.001$). **Conclusions:** More than 10% of newly diagnosed cancer patients with Medicare alone faced OOP costs greater than their income. Proposals to increase cost-sharing in the Medicare population should include provisions that protect patients from health shocks such as cancer, potentially though OOP cost limits or value-based exceptions.

6623 Poster Session (Board #180), Mon, 1:15 PM-4:45 PM

Out-of-pocket cost trends for Medicare patients with newly diagnosed cancer. *First Author: Amol Narang, Department of Radiation Oncology and Molecular Sciences, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: While rising cancer care costs have been well-documented, the extent to which these costs have translated into increased patient financial burden is unclear. To address this question, we used a nationally, representative panel survey to characterize trends over time in the out-of-pocket (OOP) costs of newly diagnosed cancer patients. **Methods:** Medicare-eligible, community-dwelling participants in the biennial Health and Retirement Study who reported a new cancer diagnosis between 2002-2012 were identified (N = 1409). Respondent-reported OOP costs included the following categories: hospital stays, doctor visits, outpatient surgery, prescription drugs, home health, dental care, and special facilities. A multivariate generalized linear model and quantile regression were used to assess the mean, median, and 90thpercentile of OOP costs. Adjusted levels of OOP costs were compared over time using a contrast test. **Results:** Mean annual OOP costs decreased from $7868 (95% CI: $6477 - $9259) for patients with a new cancer diagnosis at the 2002 survey to $4242 (95% CI: $2642 - $5841) for patients with a new cancer diagnosis at the 2012 survey, a decline of $3626 (95% CI: $1508 - $5745, $p = 0.001$). Median annual OOP costs declined by $580 (95% CI: $66 - $1095, $p = 0.03$). The steepest decline in OOP costs occurred between 2004 and 2008 (mean: $5070, 95% CI: $2944 - $7195, $p < 0.001$; median: $1031, 95% CI: $515 - $1547, $p < 0.001$), while OOP costs did not significantly change between 2008 and 2012 (mean: $779, 95% CI: -1411 – 2969, $p = 0.486$; median: $17, 95% CI: -515 – 549, $p = 0.949$). The 90th percentile of annual OOP costs similarly declined over the study period from $13,203 (95% CI: $11,403 - $15,002) to $8063 (95% CI: $5,995 - $10,131), a decline of $5,140 (95% CI: $2,340 - $7,880, $p < 0.001$). **Conclusions:** Despite the growing costs of cancer care,Medicare patients with newly diagnosed cancer were increasingly shielded from high OOP costs over the study period, with a sharp decline between 2004 and 2008 which may be attributable to the introduction of Medicare part D. Given the more recent plateau in OOP costs and proposals to increase cost-sharing in this population, close monitoring of OOP cost trends will be important for avoiding excessive financial burden.

TPS6624 Poster Session (Board #181a), Mon, 1:15 PM-4:45 PM

Patients' competence in oral cancer therapies. *First Author: Christoph Riese, Scientific Institute of Office-based Hematologists and Oncologists -WINHO, Cologne, Germany*

Background: Oral agents for cancer treatment are increasingly prescribed. Regardless the benefits of oral agents, oral cancer medications have a considerable potential for side-effects, toxicity and drug interactions. Inadequate use of medication therefore leads to ineffectiveness of medication and in some cases to early breakup of therapy. This type of therapy requires a high level of self-management competence of the patient and her/his social setting. A standardized recurring patient education program by oncology nurses may influence the handling of the oral agents in a positive way. We evaluated whether providing adequate information on the clinical picture, treatment options, side effects, and the proper handling of medication influences therapy adherence, self-management ability, and eventually therapeutic success. **Methods:** The cluster randomized controlled study was conducted from March until December 2014. This trial took part in total 28 office based oncology practices all over Germany. The oncology nurses for the intervention group were specially trained for the education program in techniques of motivational communication and the usage of oral agents. The intervention (n = 17 practices) was conducted in addition to the counselling for therapy, by the oncologist. The control group received only the oncologists counseling. Primary endpoint was the patient's competence measured by a combination of the tools: self-efficacy, quality of life and therapy related knowledge. Secondary endpoints are side-effects, health related stress, overall dose and break up rate. The analysis of the data is still ongoing and will be finished in April 2015. Clinical trial information: VfD_PACOCT_12_003487.

TPS6625 Poster Session (Board #181b), Mon, 1:15 PM-4:45 PM

Health and economic outcomes of two different follow up strategies in effectively cured advanced head and neck cancer patients. *First Author: Lisa F. Licitra, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: optimal timing and type of examinations for the follow up (FUP) of head and neck squamous cell cancer (HNSCC) survivors have not been established yet. There is also a need to find out which is the most cost-effective FUP program in this population. The present trial aims at comparing a more intensive radiologic FUP approach with a less intensive one, also evaluating its economical impact on healthcare system. **Methods:** this is a randomized, phase II, multicenter trial conducted in 15 Centers throughout Italy and Switzerland. Patients with stage III-IV SCC of oral cavity, oropharynx, larynx or hypopharynx having already received radiation therapy as part of their curative treatment and in complete remission at six months are randomized in two arms according to different FUP approaches. A non intensive FUP approach (ARM A) foresees only a radiologic evaluation (locoregional CT scan or MRI) within 6 months since treatment end and subsequently only at signs or symptoms occurrence (according to NCCN guidelines). An intensive FUP approach (ARM B) consists of scheduled radiologic evaluations (CT scan or MRI of head and neck) 2 times/year in the first 2 years and 1 time/year in the third and fourth year; PET scans are requested yearly in the first 3 years for patients with smoking history. FUP visits consist of physical and fiberoptic endoscopic examinations of head and neck district, laboratory tests, quality of life questionnaires and evaluation of out-of-pocket costs and productivity losses; timing of FUP visits is the same in both arms. An estimated 330 patients (randomized 1:1) are being enrolled over the first year; health outcomes and costs will be assessed over the next two years. The percentage of potentially salvageable recurrences or second primaries, as well as the cause-specific survival and the overall survival of recurring patients will be evaluated in both groups. Incremental cost-effectiveness ratio (cost/life year gained) and cost-utility ratios (cost/QALY) will be calculated referring to WHO thresholds of 1-3 times per capita gross domestic product. ClinicalTrials.gov Identifier: NCT02262221. The trial is funded by a grant from the Swiss Bridge Foundation. Clinical trial information: NCT02262221.

7000 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Correlation of acute myeloid leukemia (AML) stem cell phenotype with cytogenetic/molecular features and prognosis. *First Author: Jonathan Michael Gerber, Levine Cancer Institute, Charlotte, NC*

Background: Emerging evidence supports the clinical significance of leukemia stem cells (LSCs).We previously found that patients with AML exhibited 1 of 3 distinct LSC phenotypes based on CD34, CD38, and aldehyde dehydrogenase (ALDH): 1. $CD34^-$, 2. $CD34^+CD38^-ALDH^{intermediate}$ ($ALDH^{int}$), or 3. $CD34^+CD38^-ALDH^{high}$ ($ALDH^{high}$) [Gerber, et al. *Blood*, 2012]. We hypothesized that LSC phenotypes might correlate with cytogenetic/molecular features and treatment outcomes. **Methods:** Diagnostic samples from 98 patients with newly diagnosed normal or unfavorable cytogenetic AML, enrolled on clinical protocol NCT01413880, were analyzed by FACS. Sorted cell populations were assayed by FISH and/or PCR for leukemia-specific abnormalities. Fisher's exact and Mantel-Haenszel tests were used to analyze differences in risk factors and outcomes by LSC phenotype. **Results:** LSCs were $CD34^-$ in 21 cases; $ALDH^{int}$ in 44; and $ALDH^{high}$ in the remaining 33. Poor risk cytogenetics and/or FLT3-ITD mutations were uncommon in the $CD34^-$ (4/21 = 19%) and $ALDH^{int}$ (17/44 = 39%) cases, but were frequent in the $ALDH^{high}$ cases (28/33 = 85%, $p < 0.001$). NPM1 mutations were detected in 14/21 (67%) of the $CD34^-$ LSC patients vs. just 8/77 (10%) of the patients with $CD34^+$ LSCs ($p < 0.001$). Both patients with t(9;11) had $CD34^-$ LSCs ($p < 0.001$), while antecedent MDS or MPN ($p = 0.04$) were more common in patients with $ALDH^{high}$ LSCs. Only 15/33 patients (45%) with $ALDH^{high}$ LSCs achieved complete remission, compared to 29/43 patients (69%) with $ALDH^{int}$ LSCs and 19/22 patients (86%) with $CD34^-$ LSCs ($p < 0.01$). Among patients who did not undergo allogeneic stem cell transplant, long term disease-free survival was 0% (0/6) in patients with $ALDH^{high}$ LSCs vs. 31% (4/13) with $ALDH^{int}$ and 62% (8/13) with $CD34^-$ LSCs ($p = 0.04$). **Conclusions:** LSC phenotype correlates with cytogenetic/molecular risk factors and response, permitting rapid risk-stratification of AML patients. This may be of particular use for patients with $ALDH^{high}$ LSCs, who appear to be at high risk – more likely to harbor adverse cytogenetic/molecular features and prove refractory to chemotherapy. Earlier identification would facilitate access to clinical trials of novel induction approaches.

7001 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Association between KIR genes and risk of MDS. *First Author: May Daher, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Myelodysplastic syndrome (MDS) represents a spectrum of clonal hematopoietic disorders affecting the myeloid lineage, characterized by cytopenias and dysplastic features. MDS is risk-stratified according to International Prognostic Scoring System (IPSS) scores. The major clinical complication in these disorders, especially in the high-risk group, is the potential to evolve into acute myeloid leukemia (AML). Evidence is accumulating that genetic factors play an important role in conferring susceptibility/resistance to MDS. In this regard, activating killer-cell immunoglobulin-like receptor (KIR) genes expressed in natural killer cells (NK cells) are of particular interest. Humans may inherit different numbers of the six distinct activating KIR genes. Little is known about the impact of this genetic variation on the innate susceptibility or resistance of humans to develop MDS. **Methods:** We addressed this issue by performing a case-control study involving 180 MDS patients (120 with high IPSS, 60 with low IPSS) and 117 healthy donors. DNA samples were collected in both cases and controls and analysis of activating KIR genes was performed using PCR. **Results:** Our results showed that patients with high-risk MDS had significantly lower numbers of activating KIR genes compared to patients with low-risk MDS (P = 0.009) and compared to healthy controls (P = 0.00001). Patients with low-risk MDS also had fewer activating KIR genes when compared to controls (P = 0.04). Importantly, inheritance of each additional activating KIR gene had a protective effect against development of high risk MDS (RR 0.7, P < 0.001). **Conclusions:** These results suggest that inheritance of a higher number of activating KIR genes is protective against MDS, and that once the disease develops, harboring a lower number of KIR genes is associated with higher risk disease. Hence, our study provides novel insights concerning the pathogenesis of MDS in adults and has implications for the development of new immunotherapies using NK cells with potential of controlling the disease and preventing progression to high risk disease and eventually to AML.

7002 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

The international Prognostic Index for patients with CLL (CLL-IPI): An international meta-analysis. *First Author: Nadine Kutsch, Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University Hospital Cologne, Cologne, Germany*

Background: In the era of more effective treatments for CLL, the established clinical staging systems [Rai/Binet] do not accurately discriminate between prognostic groups. There are several new prognostic markers, but no system integrates the major clinical, biological and genetic variables into one widely accepted score. Therefore we performed a comprehensive analysis of 26 prognostic factors to develop an internationally applicable prognostic index for CLL patients (pts) [CLL-IPI]. **Methods:** Our full analysis set (FAS) was collected from 8 phase 3 trials from France, Germany, UK, USA and Poland [3472 pts at early & advanced stage; median age 61 years (yr) (range 27 - 86); median observation time (OT) 80 months (ms)]. The FAS was randomly divided into training and internal validation datasets [TD, 2308 (67%); IVD, 1164 (33%)]. Methods of multivariable statistics were applied and the main end point was overall survival (OS). Handling of missing data was performed by complete case analysis. The model was externally validated in a third dataset comprised of 845 newly diagnosed CLL pts from Mayo Clinic [median age 62 yr (range 25 - 89); median OT 63 ms]. **Results:** Based on 1192 (52%) pts from the TD, 5 independent predictors for OS were identified: age, clinical stage, del(17p) and/or *TP53* mutation, *IGHV* mutation status and β_2-microglobulin (B2M) level. Using weighted grading, a prognostic index was derived separating 4 different pt groups: low (score 0-1), intermediate (score 2-3), high (score 4-6) and very high risk (score 7-10) with significantly different OS [93%, 79%, 64% and 23% OS at 5 yr for the low to very high risk group respectively, $p < 0.001$; *C*-statistic c = 0.72 (95% CI, 0.69-0.76)]. This multivariable model was confirmed on the IVD [575 (49%) pts; c = 0.777 (0.73-0.82)] and the 4 risk groups were reproduced with 97%, 91%, 68% and 21% 5-yr OS [($p < 0.001$), c = 0.79 (0.74-0.85)] on the Mayo set. **Conclusions:** The resulting CLL-IPI combines the most important genetic risk factors (*IGHV*, del(17p)/*TP53* mutation) with clinical stage, age, and B2M into an easily applicable prognostic score for CLL pts. Moreover, it both discriminates between prognostic groups and is informative regarding current treatment recommendations.

7003 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Results of a first-in-human, phase I/II trial of ASP2215, a selective, potent inhibitor of FLT3/Axl in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML). *First Author: Mark J. Levis, Sidney Kimmel Comp Cancer Ctr at Johns Hopkins, Baltimore, MD*

Background: FLT3 Internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations are seen in 30% of AML patients (pts) and are associated with poor survival. Secondary FLT3-TKD mutations are associated with treatment failure with tyrosine kinase inhibitors. ASP2215 is a potent inhibitor of FLT3 and Axl with activity against FLT3-ITD and FLT3-TKD. **Methods:** A phase I/II trial was conducted to investigate safety and efficacy in pts with R/R AML. The dose escalation followed a 3+3 design and evaluated doses from 20 to 450 mg once daily. A parallel multi-dose expansion cohort was initiated based on the efficacy seen in dose escalation. **Results:** 166 pts have enrolled between October 2013, and December 2014, 25 in the dose escalation and 141 in the dose expansion cohorts. At the 450 mg dose, 2 pts had a DLT (grade 3 diarrhea and ALT/AST elevation), and the maximum tolerated dose was determined to be 300 mg. Common possibly or probably drug related treatment emergent adverse events of any grade include fatigue (13%), constipation (10%), anemia (8%), nausea (8%), diarrhea (7%), thrombocytopenia (6%), decreased platelet count (6%), vomiting (6%), dizziness (6%), peripheral edema (5%), increased transaminases (5%) and hypomagnesemia (5%). 120 pts are evaluable for response. Overall response rate (ORR) was 57% in 82 pts with FLT3 mutations, and 63% in 68 pts in the 80 mg and higher dose levels. A plasma inhibitory activity assay confirmed effective, sustained in vivo FLT3 inhibition consistently in pts receiving doses of 80 mg and above. **Conclusions:** ASP2215, a potent inhibitor of FLT3/Axl, is well tolerated in patients with R/R AML and results in a high degree of clinical activity. Randomized phase III trials of ASP 2215 at 200 mg per day in newly diagnosed and R/R AML are planned. Clinical trial information: NCT02014558.

	FLT3 mutated		
Response	20-300 mg n (%) (82 pts)	≥ 80 mg n (%) (65 pts)	FLT3 wild type n (%) (38 pts)
Complete Remission (CR)	4 (5%)	3 (5%)	0
CR, incomplete platelet recovery (CRp)	4 (5%)	4 (6%)	0
CR, incomplete hematologic recovery (CRi)	27 (33%)	25 (38%)	3 (8%)
Partial Remission (PR)	12 (15%)	10 (15%)	1 (3%)
Composite CR (CR+CRp+CRi)	35 (43%)	32 (49%)	3 (8%)
ORR (CRc+PR)	47 (57%)	42 (65%)	4 (11%)

7004 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Clinical activity of ERY001 (erythrocyte encapsulated l-asparaginase) and native l-asparaginase (L-ASP) in combination with COOPRALL regimen in phase III randomized trial in patients with relapsed acute lymphoblastic leukemia (ALL). *First Author: Yves Bertrand, Institut d'Hémato-Oncologie Pédiatrique, Hospices Civils de Lyon, Lyon, France*

Background: Asparaginase is a cornerstone in the treatment of ALL, but its utility is limited by toxicities including hypersensitivity. Clinical allergy is associated with inactivation of asparaginase by antibodies (A-Abs), which can also neutralize asparaginase without any clinical signs of hypersensitivity (silent inactivation). ERY001 improves pharmacokinetics, tolerability and maintain circulating asparaginase (ASPA) activity due to the protective barrier of the erythrocyte membrane. **Methods:** This open, randomized international Phase 3 study enrolled pts with relapsed ALL. The co-primary endpoints were the duration of ASPA activity $>$ 100IU/L and the incidence of ASPA hypersensitivity during induction. Key secondary endpoints were complete remission (CR), minimal residual disease (MRD), event free survival (EFS) and overall survival (OS).The study was powered to detect 3-fold difference in the incidence of allergic reactions between treatments. Pts (n = 80), aged 1-55 years were randomized to ERY001 (150 IU/kg, n = 26 or L-ASP (10,000 IU/m^2, n = 28), or to ERY001-exp (prior allergy, n = 26). **Results:** In the non-allergic pts, ERY001 significantly reduced the incidence of ASPA hypersensitivity (0% vs 43%; $p < 0.001$). ASPA activity $>$ 100 IU/l was 21 $\pm$5 vs 9$\pm$ 8 days in ERY001 and L-ASP, respectively ($p < 0.001$). The CR rate: ERY001 (65%, 95% CI: [51.6:89.8]) vs L-ASP (39%, 95% CI: [23.3:63.1]; p = 0.026). Allograft was successfully performed in 65% of ERY001 vs. 46% of L-ASP. The proportion of patients who achieved MRD $< 10^{-3}$ in F1-F2/VANDA was 35% and 25% in ERY001, and L-ASP arms, respectively. At 12 mo, EFS rate was 65% and 49% in ERY001 and L-ASP arm, respectively. Treatment with ERY001 was well tolerated **Conclusions:** ERY001 provides an alternative option for patients with relapsed ALL, which is well tolerated and efficacious. Clinical trial information: NCT 01518517.

LBA7005 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Ibrutinib combined with bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): First results from a randomized, double-blind, placebo-controlled, phase III study. *First Author: Asher Alban Akmal Chanan-Khan, Mayo Clinic, Jacksonville, FL*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

LBA7006 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Results of the PERSIST-1 phase III study of pacritinib (PAC) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF). *First Author: Ruben A. Mesa, Mayo Clinic Cancer Center, Scottsdale, AZ*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

7007 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Long-term follow-up of patients with acute myelogenous leukemia receiving an autologous telomerase-based dendritic cell vaccine. *First Author: Hanna Jean Khoury, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: A phase II clinical trial was conducted in which subjects with AML were administered a telomerase-based dendritic cell immunotherapy (AST-VAC1; hTERT-DCs). The hTERT-DCs were prepared from leukapheresis collections from 33 subjects and were transfected with an mRNA encoding telomerase (hTERT) and the lysosomal sorting signal, LAMP-1, which enhances immunostimulatory activity. hTERT is essential for maintaining the proliferative capacity of tumor cells. **Methods:** AML patients were eligible to receive hTERT-DCs if they were in CR1 or CR2 with intermediate or high risk cytogenetics or if they were in early relapse with $<$ 20% marrow blasts. The hTERT-DCs were prepared after induction therapy and before or after completion of consolidation cycles. The hTERT-DCs were administered as 6 weekly followed by 6 biweekly intradermal injections. **Results:** Twenty-one patients (median age: 55) in complete remission (16 CR1 and 3 CR2) and or early relapse (2) received at least 3 injections of the hTERT-DCs. Only one grade 3 or 4 adverse event, (idiopathic thrombocytopenia), possibly related to the immunotherapy was observed during the first year. The two patients who were vaccinated during early relapse progressed rapidly and did not receive the full dosing regimen of hTERT-DCs. Of the 19 patients that were in CR, 14 received all 12 doses of hTERT-DCs. Fifty-eight percent (11/19) developed cellular immune responses to hTERT as assessed by peptide ELISpot analysis. Eleven of 19 patients (median follow-up 52 mos.) are still in remission as of last follow-up; seven developed detectable cellular immune responses to hTERT. Of the 19 CR patients, 7 were $\geq$ 60 yo at the time of hTERT-DC immunotherapy. Four of 7 patients $\geq$ 60 yo remain relapse free 52-59 months post DC-hTERT immunotherapy with all four developing immune responses to hTERT. The three patients that received DC-hTERT while in CR2 were in remission as of their last follow-up of 24, 50 and 59 months with two having hTERT immune responses. **Conclusions:** The results suggest that immunotherapy with hTERT-DCs is safe, can stimulate an immune response to telomerase, and may provide anti-tumor immune responses even in high risk patients with AML Clinical trial information: NCT00510133.

7008 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Allogeneic transplantation for myelofibrosis: Final analysis of a prospective study after a median follow up of 5 years. *First Author: Uday R. Popat, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We report final results of a prospective phase II clinical trial of busulfan(bu) and fludarabine(flu) conditioning in patients with myelofibrosis(MF). After observing a higher relapse rate in the initial cohort, we increased the intensity of conditioning regimen for subsequent patients. Here we report updated mature results with a median follow up of 5 years. **Methods:** Patients with advanced MF were eligible if they had adequate organ function and at least 9/10 HLA matched related or unrelated donor. Of the 46 patients, first 15 (bu low group) received IV busulfan 130 mg/m^2/day x 2 (day -3,-2). Of the remaining 31 (bu high group), 27 received IV busulfan dose to a target daily AUC of 4000 μmol.min x 4 (day -5 to -2) and 4 patients received a fixed dose of 100 mg/m^2/day x 4 (days -5 to -2). All patients received fludarabine 40mg/m^{2}x 4 (day -5 to -2). **Results:** 23 males and 23 females with a median age of 58 years (27-74) had intermediate (28) or high-risk (18) disease as per DIPSS plus criteria. Donors were matched sibs (19), matched unrelated (23), or mismatched unrelated (4). All patients engrafted with a median time to neutrophil engraftment of 13 (0-27) days and a median time to platelet engraftment of 24 (0-268) days. Cumulative incidence (CI) of grade II-IV, grade III, IV acute GVHD, and Chronic GVHD w 22%, 7%, and 40%, respectively. With a median follow up of surviving patients of 5.1 years (range 1-8.3 years), 3 year overall survival (OS), event-free survival (EFS), cumulative incidence (CI) of non-relapse mortality (NRM), and CI of relapse were 69%, 48%, 13%, and 39%, respectively. Multivariate analysis showed that Bu-high dose (HR 0.44; p = 0.07) was associated with lower relapse rate. Bu-high dose (HR 0.5; p = 0.09), DIPSS plus high (HR 2.69; P = 0.02) and Age (HR 1.05; P = 0.08) were predictors of EFS. DIPSS plus high (HR 5.99; P = 0.001) and Age (HR 1.07; P = 0.03) were adverse predictors of OS. **Conclusions:** Allogeneic transplantation results in long-term survival in patients with myelofibrosis with better outcome seen in earlier phase of the disease. PK guided myeloablative busulfan (AUC 16,000 μmol.min) appears promising in reducing relapse rate without increasing non-relapse mortality.

7009 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Association of reduced intensity conditioning (RIC) allograft (alloHCT) as first transplant approach in relapsed/refractory grade 3(G-3) follicular lymphoma (FL) with improved outcomes in long-term survivors. *First Author: Evgeny Klyuchnikov, Department for Stem Cell Transplantation, University Cancer Center, Hamburg, Germany*

Background: No studies to date have evaluated the role of RIC alloHCT compared to autologous (auto) HCT in pts with G-3 FL, in the rituximab-era. **Methods**: Adult pts with relapsed/refractory G-3 FL undergoing first RIC alloHCT or first autoHCT and reported to CIBMTR during 2000-12 were eligible. Pts with large cell transformation and those not receiving rituximab before HCT were excluded. **Results**: Characteristics of 197 pts included in this analysis are shown in the table below. AlloHCT pts were younger, more heavily pretreated, and had longer interval between diagnosis and HCT. The 5-yr adjusted probabilities of non-relapse mortality (NRM), relapse, progression-free survival (PFS) and overall survival (OS) of autoHCT vs. alloHCT groups were 4% vs. 27% (p < 0.0001); 61% vs. 20% (p < 0.0001); 36% vs. 51% (p = 0.06) and 59% vs. 54% (p = 0.7) respectively. 5-year incidence of second malignancies was similar (alloHCT = 8%; autoHCT = 9%). On multivariate analysis autoHCT was associated with reduced NRM (RR = 0.20; p = 0.001). Within the first 11 months post HCT, auto- and alloHCT were similar in terms of relapse and PFS. Beyond 11 months post HCT, autoHCT was associated with higher relapse (RR = 21.8; p = 0.003) and worse PFS (RR = 3.2; p = 0.005). In the first 24 months post HCT, autoHCT was associated with improved OS (RR = 0.42; p = 0.005), but beyond 24 months it was associated with lower OS (RR = 3.6; p = 0.04). **Conclusions**: RIC alloHCT as first transplant approach can provide better long-term survival outcomes for G-3 FL.

Table	AlloHCT (%)	AutoHCT (%)	P-value
	61	136	
Median age, years	53 (36-64)	57 (27-76)	0.01
KPS ≥ 90	42 (69)	86 (63)	0.21
Stage III-IV at diagnosis	52 (85)	105 (77)	0.11
Prior rituximab-resistance	30 (49)	84 (62)	0.12
Median lines of therapy	3 (1-5)	3 (1-5)	0.01
Duration of first response			0.31
< 1 year	22 (36)	44 (32)	
≥ 1 year	34 (56)	87 (64)	
Time from diagnosis to HCT, months	32 (5-159)	24 (6-224)	0.02
Type of donor			
Matched sibling	36 (59)		
8/8 MUD	23 (38)		
7/8 MUD	2 (3)		
PB graft	58 (95)	135 (99)	0.05
TBI in conditioning	9 (15)	8 (6)	0.04
Chemosensitive at HCT	49 (80)	123 (90)	0.07
Median follow up	57 (5-132)	59 (3-145)	

7010 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Efficacy and safety of CD19-targeted 19-28z CAR modified T cells in adult patients with relapsed or refractory B-ALL. *First Author: Jae Hong Park, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Adult patients (pts) with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL) have dismal prognosis. We previously reported high anti-tumor activity of autologous T cells genetically modified to express 19-28z chimeric antigen receptor (CAR) targeting CD19 in adult pts with ALL. Herein, we report the long-term outcome of our phase I trial in adults with R/R ALL (NCT01044069). **Methods:** Adult pts with R/R B-ALL underwent leukapheresis, and T cells were transduced with a gammaretroviral vector encoding a CAR construct composed of anti-CD19 scFv linked to CD28 and CD3ζ signaling domains (19-28z). All pts received conditioning chemotherapy followed by 1–3x10^6 19-28z CAR T cells/kg. **Results:** 33 pts have been treated, and 32 pts are evaluable for response. The median age was 54 years (range, 22-74). 12 pts (36%) had Ph+ ALL, 11 pts (33%) had prior allogeneic stem cell transplant (allo-SCT), and 14 pts (42%) had ≥ 3 prior lines of therapy. At the time of CAR T cell infusion, 16 had morphologic disease (> 5% blasts in BM) and the remaining 16 pts had minimal residual disease (MRD). 13/16 pts with morphologic disease (81%) and 16/16 pts with MRD (100%) were in complete remission (CR) after 19-28z CAR T cell infusion, yielding an overall CR rate of 91% (29/32). Of the 28 MRD evaluable patients, MRD negative CR rate was 82%. 11 pts underwent allo-SCT following the CAR T cells. As of 1/25/15, the median follow-up was 5.1 months (range, 1.0-37.6+), with 14 pts having ≥ 6 months of follow-up. 6-month overall survival (OS) rate of all patients was 58% (95% CI: 36-74). Among the pts who achieved CR, OS rate at 6 months for pts who had allo-SCT vs. no allo-SCT following CAR T cells was 70% (95% CI: 33-89) vs. 61% (95% CI: 29-82; p = 0.30). Severe cytokine release syndrome (sCRS) requiring vasopressors or mechanical ventilation for hypoxia was observed in 7 patients, effectively managed with IL-6R inhibitor and/or corticosteroids. **Conclusions:** 19-28z CAR T cells can induce a high CR rate of 91% in adult patients with R/R ALL. The risk of sCRS correlates with disease burden and can be effectively managed. These findings strongly support the use of 19-28z CAR T cells in adults with R/R ALL and warrants investigation in a phase II trial. Clinical trial information: NCT01044069.

7011 Poster Discussion Session; Displayed in Poster Session (Board #1), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Long-term follow-up of a phase Ib trial of idelalisib (IDELA) in combination with chemoimmunotherapy (CIT) in patients (pts) with relapsed/refractory (R/R) CLL including pts with del17p/*TP53* mutation. *First Author: Jacqueline Claudia Barrientos, Hofstra North Shore - LIJ School of Medicine, New Hyde Park, NY*

Background: IDELA is a first-in-class PI3Kδ inhibitor approved in combination with rituximab for pts with relapsed CLL. **Methods**: Pts with R/R CLL were treated continuously with 150 mg BID oral IDELA and a limited # of cycles (C) of CIT to evaluate safety and efficacy of combination regimens. Pts could enroll in extension study after 48 wks. Responses were evaluated by published criteria (Hallek 2008; Cheson 2012). **Results**: 114 pts (37F/77M) median (med) age 65 (range 41-87) yrs enrolled with: extensive prior therapies (med 3, range 1-9), refractory disease (51%), high risk Rai (60%), del17p/*TP53* mutation (29%), del11q (13%), unmutated *IGHV* (79%). Med exposure was 14.6 (range 0-49) mos. 61 pts (54%) enrolled in extension study. 21 (34%) were continuing on study. Most common and select AEs independent of causality (any Grade/Gr ≥ 3): diarrhea/colitis (52%/19%), pyrexia (45%/4%), cough (37%/1%), nausea (29%/1%), fatigue (32%/4%), pneumonia (23%/15%), dyspnea (22%/3%), rash (21%/4%), pneumonitis (4%/4%). AST/ALT elevation Gr ≥ 3 was seen in 12%. Most common reasons for discontinuation were AEs (25%) or PD (25%). 2 pts discontinued due to AST/ALT elevation, 1 due to Richter's transformation. 20 (18%) deaths were reported on study; 6 pts experienced PD before death. ORR was 82.5% in all pts, 70% in pts with del17p/*TP53* mut, and 87% among pts without. SD/PD was reported in 10%/3%. Med overall PFS was 26.1 mos, 20.3 mos for pts with del17p/*TP53* mut, and 36.8 mos for pts without. Med OS for all pts or pts with del17p/*TP53* mut was not reached. Estimated OS at 36 mos was 73.1% for all pts, 57.3% for pts with del17p/*TP53*, and 78.3% for pts without. **Conclusions**: IDELA in combination with CIT shows a manageable safety profile without increased toxicities and has substantial clinical activity in heavily pretreated, refractory, and high-risk CLL including presence of del17p/*TP53*mutation. Phase 3 trials of IDELA with O or BR in pts with R/R CLL are ongoing (NCT01659021, NCT01732926). Clinical trial information: NCT01088048.

Idelalisib +.						
Rituximab (R) N=19	Ofatumumab (O) N=21	Bendamustine (B) N=18	BR N=15	Fludarabine (F) (oral) N=12	Chlorambucil (Chl) N=15	ChlR N=14
8 wks		up to 6 C			up to 12 C	

7012 Poster Discussion Session; Displayed in Poster Session (Board #2), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Dose adherence and baseline exposure analysis of the ibrutinib 420 mg dose administered to patients with previously treated chronic lymphocytic leukemia (CLL). *First Author: Paul M. Barr, Wilmot Cancer Institute, University of Rochester, Rochester, NY*

Background: Ibrutinib (ibr), a first-in-class, once-daily, oral, covalent inhibitor of Bruton's tyrosine kinase (BTK), is rapidly eliminated from plasma after oral administration (Advani, JCO 2013). Complete or near complete BTK active site occupancy (median > 90%) is achieved at 4 hours and maintained at 24 hours with ibr 420 mg once-daily (O'Brien, Lancet Oncology 2013). At 140 or 280 mg doses, fewer patients (pts) attained complete BTK occupancy (Poggesi, AACR 2014). This analysis evaluated the effect of the ibr 420 mg once-daily dose on IRC-assessed progression-free survival (PFS) in pts with previously treated CLLfrom thephase 3 RESONATE trial. **Methods**: Dose intensity (DI) was defined as the proportion of actually administered vs planned doses of 420 mg. DI was also defined in first 8 weeks to compare statistically with post-week 8 PFS. Steady-state AUC/C_{max} was estimated per NONMEM modeling using 2 timepoint samples (weeks 1 and 4). Missed doses had to be consecutive. **Results**: Ibr-treated pts (n = 195) had a mean DI of 95% (median 100%) with 8.3 months of treatment. The majority of dose interruptions restarted at 420 mg; 3.6% of pts had 1 and 0.5% had 2 dose reductions due to AEs. Pts with higher DI experienced longer PFS (median NR) compared to lower DI (11 months). Using an adjusted mean DI of 96% in first 8 weeks and post week-8 PFS, this trend was confirmed with HR = 0.4 (P= 0.0127). Pts with higher DI had a lower rate of progression regardless of del17p, p53 mutation, or del11q CLL. In 179 pts receiving ibr 420 mg with PK assessment at weeks 1 and 4, no difference was seen in median PFS with lower vs higher ibr exposure (AUC or C_{max}). There were fewer PFS events in pts not missing (n = 136) vs those missing (n = 59) ibr doses for ≥ 8 consecutive days (13% vs 31%, respectively), with median PFS of NR vs 11 months, respectively. The mean duration of these missed doses was 26 days. **Conclusions**: A higher mean dose intensity of ibr is associated with improved PFS, with patients missing more than 1 week of treatment experiencing more PFS events. These results, and the established clinical profile, support the clinical utility of sustained adherence to the once-daily 420 mg dose of ibr in patients with previously treated CLL. Clinical trial information: NCT01578707.

7013 Poster Discussion Session; Displayed in Poster Session (Board #3), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Prognostic testing patterns in CLL pts treated in U.S. practices from the Connect CLL registry. *First Author: Anthony Mato, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Genetic aberrations detected by fluorescence in situ hybridization (FISH) and cytogenetic (CG) testing provide prognostic information for CLL pts. The identification of genetic abnormalities has particular relevance in choosing immunochemo- or kinase inhibitor therapies, SCT or clinical trial. Here, we analyze factors influencing decisions to perform FISH or CG testing. **Methods:** Connect CLL is a large, prospective, longitudinal, multicenter, observational registry of 1494 CLL pts at 179 community (n=1,311), 17 academic (n=155), and 3 government (n=28) sites. Pts were enrolled within 2 months of initiating any line of therapy (LOT). Univariate (UV) and multivariate (MV) logistic regression analyses were conducted to identify characteristics associated with a decision to perform genetic testing at LOT1 and at LOT≥2. **Results:** FISH or CG was performed at study enrollment in 861/1,494 (58%) pts (36% CG, 49% FISH, 28% both). 65% of 889 pts were tested for FISH/CG prior to LOT1, 50% of 260 in LOT2, 45% of 345 in LOT>3. Of 861 pts tested at enrollment, 29% had FISH/CG retested with a subsequent LOT. In UV analyses (14 predictors), FISH/CG were more often performed at academic sites (p .005), in pts age ≤75 (p .0002), at enrollment at LOT1 vs. LOT ≥2 (p < .0001), in private insurance pts (p .002) and Rai stage ≥2 (p<.0001). Table 1 describes independent predictors of performing genetic testing stratified by LOT and practice setting. **Conclusions:** Our results indicate that only a fraction of CLL pts are tested/re-tested for genetic alterations by FISH/CG. Given the significance of identifying del17p or complex CG in selecting each LOT, these results indicate a need for increased awareness of the importance of this testing.

MV analysis: Predictors of FISH/CG.

Time point/Practice setting	Covariate	OR 95% CI
LOT1/All sites	Academic vs community-govt site	1.76 1.03-2.99
	White vs other	1.90 1.13-3.17
	Private insurance	1.44 1.08-1.92
LOT1/Community-Govt sites	White vs other	2.40 1.26-4.58
	Age≤75 vs. < 75	1.44 1.01-2.05
	RAI stage ≥2 vs. 1	1.52 1.07-2.14
LOT≥2:/All sites		
	White vs other	0.34 0.17-0.68
	Age≤75	1.45 1.01-2.07
LOT≥2/Community-Govt sites	White vs other	0.41 0.16-1.04
	Age≤75	1.65 1.05-2.61
	RAI stage ≥2	1.74 1.12-2.71

7014 Poster Discussion Session; Displayed in Poster Session (Board #4), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Association of relapse of FLT3-ITD AML with normal karyotype with internal tandem duplication allelic burden, base-pair insertion length, and NPM1 status. *First Author: Sarah L Sammons, Division of Hematology/Oncology, Department of Medicine, University of Maryland Greenebaum Cancer Center, Baltimore, MD*

Background: FMS-like tyrosine kinase internal tandem duplication (FLT3-ITD) mutation in normal karyotype AML (NK-AML) is a poor prognostic feature. The prognostic significance of the mutant to wild type allelic ratio and base pair insertion length (bpInsLng) of FLT3-ITD with or without Nucleophosmin (NPM1) mutation remains controversial in this population. **Methods:** The medical records of 149 patients with NK-AML were reviewed (2007-2014) including subject and disease characteristics, and treatment outcomes. Patients with any cytogenetic abnormality were excluded. Treatment failure was defined as relapsed or refractory disease after chemotherapy regardless of transplant. Death of any causes was considered an event. A FLT3-ITD mutation was detected as the presence of a migrating PCR product larger than the wild-type product (330-bp). ITD allelic burden (AB) was calculated as the ratio of ITD to wild type allele expressed as a percentage. Time to failure was analyzed using the Kaplan-Meier estimate and the Mantel-Cox logrank test. Patients who were alive with no evidence of disease at the last follow-up were treated as censored observations. The protocol was approved by the IRB. **Results:** The mean age of patients was 58±14 years (range 22-88). FLT3 mutation status was available in 139 cases; 45 (30.2%) carried FLT3-ITD with assessment of AB and bpInsLng available in 29. The median ITD AB was 33% (range 3-433). For the time to failure analysis patients were classified as low or high allelic burden using the median value as the cut point. The median length of the mutant fragment was 372-bp (range 345-500). NPM1 mutation was detected in 38 (26%) patients. In FLT3-ITD population regardless of NPM1 status, patients with AB higher than median value (33%) had significantly higher hazard rate of treatment failure than those with low AB (hazard ratio = 5.4, 95% CI: 1.5-19.5, p = 0.004). ITD bpInsLng lower or higher than the population median value did not predict treatment failure rate (p = 0.6). **Conclusions:** In patients with FLT3-ITD NK-AML, ITD AB > 33% can significantly predict higher relapse rate irrespective of mutant bpInsLng and NPM1 status.

7015 Poster Discussion Session; Displayed in Poster Session (Board #5), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Activity of the mitochondrial metabolism inhibitor cpi-613 in combination with high dose Ara-C (HDAC) and mitoxantrone in high risk relapsed or refractory acute myeloid leukemia (AML). *First Author: Timothy S. Pardee, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC*

Background: CPI-613 is a novel agent that targets mitochondrial metabolism. It inhibits mitochondrial respiration in AML cells and in a single agent phase I study was active for several patients with myeloid malignancies-.This trial was designed to determine the maximum tolerated dose (MTD) and efficacy of CPI-613 in combination with HDAC and mitoxantrone in relapsed or refractory AML. **Methods:** CPI-613 was given daily on days 1 through 5 starting at a dose of 500 mg/m^2. Beginning on day 3, HDAC (3,000 mg/m^2 or 1,500 mg/m^2 for age ≥ 60) was given every 12 hours for 5 doses and mitoxantrone at 6 mg/m^2 was given daily for 3 doses. If residual disease was present on day 14, a second cycle could be given. Patients who achieved a complete remission with or without complete count recovery (CR or CRi) could receive additional cycles with the goal of stem cell transplantation when possible. **Results:** A total of 48 patients are evaluable. The median age is 60 (range 21-79). Fourteen patients had refractory disease and 11 received one or more previous lines of salvage therapy. Cytogenetics were poor risk in 23, intermediate in 20, good in 4 and one patient had CML blast crisis. The overall response rate was 48% (19CR+4CRi). Three of five patients with FLT3 mutations achieved a CR/CRi (60%). Patients age ≥ 60 had a CR/CRi rate of 46% (12/26). Surprisingly, patients with poor-risk cytogenetics had a CR/CRi rate of 48% (11/23). In a historical cohort of poor-risk patients treated with HDAC, mitoxantrone and asparaginase, only 25% responded. Median survival for the entire cohort is 6.4 months. Six patients (12.5%) died on or before day 30. The CPI-613 dose has been escalated to 2750 mg/m^2 with the MTD not yet determined. Stem cell transplantation was performed on 23% (11/48) of patients. Samples from patients before and after CPI-613 showed induction of phosphorylation of the E1α subunit of pyruvate dehydrogenase and AMPK consistent with the proposed mechanism of action. **Conclusions:** CPI-613 in combination with HiDAC and mitoxantrone is a promising salvage regimen and these data support additional studies especially in older patients and those with high-risk disease. Clinical trial information: NCT01768897.

7016 Poster Discussion Session; Displayed in Poster Session (Board #6), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Safety and tolerability of the combination of ATRA + arsenic trioxide (ATO) + gemtuzumab ozogamicin (GO) in high-risk acute promyelocytic leukemia (APL): Initial report of the SWOG/Alliance/ECOG S0535 trial. *First Author: Jeffrey E. Lancet, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: High-risk APL remains a therapeutic challenge, with significant rates of early mortality and relapse. Recent evidence confirmed excellent outcomes in low-risk APL with the combination of ATO and ATRA (Lo-Coco, NEJM 2013), and a previous pilot study indicated the efficacy of a combination of ATO + ATRA + GO in a subset of high-risk APL (Ravandi, JCO 2009). SWOG designed a larger phase 2 study to confirm the safety and efficacy of this combination in high-risk APL. **Primary Objectives**: 1) assessment of early (6 week) death rate; 2) assessment of 3-year continuous complete remission (CCR) **Methods:** Adult patients with newly diagnosed high-risk APL (WBC $\geq$ 10k/uL) were eligible. Induction therapy consisted of: ATRA (45 mg/m^2/day) - day 1 until CR; ATO (0.15 mg/kg/day) – day 10 until CR; GO 9 mg/m^2- day 1. Patients in CR received consolidation with ATO x 2 cycles, followed by ATRA + daunorubicin x 2 cycles, followed by GO x 2 cycles. Subsequent maintenance therapy consisted of ATRA + 6-MP + methotrexate for up to 1 year. **Results:** From 2008 to 2013, 73 patients were enrolled and evaluable for toxicity. Median age was 46.5 years, with 52% females and 48% males. Sixty-two (85%) patients completed induction therapy as planned, and 48 patients (66%) completed all planned consolidation. Six of 73 patients (11%) died within 6 weeks of treatment initiation (95% confidence interval 6-21%), supporting rejection of the null hypothesis (30% early death rate). The most common treatment-emergent grade 3-4 adverse events (AE) during induction included: febrile neutropenia (33%), AST/ALT elevation (12%), hypoxia/differentiation syndrome (11%), hyperglycemia (11%), headache (11%), prolonged QTc (11%). Amongst 59 patients receiving consolidation, the most common treatment-emergent grade 3-4 AEs included: febrile neutropenia (52%), headache (14%), fatigue (14%), and nausea (12%). The efficacy analysis of CCR is ongoing. **Conclusions:** The combination of ATO + ATRA + GO appears safe and well-tolerated in patients with high-risk APL, with an acceptable early mortality rate. 3-year CCR assessment is not yet mature. Clinical trial information: NCT00551460.

7017 Poster Discussion Session; Displayed in Poster Session (Board #7), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Correlation of overall survival (OS) with bone marrow blast (BMBL) response in patients (pts) with myelodysplastic syndrome. *First Author: Lewis R. Silverman, Mount Sinai Medical Center, New York, NY*

Background: BMBL % is the prognostic variable with the greatest impact on outcome in MDS patients at diagnosis and subsequent time points. Current composite response criteria (IWG, Cheson 2006) do not consistently correlate with OS. Treatment impact of BMBL as an independent response criterion has not been adequately evaluated. **Methods:** We evaluated the correlation between OS and BMBL in pts with higher-risk (HR) MDS from 4 datasets from 7 studies with 887 pts: ONTIME, a Phase III randomized study of 2nd-line rigosertib (RIG) vs best supportive care (BSC) (N = 299; Silverman, ASH 2014); 4 Phase I/II studies of RIG in pts with MDS/AML (N = 39; Silverman, Hematol Oncol 2014); AZA-001, a Phase III study of azacitidine (AZA) vs 3 conventional care regimens (N = 358; Fenaux, Lancet Oncol 2009; Gore, Haematologica 2013); Cancer & Leukemia Group B (CALGB) Study 9221, a Phase II, randomized trial of 1st-line AZA vs BSC (N = 191; Silverman, J Clin Oncol 2002). Change in blasts was defined similarly: BM complete response is BMBL $\leq$ 5% and $\geq$ 50% decrease from baseline; BM partial response is $\geq$ 50% decrease from baseline, but BMBL still $>$ 5%; stable disease is $<$ 50% decrease or increase from baseline. **Results:** In ONTIME, landmark time-dependent analyses showed correlation of BMBL response/stabilization with OS at 4 wks (P= 0.011) and 12 wks ($P<$ 0.001). In the 4 Phase I/II studies, BMBL response/stabilization at 4–8 weeks was associated with a quadrupling of median OS ($P<$ 0.001). In Study AZA-001, time-dependent analysis of BMBL stabilization was associated with a significantly reduced risk of death in both treatment cohorts ($P<$ 0.001). In Study 9221, landmark analysis of BMBL response/stabilization showed a 6-fold improvement in OS ($P<$ 0.001). **Conclusions:** These studies, spanning more than a decade with different therapeutic agents and settings, demonstrate a consistent positive correlation between BMBL response and OS in pts with HR-MDS, including pts on supportive care. This suggests that use of reduction/stabilization in BMBL can serve as a new early response parameter, as an intermediate clinical endpoint for evaluation of new agents, and as a biomarker for disease progression in HR-MDS itself.

7018 Poster Discussion Session; Displayed in Poster Session (Board #8), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Effect of long noncoding RNA *RUNXOR* on the epigenetic regulation of *RUNX1* in acute myelocytic leukemia. *First Author: Hong Wang, Cancer Center, First Hosipital of Jilin University, Changchun, China*

Background: *RUNX1*, a master regulator of hematopoiesis, is the most commonly perturbed target of chromosomal abnormalities in hematopoietic malignancies. About 30%–40% of acute myeloid leukemia (AML) patients carry the t(8;21) translocation. However, little is known regarding the molecular mechanisms underlying *RUNX1*-associated translocation. Long non-coding RNAs (lncRNAs) have been implicated in a variety of important biological processes by epigenetic mechanisms. **Methods:** Using a novel R3C (**R**NA-guided **C**hromatin **C**onformation **C**apture) method developed in our lab, we identified lncRNAs that participate in the regulation of *RUNX1 in AML*. Full length of lncRNAs was characterized by Marathon cDNA Amplification Kit. Expression of lncRNAs in AML was quantitated by qPCR. Reverse transcription-associated trap (RAT) and chromatin conformation capture (3C) assays were used to map DNA/RNA interaction. The protocol of AML patients bone marrow and peripheral blood cell samples was approved by the Human Medical Ethical Review Committee from Jilin University First Hospital and informed consent was obtained from each AML patient and normal donor. **Results:** 1)We discovered a novel intragenic 216 kb long noncoding RNA within the *RUNX1* locus, named *RUNXOR* (***RUNX1*** **o**verlapping **p**romoter-derived **n**oncoding **R**NA). *RUNXOR* was transcribed from an upstream promoter that overlaps all of the *RUNX1* gene's exons and introns. 2) *RUNXOR*lncRNA was overexpressed both in AML cell lines and AML patients' bone marrow, and was upregulated by Chemotherapeutic drug Ara-C. 3) *RUNXOR* lncRNA interacted with the promoter and enhancer of *RUNX1*. By recruiting histone methyltransferase EZH2, it induced H3K27 modification and epigenetically regulated *RUNX1*. 4) Using the 3C assay, we showed that *RUNXOR* interacted with the most frequent translocation break regions in translocation related genes, including *EVI1, ETO, TEL*, and *CBFA2T3*. **Conclusions:** This study identifies *RUNXOR* as a novel lncRNA involved in long range DNA interaction of *RUNX1 in AML*. The lncRNA may function as a putative tumor suppressor by epigenetically regulates *RUNX1* and scaffolds the translocation associated DNA in AML.

7019 Poster Discussion Session; Displayed in Poster Session (Board #9), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

NFAT2 to regulate anergy induction in CLL through Lck. *First Author: Melanie Maerklin, Department of Hematology, Oncology and Immunology, University of Tuebingen, Tuebingen, Germany*

Background: NFAT2 is a highly phosphorylated transcription factor which regulates developmental and activation programs in diverse cell types. CLL constitutes a heterogeneous disease with some patients exhibiting an indolent course for many years and others progressing rapidly and requiring early treatment. A defined subgroup of patients shows enhanced responsiveness to stimulation of the B cell receptor (BCR) complex and more aggressive disease. In contrast, another subset of CLL patients with more indolent course is characterized by an anergic B cell phenotype referring to B cell unresponsiveness to IgM ligation. Here, we analyzed the role of NFAT2 in the pathogenesis of CLL and in anergy induction in CLL cells. **Methods:** We crossed conditional CD19-Cre NFAT2 knock out mice with the Eμ-TCL1 transgenic mice, which develop a human-like CLL. We analyzed TCL1+NFAT2 ko mice and TCL1 mice without a NFAT2 deletion served as controls. We performed a comparative gene expression analysis, Ca^{2+}mobilization assays and Western Blots for multiple downstream signaling molecules on both CLL cells. **Results:** Mice with NFAT2 ko exhibited a significantly more aggressive disease course with accelerated accumulation of CLL cells and a dramatically reduced life expectancy. We detected a substantially altered expression profile of genes associated with B cell anergy in the TCL1+NFAT2 ko mice. The vast majority of these genes was expressed significantly less in the absence of NFAT2 with Lck, Pacsin1 and Cbl representing the biggest hits. While anergic CLL cells from TCL1 mice exhibited an unresponsive phenotype with respect to Ca^{2+} flux upon IgM ligation, TCL1+NFAT2 ko mice showed a normal capacity to mobilize $Ca^{2+}$and a normal activation of the downstream signaling. IgM stimulation did not activate normal phosphotyrosine induction in TCL1 mice. However TCL1 mice showed a strong activation of the anergy regulator Lck. **Conclusions:** Genetic loss NFAT2 leads aggressive disease and controls the expression of several important anergy-associated genes. We identified Lck as a critical target of NFAT2 in this context. Taken together, our data demonstrate that the NFAT2-Lck axis plays an essential role in the pathogenesis of CLL and implicate it as a potential target in its treatment.

7020 Poster Discussion Session; Displayed in Poster Session (Board #10), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

GATA-1, FOG-1, and FLI-1 regulation in essential thrombocythemia independently from JAK2 and CALR mutations. *First Author: Ciro Roberto Rinaldi, University of Lincoln, Lincoln, United Kingdom*

Background: GATA-1 is the founding member of the GATA transcription factor family and it is essential for cell maturation and differentiation within the erythroid and megakaryocytic lineages. We and others have demonstrated that elevated GATA-1 expression is found in the bone marrow of Essential Thrombocythemia (ET) patients, independent of *JAK2V617F* and *CALR* mutations. GATA-1 is able to coordinate lineage specification through its ability to bind both DNA and protein partners that include; Friend of GATA (FOG-1) and the Friend leukemia integration 1 (FLI-1) transcription factors. FOG–1 is vital for megakaryocyte and erythroid–lineage commitment and its expression largely overlaps spatiotemporally with that of GATA-1. FLI-1 is an ETS family member that is expressed at high levels in megakaryocytic progenitors. In conjunction with GATA-1, FLI-1 targets those genes responsible for megakaryopoiesis. **Methods:** Following on from our earlier work we analyzed the expression levels of GATA-1 in relation to its interacting transcription factors, FOG-1 and FLI-1 in megakaryocyte development. Peripheral blood specimens were collected from 36 patients diagnosed with ET, 17 JAK2 mutated (47%), 4 CALR (11%) mutated, 1 MPL mutated (3%) and 14 with no molecular abnormalities, and compared with a cohort of healthy volunteers. Samples were enriched for the mononuclear fraction by Ficoll separation. Total RNA was extracted and analyzed by Real Time PCR for GATA-1, FOG-1 and FLI-1 expression relative to the housekeeping gene GAPDH using the $2^{-\Delta\Delta CT}$ method. **Results:** We confirmed the data obtained in bone marrow demonstrating that GATA-1 is significantly up-regulated in ET patients and that GATA-1 overexpression is independent from *JAK2V617F* and *CALR* mutations. However, the transcription factors FOG-1 and FLI-1 do not appear to be subject to the same regulatory control in ET as that of GATA-1. **Conclusions:** These results suggest that GATA-1 is specifically deregulated in essential thrombocythemia.

7021 Poster Discussion Session; Displayed in Poster Session (Board #11), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

A multi-institution phase I trial of ruxolitinib in chronic myelomonocytic leukemia (CMML). *First Author: Eric Padron, Moffitt Cancer Center, Tampa, FL*

Background: CMML is a lethal myelodysplastic/myeloproliferative neoplasm (MDS/MPN) characterized by peripheral monocytosis and bone marrow (BM) dysplasia with limited therapeutic options. Preclinical studies have identified the JAK2 inhibitors as therapeutic candidates. We conducted the first phase 1 clinical trial exploring the safety and efficacy of ruxolitinib, an FDA approved JAK1/2 inhibitor, in patients with CMML. **Methods:** All CMML WHO subtypes were included without regard to previous therapy. Key exclusion criteria included an ANC $< 0.25x10^3$ c/dL and a platelet count $< 35x10^3$c/dL. The use of GM-CSF analogs was prohibited. Four cohorts were enrolled using a "rolling six" study design, with doses ranging from 5mg BID to 20mg BID in 5mg dose escalations. Descriptive statistics were used to report baseline characteristics and response rates. The study was registered at clinicaltrials.gov NCT01776723 **Results:** Between March 2013 and January 2015, 19 patients (pts) were enrolled and treated with ruxolitinib. The Median age was 71 years and all pts had CMML-1. MPN-CMML by FAB criteria constituted 67% of pts and 47% had higher-risk disease by the Global MD Anderson Scoring System. Eleven pts (58%) received prior therapy and 8 pts (42%) received a prior hypomethylating agent. No dose limiting toxicities for ruxolitinib were identified. One subject had Grade (G)3 thrombocytopenia with no other drug-associated G3 or G4 adverse events. The mean duration of therapy was 122 days (range, 28-409 days). Of 15 pts evaluable for response, 3 had hematologic improvement and one pt had a partial response per 2006 IWG criteria. Six of 9 pts with splenomegaly had a $> 50\%$ reduction in spleen size. Fourteen of 15 pts with reported B-symptoms had clinically meaningful or complete resolution on ruxolitinib. There was no change in allelic burden of somatic mutations in responders; broad spectrum cytokine profiling will be available at the time of presentation. **Conclusions:** The recommended phase 2 dose of ruxolitinib is 20mg BID. We demonstrate that ruxolitinib has promising activity in CMML with particular benefit in those with disease related B-symptoms. A phase 2 study is planned to further test the efficacy of ruxolitinib in CMML. Clinical trial information: NCT01776723.

7022 Poster Discussion Session; Displayed in Poster Session (Board #12), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Propensity score analysis: Frontline therapy with high-dose (HD) imatinib vs. 2nd generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia in chronic phase. *First Author: Koji Sasaki, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The clinical efficacy of the second generation of tyrosine kinase inhibitors (TKI) has not been compared to that of HD imatinib in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP). **Methods:** Response and survival for 374 pts with newly diagnosed CML-CP enrolled in four consecutive or parallel prospective clinical trials of imatinib 800 mg daily, dasatinib, or nilotinib were analyzed. Logistic regression was used for propensity score (PS) calculation from baseline pt characteristics including age at diagnosis, gender, race, Sokal scores, white blood cell, hemoglobin, platelet, blasts in peripheral blood and bone marrow, albumin, urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, the proportion of Philadelphia chromosome by conventional karyotype and fluorescence in situ hybridization, the presence of clonal evolution, the type of BCR-ABL transcript, and time from diagnosis to therapy. PS analysis with 1:1 matching was performed with the nearest matching method. The Kaplan-Meier method was used to calculate OS, EFS, TFS, and FFS. **Results:** Of the 374 pts analyzed, 158 were treated with HD imatinib, 109 with nilotinib, and 107 with dasatinib. The median follow-up was 124 months, 49 months, and 54 months, respectively. PS matching identified 81 pts in imatinib vs. dasatinib and 84 pts in imatinib vs. nilotinib, respectively. The cumulative best response, five-year OS, EFS, TFS, and FFS are summarized in the table below. **Conclusions:** High-dose imatinib may have similar efficacy compared to second generation TKIs without clear difference in response or long-term survival endpoints.

Main outcomes after PS matching.

	IM800 [n = 84]	Nilotinib [n = 84]	P	IM800 [n = 81]	Dasatinib [n = 81]	P
BCR-ABL < 10% at 3 months	96	94	.724	97	95	.683
Cumulative Response within 1 year, (%)						
CMR	19	18	.945	21	16	.511
MR4.5	49	42	.670	46	42	.847
MMR	83	82	.247	81	77	.878
CCyR	93	93	.540	89	91	.248
Cumulative Response within 3 year, (%)						
CMR	35	26	.306	33	30	.612
MR4.5	64	55	.325	64	65	.869
MMR	90	87	.939	88	85	.646
CCyR	94	89	.708	90	93	.576
5-y Outcome, (%)						
FFS	72	70	.989	69	75	.679
TFS	96	90	.361	92	93	.685
EFS	89	87	.728	82	90	.210
OS	94	92	.863	91	98	.219

7023 Poster Session (Board #), Sun, 8:00 AM-11:30 AM

Results of a phase III randomized, controlled study evaluating the efficacy and safety of idelalisib (IDELA) in combination with ofatumumab (OFA) for previously treated chronic lymphocytic leukemia (CLL). *First Author: Jeffrey Alan Jones, Ohio State University, Columbus, OH*

Background: IDELA (Zydelig) is a selective oral PI3Kδ inhibitor approved in combination with rituximab for previously treated pts with CLL. This open-label study (NCT01659021) compared IDELA + OFA v OFA in pts with relapsed CLL. **Methods**: Pts with CLL progressing ≤ 24 mo from last therapy, who had received ≥ 2 cycles of a purine analogue or bendamustine, were randomized 2:1 to either Arm A (IDELA 150 mg BID continuously plus OFA, 300 mg IV wk 1, then 1 gm IV wkly x 7 and q 4 wk x 4) or Arm B (OFA, same as Arm A except 2 gm was substituted for 1 gm dosing). Stratification was performed for relapsed v refractory, del17p and/or TP53 mutation, and *IGHV* mutation. IRC-assessed response and PD based on imaging using modified IWCLL 2008 criteria. The 1° endpoint was PFS and 2° endpoints were confirmed ORR, lymph node response (LNR), OS, PFS in pts with del(17p) and/or TP53 mutation, and CR rate. Results are from the final analysis. **Results:** Pt attributes were balanced in the 2 arms: Med age 67; Rai II/III/IV 18/13/51%, med no. prior regimens 3, refractory 49%, del17p/TP53mut 40%, *IGHV* unmut 78%. Exposure, disposition, and efficacy are shown in Table. Results were consistent across risk groups. Gr ≥ 3 AEs in Arm A included diarrhea/colitis (20.2%), pneumonia (12.7%), and febrile neutropenia (11.6%). **Conclusion:** IDELA + OFA yielded superior PFS, ORR, and LNR compared to OFA in relapsed CLL, including within high-risk subgroups. Safety was manageable with a profile similar to that previously observed in CLL trials. The open label design may have led to an imbalance in dropout, with a higher rate in Arm B. Clinical trial information: NCT01659021.

	Arm A (IDELA/OFA)	Arm B (OFA)	HR / OR[2]
Pts randomized/dosed	174/173	87/86	
Months on study (range)	13.6 (1.1-24)[1]	5.8 (0-20)	
Reason for study D/C[3] (%)			
PD	34 (19.5)	41 (47.1)	
Death	22 (12.6)	6 (6.9)	
AE / MD decision	21 (12)	19 (21.8)	
Withdrew consent/other	13 (7.5)	15 (17.2)	
Med PFS, mo	16.3	8.0	HR = 0.27, p < 0.0001[4]
ORR, %	75.3	18.4	OR = 15.9, p < 0.0001[4]
LNR, %	93.3	4.9	OR = 487, p < 0.0001[4]
Med OS, mo	20.9	19.4	HR = 0.74, p = 0.27
Med PFS: del17p/TP53mut, mo	13.7	5.8	HR = 0.33, p < 0.0001

[1]IDELA med exposure 12.3 mo (0.2-23.9); [2]odds ratio; [3]per MD; [4]null hypothesis formally rejected.

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7024 Poster Session (Board #13), Sun, 8:00 AM-11:30 AM

A multicenter open-label phase 1b/2 study of ibrutinib in steroid dependent or refractory chronic graft versus host disease (cGVHD). *First Author: David Bernard Miklos, Stanford University, Stanford, CA*

Background: Chronic GVHD (cGVHD) is a common and serious complication after allogeneic stem cell transplantation (SCT). Both B and T cell-mediated mechanisms have been implicated in the pathophysiology of cGVHD. There are no approved therapies for cGVHD. In murine models, ibrutinib (ibr) reduces the severity of cGVHD (Dubovksy JCI 2014). In humans, ibr was tolerable in post-SCT patients (pts) and may improve donor chimerism and/or graft-vs-leukemia effects while reducing cGVHD (Miklos ASH 2014, Coutre ASH 2014). **Methods**: This ongoing phase 1b/2 study was designed to evaluate the safety and efficacy of ibr in pts with steroid-dependent/refractory cGVHD. Eligible pts had to have $\leq$ 3 prior regimens for cGVHD and either $>$ 25% BSA erythema or an NIH mouth score $>$ 4. Phase 1b was designed to determine the recommended phase 2 dose (RP2D) with the initial being 420 mg. Response was assessed every 3 months using the NIH consensus cGVHD Activity Assessment. **Results**: 6 pts (median age, 56 yrs, mean Karnofsky score, 85) were enrolled in phase 1b. Median time from transplant was 23 mo. Median time on ibr was 19.3 wks. Ibr dose was reduced to 280 mg in 1 pt due to recurrent stomatitis. Most common treatment-emergent AEs included fatigue (n = 5), diarrhea (n = 4), ecchymosis/bruising (n = 3) and stomatitis (n = 2), all grade 1/2. SAEs (all grade 3) occurred in 2 pts including one pt with pneumonia and another with pyrexia and fungal brain abscess. The latter was the only event leading to discontinuation of ibr (at 10.9 weeks). Preliminary analysis of efficacy for pts receiving at least 3 months of treatment indicated that all 5 evaluable pts achieved PR. The 2 pts evaluable at 6 months remain in PR. Improvements in clinician assessed GVHD-score, skin erythema and mouth score were observed in pts at these early time points. RP2D was determined to be 420 mg. **Conclusions**: Ibrutinib given for steroid-dependent/refractory cGVHD was well tolerated; AEs were consistent with the known safety profile for ibrutinib. The efficacy data observed at this early time point is preliminary and needs confirmation in a larger number of pts for longer duration. Phase 2 enrollment is ongoing. Clinical trial information: NCT02195869.

7025 Poster Session (Board #14), Sun, 8:00 AM-11:30 AM

Symptomatic BK virus as a significant independent predictor of immune suppression and poor overall survival in allogeneic hematopoietic stem cell recipients. *First Author: Ala Abudayyeh, The University of Texas MD Anderson Cancer Center, Division of Internal Medicine, Section of Nephrology, Houston, TX*

Symptomatic BK virus as a Significant Independent Predictor of Immune Suppression and Poor Overall Survival in Allogeneic Hematopoietic Stem Cell Recipients **Background:** BK virus (BKV) infections are known indicators of immune suppression in hematopoietic stem cell transplant (HSCT) recipients; they can lead to hemorrhagic cystitis, ureteral stenosis, renal dysfunction and prolonged hospital stays. In this study we looked at all transplant associated variables and the patient's immune status to evaluate what factors predicted for the risk of BKV viuria. We hypothesized that BKV infection is a marker of poor immune recovery and survival outcomes in HSCT recipients. **Methods:** We analyzed all engrafted patients undergoing first allogeneic HSCT at MD Anderson Cancer Center between January 2004 and December 2012. We evaluated their immune panels and their transplant associated factors. BKV positivity was defined as BKV detection in urine by PCR testing. Overall survival outcome was defined as the time from the day of stem cell infusion to the day of death. **Results:** We identified a total of 2477 patients with a median age of 52 years. BK viruria was manifest in 25% (n = 629) of the patients. The median time from transplantation to BK viruria development was 42 days. On multivariate analysis, age; female sex; acute GVHD; chronic GVHD; myeloablative conditioning regimen; cord blood transplantation; low CD3, CD4, CD8, and CD56 levels; and a low platelet count were significantly associated with BKV infection with mostly p values of ($P < 0.001$). In addition, BKV infection was associated with a lower overall survival duration ($P < 0.001$). Patients with BKV infections were more likely to be immunosuppressed for the first 3 years after transplantation than were patients without BKV infections. **Conclusions:** This study for the first time reports a significant association between BKV reactivation following allogeneic HSCT and decreased overall survival. In addition, this study provides valuable information on the immune status of HSCT recipients with BKV infections to help us formulate plans for more effective prevention and treatment of this infection.

7026 Poster Session (Board #15), Sun, 8:00 AM-11:30 AM

The relationship between *HIF* family gene expression in allogeneic T-cell products and acute graft-versus-host disease. *First Author: Joseph Rimando, National Institutes of Health, Bethesda, MD*

Background: Allogeneic hematopoietic cell transplantation (HCT) provides beneficial graft-versus-tumor effects (GVT) but is limited by graft-versus-host-disease (GVHD). In murine models and clinical trials, our group has shown that *ex vivo*-manufactured rapamycin-resistant donor T cells (T-rapa cells) provide a favorable balance of GVT and GVHD effects. Recently, T cells cultured in rapamycin for 6 days (TR_6) were found to mediate increased GVHD relative to T cells cultured for 12 days (TR_{12}); specifically, TR_6 recipients had approximately 40% acute GVHD whereas TR_{12} recipients had approximately 10% acute GVHD. The *HIF* gene family allows T cells to survive at hypoxic sites including potential GVHD target sites. We thus hypothesized that the increased GVHD mediated by the TR_6 cells relative to the TR_{12} cells might be due in part to differences in *HIF* family gene expression. **Methods:** We used microarray gene expression analysis (Agilent Platform) to find differences in *HIF* gene family expression (94 genes) between the TR_6 and TR_{12} clinical products (n = 40 products evaluated for each condition). To assess the impact of culture interval and rapamycin on *HIF* expression, we used western blotting to measure *HIF1/2* expression (see Table). **Results:** On gene expression analysis, the *HIF1/2* gene family was greatly upregulated in each TR_6 cell product relative to the TR_{12} cell products. When compared with T cells at culture initiation, T-rapa cells had decreased *HIF* family gene expression at day 3, increased expression at day 6, and decreased expression again at day 12. These RNA-based results were confirmed at the protein level with western blotting. **Conclusions:** Relative to TR_{12} cells, TR_6 cells have increased *HIF* family expression at both the RNA and protein level. Further studies will address our hypothesis that increased *HIF* expression in the TR_6 cells contributes to their increased GVHD potential.

Experimental design.

Experimental Cohort[1]	T Cell Culture[2]	Culture Duration
1	X	Initiation
2A/2B	X	4 hours
3A/3B	X	24 hours
4A/4B	X	3 days
5A/B	X	6 days
6A/B	X	12 days

[1]Cohorts A and B were without or with rapamycin (1 uM), respectively. [2]CD4+ T cells were cultured with anti-CD3/CD28 co-stimulatory beads, IL-2, and IL-4.

7027 Poster Session (Board #16), Sun, 8:00 AM-11:30 AM

Physical activity as a predictor of outcomes in hematopoietic stem cell transplantation (HSCT) recipients. *First Author: Asmita Mishra, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Prior analyses in cancer patients demonstrated lower mortality associated with greater physical activity. The association of recreational physical activity and mortality in patients receiving HSCT remains unclear. The aim of this retrospective study is to analyze the relationship between pre-HSCT self-reported physical activity by the IPAQ short form and post-HSCT outcomes. **Methods:** Data were collected from the Moffitt Cancer Center Health Research Informatics and transplant databases. Between 01/01/2011 and 11/19/2013, 238 consecutive and unique patients received either an autologous (auto) (n = 152) or allogeneic (allo) (n = 86) HSCT. IPAQ scoring algorithm was used to ascertain metabolic equivalent of task-hours (MET-hrs) per week. Based on MET-hrs/wk aggregate score, patients were subsequently divided into three activity categories: low (n = 61), moderate (n = 70), and vigorous (n = 107). **Results:** Median follow-up for survivors was 7.1 months (range 2.9-11.1 months). There was no significant difference in age, gender, KPS, CIBMTR disease risk, HCT-CI, conditioning intensity, number of prior chemotherapy regimens, and pulmonary function among the three categories (p = NS). For alloHSCT, six month overall survival differed significantly between the three groups [Low: 73% (95% CI: 50 – 87%); Moderate: 81% (59 – 91%); Vigorous: 91% (76 – 97%) P =0.0033] (Fig. 1). In univariate analysis, vigorous activity was associated with decreased risk non-relapse mortality compared to low activity (HR: 0.07 (95% CI: 0.01-0.56) P =0.0127). After adjusting for disease risk and KPS, alloHSCT recipients reporting vigorous activity had a lower mortality than those who reported low physical activity in multivariate analysis (HR: 0.189 (95% CI:0.063-0.567) P =0.0029). Self-reported physical activity is not associated with mortality, relapse-free survival, or non-relapse mortality in autoHSCT recipients (p = NS). **Conclusions:** Vigorous activity for patients undergoing HSCT is an independent predictor of survival after alloHSCT. Further studies are warranted to evaluate impact of physical activity on HSCT outcomes. An ongoing prospective single center trial assessing this is nearly complete.

7028 Poster Session (Board #17), Sun, 8:00 AM-11:30 AM

Association of higher total nucleated cell dose with improved survival in patients receiving donor lymphocyte infusion after allogeneic stem cell transplantation. *First Author: Nathan Singh, University of Pennsylvania, Philadelphia, PA*

Background: Donor lymphocyte infusion (DLI) after allogeneic stem cell transplant is an established therapy for disease relapse. Long-term survival after DLI remains poor, and identification of factors associated with improved outcomes is of significant interest. **Methods:** We retrospectively analyzed the total nucleated cell (TNC) dose of DLIs in 79 patients (pts) who received un-manipulated DLI at the University of Pennsylvania between 2000-2014. We included pts who received DLI for relapse or falling chimerism, but excluded those who received low dose ($\leq 0.5x10^8$TNC/kg) for stable mixed chimerism. Multivariable regression analyses were used to evaluate associations between cell dose, survival, best response and GVHD. Classification and Regression Tree (CART) analysis was used to identify optimal cutoff in the TNC dose. **Results:** Pts received DLI from sibling (61%) or unrelated (39%) donors, and 10% were HLA-mismatched. Median follow-up was 68 months (range 0.33-156.2). Median age was 53 years (21-75), and diseases included AML (47), MDS (15), NHL (8), ALL (2), CML (2), Hodgkin (2), myelofibrosis (2) and myeloma (1). Six pts received DLI for falling chimerism without overt relapse. The best response to DLI was complete response (CR) in 27 of 70 evaluable pts. Any GVHD and severe GVHD developed in 24 of 61 and 15 of 59 evaluable pts, respectively. We found that pts receiving $\geq 1.6x10^8$ TNC/kg had improved six-month (adjusted OR = 0.25, 95% CI [0.07-0.89], p = 0.03), one-year (aOR = 0.16, [0.04-0.77], p = 0.02), and overall survival (aHR = 0.47, [0.27-0.82], p = 0.01). A survival advantage for a higher TNC dose was also significant in the subset of AML and MDS pts (aHR = 0.41, [0.22-0.76], p = 0.005). Higher TNC dose did not correlate with development of any GVHD (aOR = 0.67, [0.22-2.06], p = 0.48) or grade III-IV GVHD (aOR = 0.51, [0.10-2.68], p = 0.43). There were also no significant differences in achieving a CR (aOR = 1.56, [0.40-6.10], p = 0.52). **Conclusions:** TNC dose of $\geq 1.6x10^8$ TNC/kg correlated with improved survival without an increased risk of developing GVHD, and thus higher target TNC doses should be considered in pts receiving DLI.

7029 Poster Session (Board #18), Sun, 8:00 AM-11:30 AM

A randomized controlled trial of ibandronate for the prevention of bone loss following allogeneic stem cell transplantation. *First Author: Xerxes Pundole, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Bone mineral density (BMD) loss occurs rapidly within the first year following allogeneic hematopoietic stem cell transplantation (alloHCT), which can lead to fractures. Nonpharmacologic prophylaxis measures are inadequate in preventing bone loss following alloHCT and the effect of ibandronate has not been evaluated. **Methods:** We performed a phase 3 single-center open-label randomized controlled trial of intravenous ibandronate to prevent BMD loss in adult recipients of alloHCT at The University of Texas MD Anderson Cancer Center. The treatment group received 3 mg of intravenous ibandronate over 15–30 seconds starting within 45 days of alloHCT and at 3, 6, and 9 months after alloHCT. All patients received daily calcium (500 mg) and daily vitamin D (400 IU) oral supplements twice daily for 12 months. We compared changes in BMD in the lumbar spine, femoral neck, and total hip at 6 and 12 months following alloHCT relative to baseline between treatment and control groups. **Results:** Of 414 patients screened, 78 were enrolled in the trial, 39 randomized to the ibandronate group and 39 to the control group. Baseline age, sex, race, underlying disease, donor type, stem cell origin, hormonal status, and baseline BMD did not differ significantly between the 2 groups. The treatment group had less BMD loss in the lumbar spine at 6 and 12 months than the control group ($P \leq 0.03$). Both groups lost more BMD in the femoral neck and total hip than in the lumbar spine at 6 and 12 months, and changes in BMD in the femoral neck and total hip at 6 months ($P = 0.33$ & $P = 0.10$ respectively) and 12 months ($P = 0.81$ & $P = 0.44$ respectively) did not differ significantly between groups. Both glucocorticoids and tacrolimus reduced BMD in the lumbar spine, but ibandronate had a significant protective effect and prevented this loss. **Conclusions:** Ibandronate prevents bone loss in the lumbar spine in patients who undergo alloHCT, particularly those who received high doses of glucocorticoids or tacrolimus. However, ibandronate does not completely prevent bone loss at the femoral neck and total hip. Pharmacologic agents with different mechanisms of action should be evaluated in this population for better prevention of bone loss. Clinical trial information: NCT00824993.

7030 Poster Session (Board #19), Sun, 8:00 AM-11:30 AM

Outcomes of hematopoietic stem cell transplant (HSCT) in HIV patients in HAART era. *First Author: Kathan Mehta, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Prior studies have shown that outcomes of HSCT in HIV patients are similar to non-HIV patients since effective implementation of HAART by 1998; but they are limited by small sample size or non-inclusion of recent data. **Methods:** We queried National Inpatient Sample, a largest inpatient dataset in US, from 1998 to 2012 for HSCT using ICD9 procedure code 41.0. HIV patients were identified by ICD9 diagnostic code of 042, 043, 044, V08 and 079.53. Primary outcome was in-hospital mortality and secondary outcomes were in-hospital complications of HSCT. **Results:** 39,517 Patients who underwent HSCT were identified (weighted N = 192,562). Among these 108 patients had HIV (weighted N = 520). There was no difference in in-hospital mortality, intubation, sepsis, bacteremia, or graft vs host disease (GVHD) between HIV and non-HIV patients after HSCT. In allogeneic HSCT, HIV patients had significantly higher incidence of non-tuberculous mycobacteria (NTM), cytomegalovirus (CMV) and fungal infections as compared to non-HIV patients. Incidence of stomatitis was lower in HIV patients after allogeneic HSCT. In autologous HSCT, herpes simplex virus (HSV) infection was more common in HIV patients (Table). **Conclusions:** While HIV patients are not at higher risk of serious in-hospital complications of HSCT, they are at higher risk of opportunistic infections (OI's). Further research is needed to prevent OI's in HIV patients after HSCT.

Outcomes of HSCT in USA.

	Autologous HSCT (weighted N = 112,365)			Allogeneic HSCT (weighted N = 80,198)		
Outcome (%)	HIV (+) patients (weighted N = 439)	HIV (-) patients (weighted N = 111,925)	P value*	HIV (+) patients (weighted N = 81)	HIV (-) patients (weighted N = 80,117)	P value*
In-hospital mortality	2.2	2.2	1.0	11.5	10.2	0.8
Intubation	3.1	2.5	0.7	6.1	8.2	0.8
Sepsis	6.3	8.1	0.5	28.8	13.1	0.1
Bacteremia	10.7	16.0	0.2	40.2	23.3	0.2
OI's						
NTM	0.0	0.1	n/a	5.4	0.2	<0.0001
CMV	0.0	0.7	n/a	22.0	6.3	0.04
HSV	10.7	2.0	<0.0001	0.0	3.2	n/a
Fungal infection	6.0	6.7	0.8	29.0	12.3	0.02
Other infections	29.1	20.5	0.06	39.9	29.9	0.5
GVHD (available from 2008)	0.0	0.7	n/a	22.9	17.9	0.6
Stomatitis	41.3	46.4	0.5	24.2	46.0	0.01
Total parenteral nutrition	9.0	13.1	0.3	11.8	23.4	0.1

* Rao-scott chi square test.

7031 Poster Session (Board #20), Sun, 8:00 AM-11:30 AM

Post-transplantation long-term events in a cohort of HIV-positive patients affected by relapsed/refractory lymphoma. *First Author: Ernesto Zanet, National Cancer Institute CRO Aviano, Aviano, Italy*

Background: The advent of highly active antiretroviral therapy (HAART) allowed to extend autologous stem cell transplantation (ASCT) to the HIV-positive population. In the literature data are scarce concerning the long-term events in this population. **Methods:** We treated consecutively 36 HIV-positive patients (pts) affected by relapsed/refractory lymphomas with ASCT. Ten pts died during or early after ASCT due to progressive disease (4 pts), chemotherapy toxicity (1 pt) and infection (5 pts). We analyzed the post-ASCT long-term data of 26 pts, reaching a complete response after ASCT. All patients received HAART concomitantly to chemotherapy. **Results:** Two pts experienced a lymphoma relapse, after 4.27 and 3.08 years from ASCT, respectively. Five patients presented with a secondary malignancy (1 patient an anal squamous cell cancer, 1 patient a squamous cell carcinoma of the larynx and 1 patient a cervical intraepithelial neoplasia (CIN) grade 2, 1 patient a melanoma of the skin, 1 patient a HL developed in a patient primarily affected by NHL, respectively), with a median time of 3.01 years from ASCT. Nine patients had OI: 3 patients developed a Pneumocystis Carinii pneumonia, 1 patient a Cytomegalovirus pneumonia, 1 patient a Mycobacterium Avium Complex pneumonia, 1 patient a Herpes Simplex Chronic Ulcer, 3 patients cutaneous relapsing Herpes Zoster, respectively. The median time of OI appearance was 0.25 years (IQR: 0.11-2.33). Two pts died: one of lymphoma relapse, the other of car accident.With a median of 6-years follow up (IQR: 4.55-9.87) the OS and PFS of the entire sample of pts were 91% and 36% at 10 years, respectively. **Conclusions:** 24 out of 26 pts are still alive and in long-term complete remission after ASCT. These data confirm the long-term efficacy of ASCT. The appearance of OI is earlier than that of second malignancies after ASCT. The secondary malignancies developed by our pts are non-AIDS-defining cancers and at least three cases are linked to a viral pathogenesis (HPV for both anal cancer and cervical cancer precursor lesion; EBV for HL). Both OI and second malignancies were successfully managed and cured and the only long-term death occurred due to lymphoma relapse.

7032 Poster Session (Board #21), Sun, 8:00 AM-11:30 AM

Ratio of total leucocyte count to C-reactive protein: Does it help differentiate engraftment fever from infective fever in patients undergoing autologous stem cell transplant? *First Author: Sachin Punatar, Tata Memorial Centre, Mumbai, India*

Background: Engraftment fever (EF) is common in 2nd week post autologous hematopoietic stem cell transplant (auto HSCT). It is difficult to differentiate from infective fever (IF). This leads to unnecessary use and cost of antibiotics. Also timely treatment of EF may prevent progression to full blown engraftment syndrome (ES). We studied the role of total leucocyte count (TLC) to C-reactive protein (CRP) ratio in differentiating EF from IF. **Methods:** Consecutive patients with breakthrough fever (BF) from d+7 to d+15 post auto HSCT, from March 2011 to August 2013, were included in this retrospective analysis. BF was defined as new onset fever preceded by an afebrile period of at least 48 hours. BF episodes were classified as IF or EF. Fever was classified as IF if blood culture was positive, or there were radiological signs of infection or if fever subsided within 48 hours of change of antibiotics. EF was defined as fever associated with rising counts without any identifiable infective focus responding to steroids. Antibiotics were added at the onset of BF. If fever persisted beyond 48 hours and no infective cause was identified, systemic steroids were started. Daily morning TLC and CRP values were obtained from patients' records. TLC:CRP ratio was calculated from day of admission to day of discharge. Optimal cut-off value of the ratio on the day of BF was obtained by plotting a receiver operating curve. Sensitivity and specificity were calculated. **Results:** Seventy patients had BF of 110 auto HSCT patients. Nineteen had multiple myeloma, 50 had lymphoma and 1 neuroblastoma. Median day of neutrophil and platelet engraftment was 10 and 13 respectively. The median day of BF was 9. Sixty two patients had EF, among whom 15 had ES. We found an optimal value of 0.056 for differentiating between IF and EF. Using a ratio $>$ 0.056 for diagnosing EF, sensitivity and specificity were 63% (95% CI – 50 – 75%) and 100% (95% CI – 63 – 100%) respectively. **Conclusions:** In 2nd week post auto HSCT, a value of the ratio of TLC:CRP $>$ 0.056 on the day of BF is highly specific for EF. Prospective studies are warranted to confirm the results. This could help reduce unnecessary use and cost of antibiotics.

7033 Poster Session (Board #22), Sun, 8:00 AM-11:30 AM

Chemomobilization with (R)-ICE (rituximab, ifosfamide, carboplatin, etoposide) compared to G-CSF and plerixafor (G+P) mobilization in lymphoid malignancies. *First Author: Lauren Westfall Veltri, West Virginia Univ, Morgantown, WV*

Background: No studies have compared the efficacy and safety of chemomobilization with (R)-ICE against G+P mobilization in patients with lymphoid malignancies. **Methods:** We analyzed 126 consecutive patients with lymphoid malignancies undergoing chemomobilization with (R)-ICE (n = 63) or G + P (n = 63), in two different institutions. **Results:** Baseline characteristics are shown in Table 1. (R)-ICE mobilization provided a significantly higher total CD34+ cell yield (median 5.5×10^6 vs. 3.4×10^6 cells/kg, $P < 0.001$), day 1 CD34+ cell yield (2.4×10^6 vs. 1.7×10^6 cells/kg, $P = 0.009$) and CD34+ cell dose given at transplant (4.9×10^6 vs. 3.4×10^6 cells/kg, $P < 0.001$). The median number of apheresis sessions required was two in each group. Neutrophil engraftment was faster with (R)-ICE mobilization (median 10 days vs. 11 days, $P < 0.001$). Similarly platelet count recovery was faster with (R)-ICE (12 days vs. 16 days, $P < 0.001$). The transfusion of packed red blood cells was significantly higher in the (R)-ICE group. Plerixafor as a rescue was used in the (R)-ICE group if day 1 cell yield was $<1.0 \times 10^6$ cells/kg (n = 12). There were no mobilization failures (failure to collect a minimum of 2.0×10^6cells/kg) in the (R)-ICE group, while four patients in the G + P group had unsuccessful collection. **Conclusions:** Our analysis demonstrates that chemomobilization with (R)-ICE, allowing for plerixafor rescue on day 1 leads to better resource utilization with only 20% needing plerixafor and resulted in a higher total CD34+ cell yield with faster engraftment and minimal toxicities.

	Mobilization Strategy		
	G+P	(R)-ICE + G-CSF	*P*-value
Median age, years (range)	56 (22-73)	49 (19-73)	0.02
Male gender	40 (63%)	44 (70%)	0.57
Race, Caucasian	61 (97%)	54 (85%)	0.05
Disease			
Hodgkin Lymphoma	15 (24%)	13 (21%)	0.83
NHL	48 (76%)	50 (79%)	
Prior Radiation	11 (17%)	13 (21%)	0.82
Pre-transplant BM cellularity (%), median (range)	43 (10-90)	56 (10-90)	0.80
Lines of Prior Chemotherapy			
1-2	51 (81%)	54 (86%)	0.63
≤ 3	12 (19%)	9 (14%)	
Pre-transplant Disease Status			
CR	34 (57%)	38 (60%)	0.40
PR	26 (43%)	23 (37%)	
SD		2 (3%)	
KPS, median (range)	80 (60-100)	90 (80-100)	<0.001
HCT CI, mean (range)	2 (0-6)	1 (0-6)	0.005

7034 Poster Session (Board #23), Sun, 8:00 AM-11:30 AM

The impact of HBO on early ALC recovery following high-dose therapy and autologous transplantation. *First Author: Omar Salah Aljitawi, University of Kansas Medical Center, Overland Park, KS*

Background: Historically, early absolute lymphocyte count (ALC) recovery (defined as ALC of 500 cells/microL day 15 of transplant) is seen in around 50% of patients receiving autologous stem cell transplantation (ASCT) and is associated with improved survival. Early ALC recovery is related to recovery of natural killer (NK) cells mediated by interluken-15 (IL-15). We are currently conducting a pilot study primarily investigating hyperbaric oxygen (HBO) as a modality to facilitate blood count recovery in ASCT setting. By lowering erythropoietin (EPO) at time of hematopoietic stem cell (HSC)/progenitor cell infusion, HBO appears to facilitate bone marrow homing of HSC/progenitors with retained multi-lineage potential. Accordingly, we hypothesized that HBO pre-treatment might facilitate early ALC recovery. **Methods:** Patients treated on the ongoing pilot study were evaluated for ALC recovery, as previously defined. Blood samples were collected at baseline (prior to high-dose chemotherapy), day 0 (prior to HBO and 6 hours later), 24- and 48-hours following HBO therapy, and on the third day of neutrophil engraftment. Plasma IL-15 was measured by ELISA. **Results:** Of the twenty patients who were treated on study, one patient did not tolerate HBO therapy and 2 patients were released to their oncologist prior to day 15 post-ASCT, accordingly 17 patients were assessable for ALC recovery. 13 out of the 17 patients (76%) achieved ALC 500 prior to day 15, and all achieved ALC 500 by day 18 post-ASCT. In our cohort, the median time to achievement of ALC 500 was 12 (8-18) days. To date, twelve patients had IL-15 levels measured in pg/ml for all time points except baseline level which was measured in 5 patients. Average IL-15 level was higher on day 0 prior to HBO therapy compared to baseline level (22.83 +/- 3.20 vs 4.94+/-1.38) and third day of neutrophil engraftment IL-15 level was higher than baseline level (13.1 +/- 1.7 vs 4.94 +/-1.38). IL-15 level peaked 48-hours following HBO therapy (31.9 +/-3.67). **Conclusions:** Compared to historic data, the rate of early ALC recovery in our HBO pilot study appears to be encouraging. HBO effects on post-ASCT ALC recovery and IL-15 warrant further evaluation. Clinical trial information: NCT02087657.

7035 Poster Session (Board #24), Sun, 8:00 AM-11:30 AM

Outcomes of ASCT for cardiac AL-amyloidosis and cardiac light chain deposition disease. *First Author: Al-Ola A. Abdallah, University of Arkansas for Medical Sciences Myeloma Institute for Research and Therapy, Little Rock, AR*

Background: Melphalan based autologous stem cell transplant (ASCT) can reverse the progression of systemic amyloidosis and light chain deposition disease (LCDD) in selected patients. However, role of ASCT in patients with cardiac involvement due to amyloidosis and LCDD is still unclear **Methods:** Our database at Myeloma Institute for Research and Therapy identified 53 patients, with biopsy proven cardiac amyloidosis and cardiac LCDD between January 2004 and December 2012. A retrospective analysis was performed to identify difference in outcomes between the patients who received ASCT or chemotherapy (CTX). **Results:** Out of these 53 patients, 5 patients were excluded because they did not receive treatment for plasma cell dyscrasia. 37 patients received ASCT and 11 patients received CTX, such as bortezomib, lenalidomide, low dose melphalan, interferon, and cyclophosphamide 66% (n = 32) patients had elevated Brain natriuretic peptide $>$ 500 Pg/ml, 40% (n = 19) had elevated lactate dehydrogenase $>$ 190, 15% (n = 7) had elevated levels of beta-2-microglobulin $>$ 3.5 mg/dl, 44% (n = 21) had elevated creatinine $>$ 1.5 mg/dl at the time of diagnosis. Echocardiogram showed speckled appearance in 19% (n = 9) patients, diastolic dysfunction was present in 58% (n = 28), systolic dysfunction was present in 27% (n = 13), 62% (n = 30) had increase diastolic intra-ventricular septum (IVSD) thickness measuring $>$ 1.3 cm. On a long term follow up, the group of patients with CA who received ASCT had median survival of 4.53 year compared to median survival of 1.85 years for those who received CTX (p = 0.69). 35% (n = 13) patients had life threatening events including severe congestive heart failure, arrhythmias and severe infections in the first 12 months of treatment with ASCT **Conclusions:** CA is aggressive disease with median survival of 8 months. Eligibility for ASCT in CA varies across institutions. Our single institution experience shows that patients with CA might benefit from ASCT with improvement in median survival as compared to those who received CTX. However ASCT should be further investigated with focused evaluation prior treatment, supportive care during and after treatment to decrease the risk of life threatening events.

7036 Poster Session (Board #25), Sun, 8:00 AM-11:30 AM

Long-term outcomes of rituximab use prior to autologous stem cell transplant (ASCT) in low-grade follicular lymphoma (FL) at the time of first progression. *First Author: Roberto Antonio Ferro, University of Nebraska Medical Center, Omaha, NE*

Background: Some studies suggest that prior use of rituximab is associated with poor outcomes following ASCT in relapsed diffuse large B-cell lymphoma (DLBCL). The effects of rituximab use prior to ASCT on long-term outcomes of FL are unclear. Rituximab in addition to ASCT has been associated with an increased risk of secondary primary malignancy (SPM) especially of solid tumors; however, this study included all lymphoma subtypes (J Clin Oncol 29:814-824, 2011). **Methods:** This is a retrospective study of 84 low grade FL patients treated by the Nebraska Lymphoma Study Groupbetween 1987-2013. We used the Chi-square or Fisher's exact tests to compare characteristics of patients who did vs. did not receive rituximab before ASCT. The Kaplan-Meier method was used to estimate overall survival (OS) and event-free survival (EFS). **Results:** 34 patients (40%) received rituximab prior to ASCT. Rituximab vs. no-rituximab groups were similar in sex distribution (males 74% vs. 54%, $p = 0.07$), more likely to be older (mean age of 51 vs. 44 years, $p = 0.0004$), have received 3 or more prior chemotherapy regimens (53% vs. 24%, $p = 0.004$) and less likely to have received total body irradiation (TBI) (3% vs. 74%, $p < 0.0001$). Rituximab group was more likely to be at second complete remission (53% vs. 14%, $p = 0.0004$) prior to ASCT. At a median follow-up of 10.2 years, 41 patients (49%) died. The 10-year EFS was similar (49% vs. 32%, $p = 0.10$) but the 10-year OS was better in the rituximab group (74% vs. 46%, $p = 0.009$). The risk of SPM (excluding non-melanoma skin cancers) was similar in the groups with or without rituximab (18% vs. 12%, $p = 0.21$). **Conclusions:** Within the limitations of this study, rituximab use prior to ASCT resulted in similar EFS but improved OS. In addition, we did not find an increased risk of SPM with rituximab use prior to ASCT. Patients who received rituximab prior to ASCT (performed at the time of first progression) have an OS of 74% at 10 years post-ASCT. Rituximab use prior to ASCT does not influence outcomes of subsequent ASCT in FL as it appears to do in DLBCL. The current study confirms that ASCT remains an excellent salvage option for patients previously treated with immunochemotherapy.

7037 Poster Session (Board #26), Sun, 8:00 AM-11:30 AM

Overall survival and treatment response in patients with myelodysplastic syndrome and acute myeloid leukemia treated with DNA methyl-transferase inhibitors vs. conventional care regimens: A meta-analysis of 5 randomized trials. *First Author: Seongseok Yun, University of Arizona, Tucson, AZ*

Background: Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are two of the most common myeloid neoplastic disorders that are characterized by genetic instability and ineffective hematopoiesis. DNA methyl-transferase inhibitors (DMTI) have been widely used for elderly MDS and AML patients who are not qualified for stem cell transplantation (SCT), however the outcomes from previous trials were inconsistent. The purpose of current meta-analysis is to assess the efficacy of DMTI compared to conventional care regimens (CCRs) in patients with high risk MDS or AML. **Methods:** Relevant articles were searched in PubMed, EMBASE and Cochrane database. Eligible studies were limited to randomized trials comparing DMTI (azacitidine or decitabine) and CCRs (best supportive care, low dose cytarabine or intensive chemotherapy) in adult patients with MDS or AML. Cochrane's Q statistic was used for the calculation of the statistical heterogeneity. Relative risks and 95% CI were calculated using random effect model and RevMan 5.3 software. **Results:** Significant OS benefit was associated with DMTI treatment compared to CCR with OS of 33.2% vs. 21.4% (RR 0.83, 95% CI, 0.71 to 0.98, $P = 0.03$). CR/PR rate was also significantly higher in DMTI group with a response rate of 23.7% vs. 13.4% (RR 0.87, 95% CI, 0.81 to 0.93). In a subgroup analysis, only azacitidine treatment showed OS improvement (RR 0.75, 95% CI, 0.67 to 0.85), but not in decitabine (RR 0.96, 95% CI, 0.92 to 1.01). Additional subgroup analysis according to cytogenetic risk and BM blast counts did not show significant RR difference. **Conclusions:** In a meta-analysis of randomized trials in patients with MDS or AML, DMTI treatment was associated with treatment response and survival benefit, although the initial treatment response failed to translate into survival benefit in patients treated with decitabine. Collectively, these results suggest that azacitidine may be the best therapeutic option in high risk MDS or AML patients who are not eligible for allogeneic SCT regardless of cytogenetic risk or degree of bone marrow involvement.

7038 Poster Session (Board #27), Sun, 8:00 AM-11:30 AM

Exosome transcriptome analysis to provide novel tools for CLL patient stratification. *First Author: Raffaele Calogero, University of Torino, Torino, Italy*

Background: Routine diagnostic techniques can detect very low levels of CLL phenotype cells. Monoclonal B-cell lymphocytosis (MBL) is a diagnostic category encapsulating individuals with an abnormal B-cell population but not meeting the diagnostic criteria for a B-cell malignancy. MBL and CLL show similar karyotypes and mRNA/miRNA expression data were shown not to be suitable for a molecular discrimination between the two diseases. Exosomes are vesicles secreted into the extracellular environment. A growing body of evidence suggests that exosome-contained coding and non-coding RNAs may be used as biomarkers for the diagnosis and prognosis of malignant tumors. **Methods:** We analyzed the exosome transcriptome of 14 CLL patients and 13 MBL patients, characterized by similar karyotypes. We collected data for coding genes, fusion transcripts, long non-coding RNAs, snRNA, snoRNA, miRNA precursors and mature transcripts, using whole-transcriptome and small RNA sequencing analyses. **Results:** A subset of 8 CLL patients was characterized by a reduced expression of four miRNAs (miR-146a-5p, miR-151a-3p, miR-22-3p, miR-584-5p), which act as tumor suppressors in various solid cancers. Six of the above mentioned patients were also characterized by an up-modulation of TPT1, which is a predictor of poor prognosis in breast cancer. It is notable that TPT1 is located on q13-14.11, however, six out of eight samples with high TPT1 expression are characterized by 63% to 95% deletion of the long arm of chromosome 13, which suggests that TPT1 exosome expression is associated to the sub-population of CLL still retaining at least part of the long arm of chromosome 13. Furthermore, using a signature based on miR-6813 and two snRNA U2 pseudogenes we managed to stratify CLL patients in 4 groups, which are independent by the patient karyotype. MBL patients clustered all in the same group together with 3 CLL patients (21%). **Conclusions:** Our work describes an exhaustive analysis of the transcriptome of exosomes circulating in the peripheral blood of CLL/MBL patients. Our data suggest that the exosome transcriptome of CLL and MBL patients carries an important amount of non-coding RNAs, which might be instrumental for CLL patients' stratification.

7039 Poster Session (Board #28), Sun, 8:00 AM-11:30 AM

Cellular immunotherapy for refractory hematological malignancies. *First Author: John Leonard Reagan, Brown University Oncology Research Group, Providence, RI*

Background: Allogeneic cellular infusion is a potent immune stimulus. We present data from our FDA approved IND Phase II clinical trial (BrUOG 273) where allogeneic haploidentical lymphocytes are infused without prior chemotherapy or radiation to create a rejection response that hypothetically breaks host tumor tolerance. **Methods:** Eligible patients have relapsed or refractory acute leukemia. HLA haplo donors undergo leukapheresis without G-CSF priming. 1-2x10^8CD3+ cells/kg were infused unprocessed immediately after collection. Peripheral blood collected 1-4, 8-24, 34-48, 72-96 and 168-192 hours post infusion were examined for effector cell populations, stimulatory/inhibitory signals, and cytokine release profiles. Wilcoxon rank sum tests were used for statistical analysis. **Results:** Five patients were infused haplo donor cells. Four developed hyperpyrexia post infusion that lasted 24-48 hours (median T 0-4 hours post infusion 98°F, median Tmax 8-192 hours post infusion 102.4°F, $p = 0.009$). Host CD8 T cells demonstrated decreased perforin expression post compared to pre-infusion (median pre 77.6%, median post 61%, $p = 0.03$) with no changes in granzyme A/B, LAMP1, or FasL expression. Rapid up-regulation of PD-1 on host CD8 T cells (median pre 5.6, median post 49.7, $p = 0.005$) was present. Non-statistically significant upregulation of PD-1 ligands occurred on leukemic blasts from 0-4 to 34-48 hours post infusion. Cytokine release profiles post infusion showed high IL-10 (median 86pg/mL) with low IFNg (median < 1pg/mL) and IL-6 (median 7.47pg/mL) levels. One of five patients demonstrated a decrease in marrow blast counts post therapy (43% pre to 21% 4 weeks post infusion). No dose limiting toxicities or durable chimerism was seen. **Conclusions:** Haplo cellular infusions are well tolerated and show biological activity in relapsed AML. One of five patients had a reduction in marrow blasts with haplo infusion alone. Host CD8 T cells were less activated post infusion compared to pre-infusion and increased inhibitory PD-1 expression post infusion. Cytokine release profiles were more anti-inflammatory than those previously described. Greater initial CD8 T cell activation +/- immune checkpoint inhibitory blockade may improve efficacy. Clinical trial information: NCT01685606.

7040 Poster Session (Board #29), Sun, 8:00 AM-11:30 AM

A meta-analysis of randomized clinical trials in acute promyelocytic leukemia (APL). *First Author: Francesco Lo-Coco, University of Rome Tor Vergata, Rome, Italy*

Background: All-trans retinoic acid (ATRA) and arsenic trioxide (ATO) have dramatically improved treatment outcomes in Acute Promyelocytic Leukemia (APL). To address the question regarding the most effective and safe regimen for 1st-line APL, a meta-analysis was performed following a systematic review of the clinical literature in APL. **Methods:** A systematic literature review on all published randomized controlled trials (RCT) in APL identified 17 papers. One additional publication was included following discussions with a clinical expert. Comparable RCTs were grouped into networks based on similar induction and consolidation regimens, resulting in three networks for meta-analysis. Network 1 consisted of RCTs with ATRA, anthracycline (AraC), and chemotherapy (Chemo) regimens. Three trials with arsenic + ATRA arms made up Network 2; observation maintenance arms from 3 studies commprised Network 3. **Results:** In Network 1, ATRA + AraC + Chemo + ATO was associated with superior event-free survival (EFS) at 4 years (yrs) vs. ATRA + Chemo and ATRA followed by Chemo + AraC. The mean odds ratios (OR) were 4.45 (CI: 2.11-9.40, p = 0.00018) and 4.73 (CI: 2.44-9.16, p = 0.00001), respectively. Relative risks (RR) were not statistically significant. Mean results showed that EFS at 7 yrs for ATRA + AraC + Chemo + ATO was likely to be higher. Other outcomes did not demonstrate a statistically significant difference in treatment arms. In Network 2, ATRA + Realgar-Indigo naturalis formula (RIF, an oral arsenic derivative) in induction was associated with a higher disease-free survival (DFS) at 2 yrs compared to ATRA or ATO monotherapy. The RRs were 49.35 (CI: 1.66-1466.53, p = 0.01) and 15.53 (CI: .46-525.2, p = 0.04), respectively. Other outcomes included 2-yr DFS for monotherapy regimens of ATRA vs. ATO, complete remission rate, and liver-related adverse events, none of which had statistically significant results. In Network 3, no in DFS at 5 yrs were observed between treatment arms. **Conclusions:** Results suggest that regimens containing ATO or RIF appear to be associated with improved outcomes compared to those which include ATRA plus Chemo without ATO. Furthermore, the regimens which included ATO or RIF were not associated with increased toxicities.

7041 Poster Session (Board #30), Sun, 8:00 AM-11:30 AM

Impact of unbalanced karyotypes at diagnosis on prognosis of CML. *First Author: Ruediger Hehlmann, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany*

Background: Major route additional cytogenetic aberrations (ACA) at diagnosis of chronic myeloid leukemia (CML) indicate an increased risk of progression and shorter survival. Since all major route ACA are unbalanced it is unclear whether other unbalanced ACA at diagnosis also confer an unfavourable prognosis. **Methods:** On the basis of 1348 Philadelphia chromosome positive chronic phase patients of the randomized CML-study IV we examined the impact of unbalanced minor route ACA at diagnosis in comparison to major route ACA on prognosis. **Results:** At diagnosis, 1175 patients (87%) had a translocation t(9;22)(q34;q11) and 74 (5.5%) a variant translocation t(v;22) only, while a loss of the Y-chromosome (-Y) was present in addition in 44 (3.3%), balanced or unbalanced minor route ACA each in 17 (1.3% each) cases and major route ACA in 21 (1.6%) cases. Patients with unbalanced minor route ACA achieved complete cytogenetic remission, major molecular remission, progression-free survival (PFS) and overall survival (OS) at similar rates as did patients with t(9;22), t(v;22), -Y, and balanced minor route karyotypes. In contrast, patients with major route ACA had a shorter OS and PFS than all other groups ($p < 0.005$ for all pairwise comparisons with major route). Five year survival probabilities were for t(9;22): 91.4% (95% CI 89.5 – 93.1), t(v;22): 87% (77.2 – 94.3), - Y: 89.0% (76.7 – 97.0), balanced: 100%, unbalanced minor route: 92.3% (72.4 – 100), major route: 52.2% (28.2 – 75.5). **Conclusions:** We conclude that only major route, but not unbalanced minor route ACA at diagnosis have a negative impact on prognosis of CML. This observation of the prognostic relevance of specific cytogenetic aberrations for a given malignancy may be of importance also to other cancers. Clinical trial information: NCT00055874.

7042 Poster Session (Board #31), Sun, 8:00 AM-11:30 AM

Fludarabine, cyclophosphamide, and multiple-dose rituximab as frontline therapy for chronic lymphocytic leukemia. *First Author: Nicholas James Short, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: FCR results in durable responses in patients with previously untreated CLL. Previous reports suggest that dose-intensified rituximab increases response rates compared to standard-dose rituximab in patients with relapsed CLL. The effect of rituximab intensification of FCR in patients with previously untreated CLL is unknown. **Methods:** We evaluated the safety and efficacy of a modified FCR regimen with multiple-dose rituximab (FCR3) in 65 patients with previously untreated CLL. The FCR3 regimen consisted of six 28-day cycles of IV fludarabine (25 mg/m^2/d) and cyclophosphamide (250 mg/m^2/d) over 3 days. For cycle 1, rituximab was given at 375 mg/m^2 on day 1 and at 500 mg/m^2 on days 2-3. For cycles 2-6, rituximab was given at 500 mg/m^2 on days 1-3. Results were compared to a historical cohort treated with FCR. **Results:** The overall response rate to FCR3 was 97%. Forty-eight patients (75%) achieved CR, 10 (16%) achieved nPR, 4 (6%) achieved PR, and 2 (3%) did not respond to FCR3. Response rates were not significantly different from the historical FCR cohort. The median time to progression (TTP) for patients achieving CR, nPR and PR was 86 months, 49 months and not evaluable, respectively (P = 0.14 for CR vs. nPR). MRD negativity by flow cytometry was achieved in 62% of patients. Median TTP was 81 months, which was similar to the median TTP of 84 months with FCR (P = 0.63). Median OS was not reached, with 58% of patients still alive at a median survivor follow-up of 9.7 years (P = 0.58 compared to FCR). Thirty-one (65%) of those patients who achieved CR, 6 patients (60%) who achieved nPR and 1 patient (25%) who achieved PR are still alive. Grade 3-4 neutropenia, grade 3-4 thrombocytopenia and major infection were observed with 45%, 5% and 1.9% of FCR3 courses (not significant compared to FCR). Therapy-related MDS or AML developed in 7 patients (11%) (P < 0.01 compared to FCR) at a median of 32 months and accounted for 26% of all deaths. **Conclusions:** In patients with previously untreated CLL, FCR3 resulted in similar response rates, TTP and OS compared to a historical cohort of patients treated with FCR. FCR3 was associated with a significantly increased incidence of therapy-related MDS/AML, which warrants further evaluation. Clinical trial information: NCT00794820.

7043 Poster Session (Board #32), Sun, 8:00 AM-11:30 AM

Safety and activity of blinatumomab for older patients (pts) with relapsed/refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) in two phase 2 studies. *First Author: Hagop M. Kantarjian, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment options for older pts with R/R ALL are limited. Blinatumomab is a bispecific T-cell engager (BiTE) antibody construct that directs cytotoxic T cells to CD19-expressing B cells, and is approved in the US for treatment of Ph- R/R ALL. In two phase 2 adult studies of blinatumomab (Topp MS, et al. *J Clin Oncol*. 2014;32:4134-40; Topp MS, et al. *Lancet Oncol*. 2015;16:57-66), 69% and 43%, respectively, achieved complete response (CR) or CR with partial hematologic recovery (CRh*). We report pooled data for the combined subsets of older pts (≥ 65 yrs). **Methods:** Pts with R/R B-precursor ALL received open-label blinatumomab by continuous IV infusion (4 weeks on/2 weeks off). Pts achieving CR or CRh* after two cycles could receive three consolidation cycles. Response was assessed by bone marrow aspiration. CR required blasts < 5%, ANC > 1000/μL and platelets > 100,000/μL. CRh* required blasts < 5%, ANC > 500/μL and platelets > 50,000/μL. Minimal residual disease (MRD) was detected by ASO-PCR of Ig heavy chain loci. **Results:** 36 older pts (median age 70 yrs, range 65-79) received blinatumomab for a median (range) of 2 (1-6) cycles. 20 (56%) pts achieved best response of CR/CRh* within two cycles, including 14 (39%) CR and 6 (17%) CRh*. Among responders, 12 (60%) had complete MRD response and 4 other pts had detectable MRD but < 10^{-4}. With median follow-up of 18.2 months, median (range) relapse-free survival for responders was 7.4 (1.0-34.0) months. With median follow-up of 29.4 months, overall survival was 5.5 (0.3-41.9) months. 10 (28%) pts were alive at last follow up; 6 in remission. 2 (10%) responders underwent allogeneic HSCT after blinatumomab. Treatment-emergent adverse events (AE) CTCAE grade ≥ 3 were reported for 31 (86%) pts, most commonly febrile neutropenia (22%) and neutropenia (19%). Neurologic AE occurred in 26 (72%) pts, including grade ≥ 3 events for 28%. 1 (3%) pt had grade ≥ 3 cytokine release syndrome. Of 7 fatal AEs, none were considered related to treatment. **Conclusions:** Older pts (≥ 65 yrs) with R/R ALL in two phase 2 studies of open-label blinatumomab had similar treatment responses and tolerability as pts in the overall study populations. Clinical trial information: NCT01209286 and NCT01466179.

7044 Poster Session (Board #33), Sun, 8:00 AM-11:30 AM

Phase 1 study of CWP232291 in relapsed/refractory acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). *First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: CWP232291, a novel peptidomimetic small molecule identified via a phenotypic drug discovery screen, shows selective inhibitory activity at submicromolar levels on a Wnt gene reporter and decreases expression of the β-catenin target genes, cyclin D1 and survivin. It has broad anti-cancer efficacy in vitro, with significant preclinical tumor regression outperforming standard cytotoxic AML drugs. **Methods:** Subjects with relapsed AML or MDS were infused CWP232291 iv over 5 -30 minutes for 7 days in 21-day cycles until disease progression in a first in human, 3+3 dose-escalation, Phase 1 design. **Results:** Results to January 27, 2015 over a dose range of 4 – 257 mg/m^2 in 56 patients (53 AML; 3 MDS) are reported. Common (≥ 10% patients) drug-related adverse events (AEs) included nausea (43%), infusion-related reaction (36%), vomiting (29%), diarrhea (16%), and anorexia (11%). Toxicity was mostly ≤ grade 2 (91%), grade 3/4 events comprised 9%, observed similarly across all dose cohorts. Related serious AEs comprised fever, nausea, and anaphylactic reaction, at 19, 54 and 198 mg/m^2, respectively. Dose-limiting toxicity included nausea, rash and anaphylactic reaction (54, 153 and 198 mg/m^2, respectively). Toxicity was managed effectively with standard-of-care medications and, in the event of recurrence, could be mitigated with prophylaxis in subsequent cycles. Within 30 minutes CWP232291 was completely converted to its active metabolite, CWP232204. CWP232204 maximum plasma concentration (C_{max}) and area under the time-concentration curve (AUC) values were dose proportional. At the highest dose with data (153 mg/m^2; n = 6), the mean terminal elimination half-life (t½) was 6.3 hrs, mean C_{max} was 9922 ng/mL, and AUC was 6797 ng●hr/mL. A complete remission was seen in one AML patient after 2 cycles at 153/118 mg/m^2, with normalization of neutrophil and platelet counts; maximum reduction from baseline in β-catenin and survivin expression were > 90% and 77%. No other objective responses were seen but higher doses showed significant reductions in these biomarkers. **Conclusions:** CWP232291 single agent efficacy was observed in AML. MTD has not been defined; accrual is ongoing. Clinical trial information: NCT01398462.

7045 Poster Session (Board #34), Sun, 8:00 AM-11:30 AM

Impact of nilotinib treatment on subclinical cardiovascular biomakers. *First Author: Martine Gardembas, Hospital University Center of Angers, Angers, France*

Background: Nilotinib is a tyrosine kinase inhibitor targeting the BCR-ABL1 oncoprotein. It has been approved for the treatment of chronic myeloid leukemia-CP. Recently, a higher rate of cardiovascular events (CVE) have been reported as part of the non hematological nilotinib related adverse events. Although the CVE events may be influenced by several factors including pro-atherogenic and anti-angiogenic properties of nilotinib, the contribution in the atherosclerotic process still remains unclear. The purpose of this cross-sectional study was to determine the impact of nilotinib treatment on subclinical atherosclerotic biomarkers. **Methods:** 15 patients (mean 44 yrs ±14 yrs, 8 men) treated with nilotinib (Nilo) were compared to 30 age- and gender-matched patients with metabolic syndrom (MS) and 30 healthy controls. Subclinical atherosclerosis was assessed by the presence of carotid, aortic and femoral plaques, intima media thickness (IMT), arterial stiffness (Beta index), ankle brachial pressure index (ABI), and brachial arterial pressure (BAP). The overall cardiovascular risk (CVR) was determined according the 10 years-Framingham CV score. Statistical differences ($p < 0.05$) between the groups were determined by Chi2 and Kruskal-Wallis or ANOVA statistics as appropriate (Stata 12.1). **Results:** Median duration exposure to nilotinib was 1299 days (range 252-2196). Plaques were significantly more frequent ($p = 0.007$) in the Nilo group (53%) than in healthy controls (13 %,) but no difference between Nilo and MS group (63%, $p = 0.371$). There were no statistically significant differences in IMT ($p = 0.271$), Beta stiffness index ($p = 0.428$), ABI and BAP. The CVR score in Nilo group was similar than in the control group ($p = 0,136$). **Conclusions:** Patients treated with nilotinib exhibited a higher amount of plaques although at a lower CVR score. These data would suggest that patients treated with nilotinib, likely develop focal lesions rather than a systemic arteriosclerotic process. Subclinical cardiovascular biomarkers could provide more targeting options for the personalized follow-up of patients treated with nilotinib. However, these preliminary data need to be confirmed in a larger longitudinal study. Clinical trial information: NCT02161978.

7046 Poster Session (Board #35), Sun, 8:00 AM-11:30 AM

Survival of de novo and secondary acute promyelocytic leukemia: A propensity matched analysis of the Surveillance, Epidemiology and End Results database. *First Author: Ranjan Pathak, Reading Health System, Wyomissing, PA*

Background: Secondary acute promyelocytic leukemia (sAPL) is an uncommon entity with no prior large population-based studies. It is unclear whether there is any difference in the overall survival (OS) of sAPL and *de novo* APL. **Methods:** We used the Surveillance, Epidemiology, and End Results (SEER) 13 database and appropriate International Classification of Disease (ICD-O-3) histology codes to identify adult patients with sAPL and *de novo* APL diagnosed between 1992 and 2011. Propensity matching was performed using the MatchIt package of R v2.15.2 to create a matched dataset of sAPL and *de novo*APL. Kaplan Meier survival and multivariate analysis (Cox proportional hazard regression model) was performed using SPSS v22.0. **Results:** sAPL (n = 109) accounted for 5.5% of all APL cases (n = 1964). Crude incidence of sAPL was 0.85 per 10,000 primary malignancies. Patients with sAPL, compared to *de novo* APL, were more likely to be older (65 vs. 44 years, $p < 0.001$), White (85% vs. 79%, $p = 0.003$) and diagnosed after year 2005 (53% vs. 40%, $p = 0.008$). The two subgroups did not differ by gender ($p = 0.665$) and marital status ($p = 0.745$). Mortality rate within 1 month of diagnosis was similar between sAPL and de novo APL (28.9% vs. 23.0%, $p = 0.20$). One-year (55% vs. 57%, $p = 0.70$), two-year (51% vs. 54%, $p = 0.79$) and five-year (42% vs. 50%, $p = 0.24$) OS rates were similar. In a multivariate analysis, sAPL was not associated with a significantly worsened OS as compared to *de novo*APL (HR 1.11; 95% CI 0.78-1.58; $p = 0.546$). OS was worse with older age at diagnosis but better in more recent years. Compared to patients < 55 years, patients 55-70 years (HR 1.86, 95% CI 1.02-3.41, $p = 0.043$) and > 70 years (HR 4.64, 95% CI 2.54-8.46, $p < 0.001$) were more likely to have worse OS. Compared to patients diagnosed before 1995, OS was better among patients diagnosed in the recent years (HR after 2005, 0.37, 95% CI 0.17-0.80, $p = 0.012$). **Conclusions:** This is the largest population-based study utilizing propensity matched analysis that demonstrates similar OS in sAPL and *de novo* APL. This indicates that the patients with sAPL can be managed very similarly to *de novo* APL and do not need to be excluded from clinical trials of APL.

7047 Poster Session (Board #36), Sun, 8:00 AM-11:30 AM

Four-year minimum follow-up of ongoing patients (pts) with chronic-phase chronic myeloid leukemia (CP-CML) in a phase 1 trial of ponatinib (PON). *First Author: Moshe Talpaz, University of Michigan, Ann Arbor, MI*

Background: PON, an approved oral tyrosine kinase inhibitor (TKI), has potent activity against native BCR-ABL and resistant mutants, including T315I. A phase 1 trial evaluated PON safety and antileukemic activity; this analysis includes 4-year minimum follow-up of ongoing pts, the longest follow-up of PON-treated pts to date. **Methods:** Pts (N = 81) with resistant/refractory hematologic malignancies received PON (2–60 mg qd) in this ongoing, open-label, dose-escalation trial (NCT00660920; enrollment 2008–2010; data cutoff, 26 Sept 2014). The median follow-up for 43 CP-CML pts was 49.9 (1.7–69.9) mo; minimum follow-up for 22 ongoing CP-CML pts was 50.2 mo. **Results:** Data are reported for CP-CML pts. Median age was 55 years; time since diagnosis 6.6 years. 60% of pts had received ≥ 3 TKIs; 63% had BCR-ABL mutations (28% T315I). At time of analysis, 51% remained on study. Most common reasons for discontinuation: adverse events (AEs) 26%; progression 9%. By intention-to-treat analysis: major cytogenetic response (MCyR) was 72%; complete cytogenetic response (CCyR), 65%; major molecular response (MMR), 56%; MR4, 42%; and MR4.5, 28%; responses are durable (**Table**). Median durations of MCyR, CCyR, and MMR were not reached. Of 22 ongoing pts at data cutoff, 18 (82%) were in CCyR; 17 (77%) had MMR or better (MMR n = 6; MR4 n = 1; MR4.5 n = 10). Most common treatment-emergent AEs were rash 65%, fatigue 60%, abdominal pain 58%, headache 58%, and arthralgia 53%. Arterial occlusive event (AE/serious AE) rates were 40%/30%, including cardiovascular (30%/21%), cerebrovascular (9%/7%), and peripheral vascular (14%/9%); venous thromboembolic event rates were 5%/0%. **Conclusions:** These data represent the longest follow-up with PON. With 4-year minimum follow-up for ongoing pts, PON continues to provide benefit to ongoing CP-CML pts with prior TKI failure. Risks and benefits should be evaluated when using PON. Clinical trial information: NCT00660920.

Stability of Response in CP-CML Pts Treated With PON.

	Responders, n	Lost Response, n[a]	Maintain Response at 4 Years, % (95% CI)[b]
MCyR	31	8	68 (44–84)
CCyR	28	8	70 (48–84)
MMR	25	11	52 (30–70)

[a]Failed to meet criteria for response at any single time point after initial response
[b]Kaplan-Meier estimate

7048 Poster Session (Board #37), Sun, 8:00 AM-11:30 AM

Safety and feasibility of anticoagulation prophylaxis with enoxaparin in acute lymphoblastic leukemia during asparaginase-based intensification therapy. *First Author: Hassan Abdulmaoula Sibai, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Venous thromboembolism (VTE) is a well-known complication in adults receiving asparaginase (ASP) for acute lymphoblastic leukemia (ALL). We previously reported 27.3% VTE rate in patients (pts) receiving a modified Dana Farber Cancer Institute (DFCI) intensification phase. Low-dose enoxaparin (ENOX) was not associated with lower rate of VTE. We describe escalated dose of ENOX in adults treated with this protocol. **Methods:** 38 pts with ALL treated with a weekly ASP-based modified DFCI intensification for 21-30 weeks, received ENOX 1 mg/kg subcutaneously daily (**adjusted-dose group**).The result was compared with a similar group of 41 pts receiving ENOX 40 mg for pts weighing $<$ 80 kg, or 60 mg for pts $\geq$ 80 kg (**low-dose group**), and to a historical cohort of 99 pts treated with the same protocol, without prophylaxis. **Results:** There was no significant difference among groups with respect to median age, weight and number of cycles. The actual mean dose of ENOX in the low-dose group was 0.62 mg/kg, as compared to 0.84 mg/kg in the adjusted-dose group. No major bleeding complications were observed. Minor bleeding rate was 5%.VTE rate in the entire cohort was 22.7%.VTE rate in pts receiving adjusted dose ENOX was 18%, as compared to 26.8% in the low-dose group. There was no significant difference in the VTE rate according to age or gender. Sites of VTE in the prophylaxis groups included lower extremity (9), sagittal sinus (3), central line related (5) and pulmonary embolism (8); some pts had $>$ 1 site. **Conclusions:** Prophylactic ENOX during intensification in adults with ALL was safe: despite dose increase to 1 mg/kg, no increase in bleeding events was observed. There was trend toward a lower rate of VTE with 1 mg/kg ENOX, particularly in patients weighing $\geq$ 80 kg; however, a larger cohort is needed to determine if the difference is significant.

	No Prophylaxis n = 99	ENOX low-dose n = 41	ENOX adjusted-dose n = 38	P-value*
Rate of VTE	27/99 (27.3%)	11/41 (26.8%)	7/38(18%)	0.42
Weight < 80 kg	18/67 (26.9 %)	4/26 (15.3%)	5/29 (17.2%)	1
Weight > 80 kg	9/32 (28.1%)	7/15 (46.7%)	2/9 (22%)	0.38
P value by weight	0.90	0.03	0.53	
Minor bleeding events		3 (6.1%)	1 (2.6%)	NS

*Comparing low dose vs adjusted dose

7049 Poster Session (Board #38), Sun, 8:00 AM-11:30 AM

Elevated blood pressure (BP) and adverse events (AEs) of hypertension (HTN) in ponatinib (PON) leukemia trials. *First Author: Hanna Jean Khoury, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: PON is a potent, multitargeted tyrosine kinase inhibitor with proven efficacy in resistant Ph+ leukemia. This analysis reports elevated BP and AEs of HTN in PON leukemia trials. **Methods:** PON safety and efficacy were evaluated in patients (pts) with relapsed/refractory hematologic malignancies in the ongoing phase (ph) 1 trial, in heavily pretreated CML/Ph+ ALL pts in the ongoing PACE (ph 2) trial, and in newly diagnosed CP-CML pts in the terminated EPIC (ph 3) trial vs imatinib (IM). Ph 1 and EPIC, but not PACE, excluded pts with uncontrolled HTN (untreated systolic/diastolic $>$150/$>$100 mm Hg in ph 1, $>$ 140/$>$ 90 mm Hg in EPIC). Elevated BP was defined by single highest measurement (systolic/diastolic): grade (G) 1/pre-HTN 120–139/80–89, G2 140–159/90–99, G3 $\geq$ 160/$\geq$ 100 mm Hg. HTN AEs were reported by investigators. **Results:** Elevated BP was frequent at trial entry; G1/G2–3 rates: 44%/42% in ph 1; 37%/47% in PACE; 51%/19% PON vs 52%/12% IM in EPIC. Any increase in BP grade from baseline was also frequent: 74% in ph 1; 68% in PACE; 68% PON vs 51% IM in EPIC. In PACE, estimated systolic/diastolic BP increases over time were low: 2.3/0.7 mm Hg/year. HTN AEs were reported in 38%, 28%, 18%, and 2% of ph 1, PACE, EPIC-PON, and EPIC-IM pts, respectively. Hypertensive crisis was reported in 2 PACE and 2 EPIC-PON pts. HTN AEs did not lead to discontinuation or death. Few pts had dose modifications for HTN AEs (0% ph1; 5% PACE; 3% EPIC-PON; 0% EPIC-IM). A retrospective multivariate analysis of pooled pts showed HTN AEs were significantly associated with PON dose intensity. **Conclusions:** Increase in BP was frequently observed in PON trials, including in pts on IM. Rates of HTN AEs were relatively lower and seen primarily with PON. While associated with PON dose intensity, HTN AEs rarely led to change in therapy. Given BP variability, AE reporting may be a more reliable indicator of clinically meaningful HTN. Clinical trial information: NCT00660920; NCT01207440; NCT01650805.

			Any Increase in BP Grade* on Study, % Pts		
	Baseline*	n	G1	G2	G3
Ph 1 N = 81	Normal	11	18	45	27
	G1	36	—	47	39
	G2	27	—	—	70
	G3	7	—	—	—
PACE N = 449	Normal	70	34	31	23
	G1	167	—	53	35
	G2	157	—	—	62
	G3	55	—	—	—
EPIC-PON N = 154	Normal	46	57	22	7
	G1	78	—	51	14
	G2	30	—	—	50
	G3	0	—	—	—
EPIC-IM N = 152	Normal	54	65	13	2
	G1	79	—	35	5
	G2	12	—	—	17
	G3	6	—	—	—
	Missing	1	—	—	—

*Single measurement; Normal: $<$120/$<$80 mm Hg

7050 Poster Session (Board #39), Sun, 8:00 AM-11:30 AM

Phase I trial of α-particle therapy with actinium-225 (^{225}Ac)-lintuzumab (anti-CD33) and low-dose cytarabine (LDAC) in older patients with untreated acute myeloid leukemia (AML). *First Author: Joseph G. Jurcic, Columbia University Medical Center, New York, NY*

Background: ^{225}Ac-lintuzumab consists of a radiometal that emits 4 α-particles linked to an anti-CD33 antibody. A phase I trial showed safety and efficacy of ^{225}Ac-lintuzumab in relapsed AML. We are conducting a multicenter, phase I trial to determine the maximum tolerated dose (MTD), toxicity, and activity of fractionated-dose ^{225}Ac-lintuzumab combined with LDAC. **Methods:** Patients $\geq$ 60 yrs with untreated AML not suitable for standard induction were eligible. Patients received LDAC 20 mg BID for 10 d every 4-6 wks for up to 12 cycles. During Cycle 1, 2 doses of ^{225}Ac-lintuzumab were given one week apart, 4-7 d following LDAC. ^{225}Ac doses were escalated using a 3+3 design. **Results:** Twelve patients (median age, 77 yrs; range, 68-87 yrs) were treated. Eight (67%) had prior myelodysplastic syndrome, for which 6 (75%) received hypomethylating agents (n = 5) or allogeneic stem cell transplant (n = 1). One (8%) had chronic myeloid leukemia in molecular remission prior to AML. Nine patients (75%) had intermediate-risk and 3 (25%) had poor-risk AML. Median CD33 expression was 74% (range, 45-100%). ^{225}Ac-lintuzumab was given at 0.5 (n = 3), 1 (n = 6), or 1.5 (n = 3) μCi/kg/fraction. Up to 4 cycles were given, and 2 patients remain on therapy. DLT was seen in one patient at 1 μCi/kg/fraction who had grade 4 thrombocytopenia and marrow aplasia $>$ 6 wks after therapy. Grade 3/4 toxicities included neutropenia (n = 2), thrombocytopenia (n = 3), febrile neutropenia (n = 6), pneumonia (n = 3), bacteremia (n = 1), cellulitis (n = 1), transient creatinine increase (n = 1), hypokalemia (n = 1), rectal hemorrhage (n = 1), and generalized weakness (n = 1). Six of 8 patients (75%) evaluated after Cycle 1 had bone marrow blast reductions (mean reduction, 68%; range, 34-100%). Five patients (63%) had blast reductions of $\geq$ 50%, but no remissions were observed to date. Median progression-free survival (PFS) was 2.4 mos (range, 1.3+-16.9 mos). **Conclusions:** Fractionated-dose ^{225}Ac-linutuzmab can be combined safely with LDAC and has antileukemic activity. Accrual continues to define the MTD. Additional patients will be treated at the MTD to determine response rate, PFS, and OS. Clinical trial information: NCI-2014-01360, NCT01756677.

7051 Poster Session (Board #40), Sun, 8:00 AM-11:30 AM

Re-exposure to blinatumomab after CD19-positive relapse: Experience from three trials in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (R/R ALL). *First Author: Max S. Topp, Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany*

Background: Blinatumomab is a bispecific T-cell engager antibody construct designed to link cytotoxic T cells and CD19-positive B cells, inducing tumor cell lysis. In this combined analysis, we evaluated outcomes for patients with R/R ALL enrolled in 3 open-label phase 2 studies (NCT01471782 [study 205], NCT01209286 [study 206], NCT01466179 [study 211]) who received retreatment with blinatumomab following hematologic relapse after initial blinatumomab response. **Methods:** Patients were $<$ 18 (205) or $\geq$ 18 (206 and 211) years of age with Ph- R/R B-precursor ALL. Blinatumomab was dosed by continuous IV infusion. A cycle was 4 weeks on, 2 weeks off. The primary endpoint was hematological remission within 2 cycles. Patients with relapse following a response of $\geq$ 3 months duration could receive up to 3 cycles of retreatment; patients with GVHD or CNS involvement were ineligible. **Results:** Eleven patients received retreatment with blinatumomab (205, n = 2; 206, n = 5; 211, n = 4). Seven (64%) were male; mean (range) age was 31 (4, 77). At the time of initial treatment, 9 (81%) had $\geq$ 1 line of prior salvage chemotherapy; 7 (64%) had prior HSCT. Among 10 patients who achieved hematological remission during the 2 cycles of initial treatment, the median (range) duration of response prior to relapse was 9 (3-11) mo. Five (45%) patients had HSCT between first blinatumomab response and relapse. Outcomes during retreatment are shown in the table. One patient was retreated a second time and obtained a CR. **Conclusions:** Four (36%) patients with R/R ALL who relapsed following initial response responded to retreatment with blinatumomab. Overall, rates of adverse events occurring during retreatment were similar to those observed in the full studies. Clinical trial information: NCT01471782, NCT01209286, and NCT01466179.

	Retreated Patients (n = 11)
Median (range) duration of retreatment, days	28 (4-85)
Hematological remission (responders)	4 (36%)†
Minimal residual disease (MRD) responses among responders (n=4)	- 1 (25%)
Complete response MRD < 10^{-4}	4 (100%)
Patients with any AEs Grade $\geq$ 3 Cytokine release syndrome Neurologic AEs	10 (91%) 8 (73%) 0 (0%) 5 (45%)

†$\leq$ 5% marrow blasts and full, partial, or incomplete recovery of peripheral blood counts.

7052 Poster Session (Board #41), Sun, 8:00 AM-11:30 AM

***RAS* mutation acquisition at transformation from myelodysplastic syndrome to acute myeloid leukemia to predict poor outcome.** *First Author: Talha Badar, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Although *RAS* mutation (m) in de novo MDS has not shown to influence outcome but it does have prognostic value when acquire later in disease course (Takahashi et al. Leukemia. 2013; 27 (10): 2081-3). We sought to further characterize the acquisition of *RAS*m at the time of transformation to AML in a large group of MDS patients and assessed its prognostic impact. **Methods:** We retrospectively analyzed 289 MDS patients who had wild type (wt) *RAS* at the time of MDS diagnosis and were referred to our institution between 2002 and 2013. Ninety eight (34%) patients had repeat mutation testing at the time of transformation to AML, and we evaluated these patients for the frequency of *RAS*m acquisition and its clinical implications. **Results:** Twenty two (22%) patients acquired *RAS*m at the time of transformation to AML. At the time of diagnosis of MDS, the median age was 65 years (range 26-83). Five percent, 14%, 22%, 25%, and 32% patients had R-IPSS very low, low, intermediate, high, and very high-risk disease, respectively. The median number of therapies patients received for MDS was 1 (range 0-4), and 8 patients had stem cell transplants (SCT). At the time of transformation to AML, the median age was 59 years (range, 27-86). In 22 (22%) patients who had poor-risk cytogenetics (complex, -7/7q-, -5/5q-, or inv 3), 14 (14%) acquired *RAS*m versus 8 (8%) who had wt *RAS* ($p = 0.33$). Most patients received either cytarabine- or hypomethylating agent-based induction regimens. Overall, 25% (12% with *RAS*m and 13% with wt *RAS*) achieved CR/CRi ($p = 0.17$), and 15 (15%) patients had SCT. The median survival after leukemia transformation in *RAS*m patients was 3.6 months compared to 7.5 months in *RAS* wt patients ($p = 0.0002$). When we excluded patients with poor risk cytogenetics, median survival was 3.9 months for *RAS*m patients versus 9.3 months for *RAS*wt ($p < 0.001$). In a multivariate analysis, *RAS*m (hazard ratio [HR] = 2.9, $p < 0.0001$) and t-MDS/AML (HR = 2.0, $p < 0.01$) were associated with poor prognosis, and SCT was associated with a favorable outcome (HR = 0.30, $p < 0.001$). **Conclusions:** Acquisition of *RAS*m at the time of transformation to AML is associated with poor outcome and it may provide opportunities for targeted therapy.

7053 Poster Session (Board #42), Sun, 8:00 AM-11:30 AM

O-desulfated heparin and chemotherapy for the treatment of AML. *First Author: Tibor Kovacsovics, Huntsman Cancer Institute-University of Utah, Salt Lake City, UT*

Background: Acute myeloid leukemia (AML) therapy is associated with pancytopenia and a high failure rate due to resistant leukemia stem cells that use CXCL12/CXCR4 to home to marrow niches. Platelet factor 4 (PF4) negatively regulates megakaryopoiesis. O-desulfated heparin (ODSH), a low anticoagulant heparin derivative, inhibits PF4 and like other heparins, may inhibit CXCL12/CXCR4. This study combined ODSH with chemotherapy for the treatment of AML. **Methods:** Adults with newly diagnosed non-APL AML were enrolled. Induction consisted of cytarabine and idarubicin (7+3). Following a bolus, ODSH was given as a continuous infusion on days 1 – 7. Patients younger than 60 received consolidation therapy with high dose cytarabine along with ODSH. Growth factors were not used during induction. Primary endpoints were safety and tolerability of ODSH, and its effect on platelet count recovery. Secondary endpoints included the effect of ODSH on complete remission (CR) rate. The effect of ODSH on CXCL12/CXCR4 was studied using an ELISA assay. **Results:** Twelve patients were enrolled (median age 56, range 22 – 74, 3 women). Three, 5, and 4 patients had good, intermediate, and poor risk disease, respectively. Two patients did not finish induction due to events unrelated to ODSH. Day 14 bone marrows were available on 11 patients and were aplastic in all without detectable leukemia. Eleven patients had a morphologic CR after 1 induction (2 with minimal residual disease). Ten patients remain in CR1. One elderly patient relapsed 6 months after completing consolidation therapy off study. Four patients received an allogeneic stem cell transplant in CR1. All patients who received a full induction were evaluable for platelet recovery and had a median day to an untransfused platelet count $\geq$ 20,000/μl of 22 (range 18 – 23). Six patients who received a full induction were evaluable for neutrophil recovery and had a median day to a neutrophil count $\geq$ 500/μL of 23 (range 20 – 27). No ODSH-associated adverse events occurred. ODSH inhibited the CXCL12/CXCR4 axis *in vitro* at concentrations achievable *in vivo*. **Conclusions:** ODSH is well tolerated when combined with intensive therapy for AML. It may enhance count recovery and treatment efficacy. Further study of this strategy is justified. Clinical trial information: NCT02056782.

7054 Poster Session (Board #43), Sun, 8:00 AM-11:30 AM

A multidrug resistant engineered CAR T cell for allogeneic combination immunotherapy. *First Author: Julien Valton, Cellectis SA, Paris, France*

Background: the adoptive transfer of CAR T cell represents a highly promising strategy to fight against multiple cancers. The clinical outcome of such therapies is intimately linked to the ability of effector cells to engraft, proliferate and specifically kill tumor cells within patients. When allogeneic CAR T cell infusion is considered, host versus graft and graft versus host reactions must be avoided to prevent rejection of adoptively transferred cells, host tissue damages and to elicit significant antitumoral outcome. This work proposes to address these three requirements through the development of multidrug resistant TCR$\alpha\beta$-deficient CAR T cells. **Methods:** Primary T cells were successfully engineered using the TALEN technology **Results:** we demonstrate that these engineered T cells displayed efficient antitumor activity and proliferated in the presence of drugs, currently used in clinic as preconditioning lymphodepleting regimens. The absence of TCR$\alpha\beta$ at their cell surface along with their drug-resistance properties could prevent their alloreactivity and enable them to resist to lymphodepleting regimens that may be required to avoid their ablation via HvG reaction. **Conclusions:** by providing a basic frame work to develop a universal T cell compatible with allogeneic adoptive transfer, this work is laying the foundation stone of the large scale utilization of CAR T cell immunotherapies.

7055 Poster Session (Board #44), Sun, 8:00 AM-11:30 AM

Allogeneic hematopoietic cell transplant (HCT) in patients (pts) $\geq$ 60 years of age with first relapsed or refractory acute myeloid leukemia (R/R AML) after treatment with vosaroxin plus cytarabine (vos/cyt) vs placebo plus cytarabine (pla/cyt): Results from VALOR. *First Author: Gary J. Schiller, UCLA, Los Angeles, CA*

Background: Increasing numbers of older pts with AML receive HCT due to wider donor availability and improvements in supportive care that reduce transplant-related morbidity/mortality. VALOR, a large phase 3 trial of vos/cyt vs pla/cyt in pts with R/R AML [NCT01191801], provided the opportunity to assess outcomes of HCT in pts $\geq$ 60 y/o with R/R AML. **Methods:** Pts were randomized 1:1 to receive cyt (1 g/m^2 IV over 2 hr, d 1-5) plus either vos (90 mg/m^2 IV over 10 min, d 1 and 4; 70 mg/m^2 in subsequent cycles) or placebo. In this posthoc subgroup analysis, we assessed complete remission (CR) rates prior to HCT, posttreatment HCT rates, HCT outcomes, and overall survival (OS) by treatment arm in R/R AML pts $\geq$ 60 y/o. **Results:** Overall, 451 pts $\geq$ 60 y/o received vos/cyt (n = 226) or pla/cyt (n = 225). Posttreatment HCTs were performed in 47 (20.8%) pts on vos/cyt and 44 (19.6%) pts on pla/cyt. Of the 91 HCT pts, 27 had achieved CR after vos/cyt vs 16 after pla/cyt. An additional 7 pts (vos/cyt) and 6 pts (pla/cyt) received subsequent therapy and went on to achieve CR, resulting in totals of 34 vos/cyt vs 22 pla/cyt pts who achieved CR prior to transplant. Median OS for pts who underwent posttreatment HCT on the vos/cyt arm was 20.2 mo vs 12.2 mo on the pla/cyt arm (HR 0.699; one sided P = 0.088). There were no clinically meaningful differences between treatment arms with respect to transplantation type, complications associated with HCT (including graft-vs-host and veno-occlusive disease), 100-day mortality, or achievement of engraftment. **Conclusions:** While HCT rates were comparable between treatment arms in this older R/R AML population, higher pre-transplant CR rates in the vos/cyt arm enabled more pts $\geq$ 60 y/o to undergo transplant while in CR as compared to the pla/cyt arm. With median OS lengthened by 8 months, a trend toward an OS benefit was observed for vos/cyt-treated pts. Additional follow-up is being conducted to further assess the impact of vos/cyt treatment on posttreatment HCT. Clinical trial information: NCT01191801.

7056 Poster Session (Board #45), Sun, 8:00 AM-11:30 AM

Cardiovascular events in patients with chronic myelogenous leukemia treated with tyrosine kinase inhibitors: A systematic review and meta-analysis. *First Author: Chatree Chai-Adisaksopha, McMaster University, Hamilton, ON, Canada*

Background: Tyrosine kinase inhibitors (TKIs) have dramatically improved survival for patients with chronic myelogenous leukemia (CML). However, there are growing evidences that TKIs may be associated with an increased risk of cardiovascular events. **Methods:** We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. Included studies were: (1) randomized controlled trials or cohort studies of adult patients (≥ 18 years) treated with TKIs for chronic phase or accelerated phase CML, (2) studies that reported at least one cardiovascular outcome (peripheral arterial occlusive disease (PAOD), ischemic heart disease or stroke/TIA). The primary outcome of this review were a composite of major cardiovascular events. The pooled incidences of cardiovascular events with corresponding 95% confidence intervals [CI] were performed using a single-proportion random-effects model. The pooled risk ratio (RR) with 95% CIs was calculated using a Mantel-Haenszel random-effects model to compare the effect between nilotinib and imatinib. **Results:** We identified 32 studies enrolling 16,218 patients (20 studies investigated nilotinib, 12 imatinib, 4 ponatinib, 1 dasatinib and 1 bosutinib). The pooled incidence rates (95% CI) of cardiovascular events were 8% (6-10%) for nilotinib, 1% (0-1%) for imatinib, 2% (1-2%) for dasatinib, 10% (5-16%) for ponatinib and 13% (11-16%) for bosutinib and 6% (3-10%) for non-TKI studies. The direct comparison between nilotinib and imatinib suggested that nilotinib treatment was associated with a significantly increased risk of the cardiovascular events (RR 1.6; 95%CI 1.4-1.8). **Conclusions:** Here, we evaluated the pooled estimates of the incidence of cardiovascular events in CML patients treated with TKIs. The pool proportions suggested that, when compared to non-TKI treated patients, patients who received imatinib and dasatinib had lesser cardiovascular events, whereas the incidence was greater among patients receiving nilotinib, ponatinib and bosutinib.

7057 Poster Session (Board #46), Sun, 8:00 AM-11:30 AM

Factors influencing outcomes in patients (Pts) with relapsed/refractory b-precursor acute lymphoblastic leukemia (r/r ALL) treated with blinatumomab in a phase 2 study. *First Author: Hagop Kantarjian, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Blinatumomab, a bispecific T-cell engager (BiTE) antibody construct, showed efficacy in r/r ALL in a large phase 2 study (Topp et al. *Lancet Oncol* 2015;16:57). We evaluated associations of baseline characteristics with outcomes. **Methods:** Pts (≥18 y) had Ph-negative r/r ALL (1st relapse <12 mo; relapse <12 mo of HSCT; ≥2ndsalvage; refractory). Blinatumomab was given by continuous IV infusion (4 wk/2 wk off) for ≤5 cycles (cycle 1: 9 μg/d days 1–7; then 28 μg/d; subsequent cycles: 28 μg/d). The primary endpoint was complete remission (CR) or CR with partial hematologic recovery (CRh) within 2 cycles. Associations of baseline factors (platelets, prior salvage, bone marrow blasts [BMB], disease stage, age, region, prior HSCT, prior relapse, LDH) with CR/CRh and overall survival (OS) were assessed (Cochran-Mantel-Haenszel test, uni- and multivariate logistic regression). **Results:** 81 (43%) of 189 pts treated achieved CR/CRh within 2 cycles. Median (95% CI) RFS was 5.9 (4.8–8.3) mo; median OS was 6.1 (4.2–7.5) mo. CR/CRh was seen in all groups, including pts ≥65 yrs (44%), with/without prior HSCT (45%/42%), and pts with ≥3 prior salvages (34%). Pts with ≥50% BMB at baseline had 29% CR/CRh vs 73% in pts with <50% BMB, similar to the 78% minimal residual disease (MRD) response rate in pts with MRD+ ALL in the BLAST study (Goekbuget et al. *Blood* 2014;124:379), suggesting low biologic resistance to blinatumomab. In multivariate analyses, lower BMB and higher platelet count were associated with CR/CRh; higher platelet count and lower LDH were associated with longer OS (Table). **Conclusions:** Blinatumomab has antileukemia activity in pts with r/r ALL, including pts with poor prognostic factors. Low baseline BMB count had the strongest association with response, supporting early blinatumomab administration. For pts with higher tumor burden, cytoreduction/higher doses may be options. Clinical trial information: NCT01466179.

	Odds Ratio for CR/CRh (95% CI)	P	Hazard ratio for OS (95% CI)	P
BMB				
<50% vs ≥50%	5.1 (2.5–10.5)	<0.0001		ns
Platelet count (10^9/L)		0.0341		<0.0001
<50 vs ≥100	0.3 (0.1–0.8)		4.2 (2.3–7.8)	
50 to <100 vs ≥100	0.3 (0.1–1.0)		2.6 (1.3–5.4)	
LDH				
≥230 vs <230		ns	1.9 (1.2–3.1)	0.0082

7058 Poster Session (Board #47), Sun, 8:00 AM-11:30 AM

Performance status and comorbidities on outcome of hypomethylating therapy in older adults (≥60 years old) with acute myeloid leukemia. *First Author: Anju Chana, Department of Medicine, SUNY-UB School of Medicine, Buffalo, NY*

Background: Outcomes of standard induction chemotherapy in older patients (pts) ≥ 60 years old with acute myeloid leukemia (AML) are significantly affected by medical co-morbidities and performance status. We asked whether these same factors impact the outcome of upfront hypomethylating therapy. **Methods:** We retrospectively reviewed 83 consecutive pts ≥ 60 yrs old with newly diagnosed AML who underwent induction therapy with hypomethylating agents at our institute between 2008-13. Sixty-nine patients received decitabine (20 mg/m^2 daily for 5-10 days) and 14 received azacitidine (75 mg/m^2 daily for 7 days). Number of underlying co-morbidities, Charlson Co-morbidity Index (CCI), Hematopoietic Cell Transplant- Comorbidity Index (HCT-CI), Eastern Cooperative Oncology Group (ECOG) performance status (PS), and overall survival (OS) were assessed. **Results:** Median age was 75.5 (range 60-92) years. Three-quarters (63) were male. Median white blood cell count was 5 x 10^9/L (range 0-121). Over half (46, 55%) the pts had secondary AML, and 31 (40%) had adverse cytogenetics. Six pts (7%) had *FLT-3* mutant and 8 (10%) had *NPM-1* mutant AML. ECOG PS was assessed as 0 (13 pts, 16%), 1 (55 pts, 66%), 2 (12 pts, 14%), and ≥ 3 (3 pts, 4%). Co-morbidities were measured as 0 (19 pts, 23%), 1 (28 pts, 34%), 2 (19 pts, 23%) or ≥ 3 (17 pts, 20%). CCI was 2-3 (6 pts), 4-5 (39 pts), 6-7 (28 pts), and ≥ 8 (10 pts). Sixteen pts (20%) achieved a complete response with an overall response date of 28%. Median OS of all pts was 9.1 (95% CI 4.5-12.4) months. ECOG was significantly associated with OS (p = 0.039) with median durations of 12.6 (PS 0), 11.3 (PS 1), 3.5 (PS 2) and 0.5 (PS ≥ 3), months, respectively. Co-morbidities, CCI, or HCT-CI were not significantly associated with survival (p = NS). **Conclusions:** Our results suggest that PS, not co-morbidities, predicts outcomes in older AML pts receiving upfront decitabine/ azacitidine. These data contrast with prior studies showing that co-morbidities, CI, HCT-CI, and PS all significantly impact outcomes of intensive induction. Prospective studies of the potential benefit of hypomethylating therapy in older AML patients with multiple co-morbidities are warranted.

7059 Poster Session (Board #48), Sun, 8:00 AM-11:30 AM

Efficacy and safety of an anti-FLT3 antibody (LY3012218) in patients with relapsed acute myeloid leukemia. *First Author: David Sanford, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: LY3012218 (IMC-EB10) is a monoclonal antibody that binds FLT3 with high affinity and prevents binding of the FLT3-ligand and downstream signaling. Preclinical data using LY301228 demonstrates anti-leukemia activity which appears to be mediated via antibody dependent cell-mediated cytotoxicity (ADCC). **Methods:** We conducted a phase 1 trial to determine the safety, pharmacokinetics, and preliminary efficacy of LY3012218 in patients with relapsed/refractory acute myeloid leukemia (AML). Patients were eligible if they were ≥ 18 years, had a performance status < 3, adequate organ function, a life expectancy of > 3 months, and were not candidates for higher intensity therapy. Exclusion criteria included stem cell transplant within < 3 months, central nervous system leukemia or isolated extramedullary disease. Patients were treated in 4 dose cohorts (5 mg/kg (n = 3), 10 mg/kg (n = 13), 20 mg/kg (n = 3), 30 mg/kg (n = 5)) and received the drug intravenously weekly on days 1, 8, and 15 for cycle 1 and days 1, 8, 15, and 22 for subsequent cycles. **Results:** 31 patients were screened and 24 patients were treated. 14 patients were male (58.3%), the median age was 70.3 years (range 26-82), the median number of prior therapies was 2 (range 1-6) and 26% had a baseline FLT3 mutation. 12 patients reported 20 serious AEs with the most frequent including: pneumonia (n = 6, 25%), neutropenia (n = 3, 12.5%) and sepsis (n = 2, 8.3%). Dose limiting toxicities of infection, vomiting (10 mg/kg), and increased transaminases (30 mg/kg) were observed, although these were not clearly related to LY3012218. No MTD was defined. The serum trough concentrations for 5 to 30 mg/kg treatments (mean of Cmin: 41.9 to 739 μg/mL) following the third infusion were above the target trough concentration (33 μg/mL) associated with antitumor activity in preclinical models. Twenty one patients were evaluated for response and all were classified as treatment failures. **Conclusions:** Treatment with LY3012218 appears safe but did not demonstrate clinical activity as a single agent in relapsed/refractory AML. The lack of efficacy may be due to an absence of ADCC with LY3012218 or the presence of ligand-independent activation of signaling pathways down-stream of FLT3. Clinical trial information: NCT00887926.

7060 Poster Session (Board #49), Sun, 8:00 AM-11:30 AM

Association between early promoter methylation changes and outcome in older acute myeloid leukemia patients treated on SWOG S0703 (NCT0065884). *First Author: Sucha Nand, Loyola Univ Cancer Ctr, Maywood, IL*

Background: Treatment of acute myeloid leukemia (AML) in older patients remains a therapeutic challenge. Current treatment options range from supportive care alone to full-dose chemotherapy. Identifying factors that predict response to therapy may help increase efficacy and avoid toxicity. **Methods**: The phase II SWOG S0703 study investigated the use of hydroxyurea and azacitidine with gentuzumab ozogamicin in the elderly AML population. This regimen appeared to have efficacy similar to the standard AML regimens, with less toxicity in the poor risk population. Here we report the laboratory findings of samples accrued as part of this study. Global DNA methylation, promoter DNA methylation of six candidate genes (*CDKN2A*, *CDKN2B*, *HIC1*, *RARB*, *CDH1* and *APAF1*), and expression analysis of these same genes were determined at several time points before and during therapy. **Results**: The goal of this study was to investigate whether DNA methylation or gene expression changes predict clinical response. Global DNA methylation was not associated with a clinical response. Samples from days 3 or 4 of treatment showed significantly decreased *CDKN2A* promoter DNA methylation in patients achieving complete remission (CR) compared to those who failed to achieve CR. Samples from day 7 of treatment showed significantly decreased *RARB*, *CDKN2B* and *CDH1* promoter DNA methylation in patients achieving CR and/or complete remission with incomplete blood count recovery (CRi) compared to those who failed to achieve CR. Of the genes assessed in this study, there was a significant negative correlation (R^2= -0.47) between *APAF1* promoter methylation and *APAF1* gene expression between pre-study and day 3 or 4 samples among patients who later went on to achieve CR. **Conclusions**: These findings offer a potentially important early insight that may inform clinicians about the likelihood of success with demethylating agents in the treatment of older patients with AML. Such information may help to decrease toxicity and improve therapeutic efficacy in these patients. Support: NIH/NCI/NCTN CA180888, CA180819 and in part by Celgene Corporation and Pfizer, Inc.

7061 Poster Session (Board #50), Sun, 8:00 AM-11:30 AM

Azacitidine in older patients with acute myeloid leukemia (AML). Results from the ALMA study according to the MRC risk index score. *First Author: Jose F Falantes, Hospital Universitario Virgen del Rocio, Seville, Spain*

Background: Treatment of patients (pts) >60y with AML remains challenging. The MRC and LRF validated a 1y survival risk index score in 2843 older AML pts treated with intensive (IC) and non-intensive (NI) chemotherapy, identifying 3 groups with different risk estimates[1]. Azacitidine (AZA) prolonged OS in older AML pts vs. conventional care (AZA-AML-001 trial)[2]. Nevertheless, comparison between AZA and IC was jeopardized by the low number of subjects randomized to AZA or IC. Aim: To assess the impact of AZA in a retrospective cohort of older AML pts, unfit for IC, stratified by the MRC/LRF risk score. **Methods:** The ALMA cohort accrued 110 unfit AML pts who received compassionate front-line AZA before 2011 in 22 Spanish sites (Ramos F et al, Leuk Res. 2014). Cytogenetic, age, white blood count (WBC), PS and AML type categorized pts as good, standard and poor-risk, as stated by Wheatley's score. **Results:** Characteristics of the ALMA cohort and distribution across MRC/LRF risk categories are shown in Table 1. After accounting for the above 5 parameters, the ALMA cohort included more poor-risk pts than the MRC/LRF series (63% vs. 31%/37% in the AML11/AML14 trials, respectively). After 28 months median follow-up, 1y survival of ALMA cohort was 66%, 40% and 31%, respectively, for the good, standard and poor-risk groups. Comparison of these estimates with those of MRC/LRF trials are also shown in Table 1. Potentially relevant clinical differences are apparent in the poor-risk group when comparing AZA to either approach. **Conclusions:** Although retrospective and non-matched, AML pts unfit for IC seemed to benefit from AZA to a similar extent to IC. Moreover, in the poor-risk subset (n=70), 1y survival with AZA was equivalent and likely superior to previous AML/MRC strategies.

ALMA cohort.

Parameter	N (%)
Age (median)	75 (56-89)
PS	0-1: 77 2: 27 >2: 6
WCB (<10^9/L)	79 (72)
Therapy-related AML & AHD	16 (14%) & 27 (24.5%)
MRC cytogenetics	Fav: 1 (0.9) Inter: 64 (58.2) Adv: 30 (27.3) NA: 15 (13.6)
Risk categories (AML11 risk)	Good: 7 (6.4) Standard: 33 (30) Poor: 70 (63.6)
1y survival estimates (%)	

MRC/LRF Risk group	AML11	AML14I	AML14NI	AML14NIA	AML14 (all)	ALMA
Good	53	60	25	36	59	66
Standard	43	48	33	42	45	40
Poor	16	30	10	14	24	31

7062 Poster Session (Board #51), Sun, 8:00 AM-11:30 AM

An alvocidib-containing regimen is highly effective in AML patients through a mechanism dependent on MCL1 expression and function. *First Author: B. Douglas Smith, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Through multiple Phase I/II studies, alvocidib (flavopiridol) has proven to be highly effective in both frontline and relapsed/refractory AML when sequentially administered before ara-C and mitoxantrone (FLAM). In frontline patients, FLAM resulted in a complete remission (CR) rate of 70% versus 46% CR with ara-C and daunorubicin (7+3). Among patients with secondary (s)AML, FLAM produced 60% CR versus 35% CR with 7+3. The clinical activity of alvocidib in AML strongly correlates with inhibition of cyclin-dependent kinase-9 (CDK9) and disruption of super enhancer mediated transcription. The myeloid leukemia cell 1 (MCL1) gene is critically regulated by CDK9 activity under SE-mediated transcriptional control. **Methods:** Studies with AML cell lines were conducted to model the sequential treatment of the FLAM regimen. MCL1 expression and apoptosis were monitored in these nonclinical experiments. To further substantiate this mechanism clinically, mitochondrial profiling was conducted on 63 archived FLAM-treated samples. **Results:** Treatment with alvocidib results in a rapid downregulation of MCL1. In AML cell lines, we observe a two-fold decrease in MCL1 following alvocidib treatment that is associated with increased sensitivity to subsequent treatment with ara-C and mitoxantrone and enhanced apoptosis. Analysis of the BH3 priming states in AML clinical samples revealed NOXA priming was significantly higher in CR bone marrow samples (44.5% primed) compared with samples from non-responders (NR) (5.2% primed) ($p = 0.006$). NOXA is known to interact most directly with MCL1, suggesting that the AML samples that are most responsive to FLAM treatment may have a high survival dependence on MCL1. Interestingly, combining NOXA priming data with cytogenetic risk factors in pts with sAML, increased the predictive power of the assay as evident by a receiver operating characteristic (ROC) analysis yielding an AUC of 0.92 with $p = 0.0002$. Importantly, the correlation between NOXA and FLAM response is distinct from priming states predicting response to other ara-C regimens. **Conclusions:** This work reveals a potential biomarker for identification of patients likely to respond to FLAM.

7063 Poster Session (Board #52), Sun, 8:00 AM-11:30 AM

Ethnic differences in survival of elderly chronic myeloid leukemia patients in pre- and post-imatinib era in the United States. *First Author: Dipesh Uprety, Abington Memorial Hospital, Abington, PA*

Background: Survival of chronic myeloid leukemia (CML) has improved since FDA approval of imatinib in May 2001. However, there is limited data on survival pattern of elderly patients. We conducted this study to evaluate ethnic differences in survival of elderly CML patients. **Methods:** We selected elderly CML patients ($\geq$ 65 years) from the Surveillance, Epidemiology, and End Results (SEER) 18 database. We analyzed one- and five-year relative survival (RS) rates of CML patients by ethnicity during pre-imatinib (1990-2000) and post-imatinib (2001-2006) time periods. We used Z-test to compare survival rates. **Results:** The database comprised of 5,802 patients. Among them, 3,183 were males and 2,619 were females. Likewise, 5,073 were Caucasians and 394 were African Americans. The median age at diagnosis was 76 years. The median follow up period was 18 months (range: 1 to 60 months). The RS of the patients improved significantly in post-imatinib era as compared to pre-imatinib era (1 year: 65.6 $\pm$ 0.9 vs 59.2 $\pm$ 1.0, Z score = 4.93; 5 year: 34.6 $\pm$ 1.1 vs 22.2 $\pm$ 0. 9, Z score = 8.45). Survival rates of Caucasians improved significantly (1 year: 59.2 $\pm$ 1.1 vs 65.6 $\pm$ 1.0, Z score = 4.49; 5 year: 22.3 $\pm$ 1.0 vs 34.3 $\pm$ 1.1, Z score = 7.59) but there was no significant improvement in survival for African Americans (1 year: 58.8 $\pm$ 3.8 vs 61.1 $\pm$ 3.7, Z score = 0.49; 5 year: 21.1 $\pm$ 3.5 vs 31.1 $\pm$ 4.0, Z score = 1.61). There was no difference in survival rates of African Americans compared to Caucasians in pre-imatinib era. **Conclusions:** Survival rates of elderly CML patients have improved significantly in post-imatinib era. This improvement in survival rates is limited to Caucasians.

7064 Poster Session (Board #53), Sun, 8:00 AM-11:30 AM

The prognostic impact of combined NPM1+/FLT3- mutational status in newly diagnosed acute myeloid leukemia (AML) patients with intermediate risk cytogenetics according to age and treatment modality. *First Author: Mehrdad Hefazi, Mayo Clinic, Rochester, MN*

Background: Combined NPM1+/FLT3- is associated with a favorable prognosis in adults with AML, treated with standard chemotherapy. The impact of this on outcome is however not well defined according to age and different treatment modalities, including chemotherapy with or without hematopoietic cell transplantation (HCT), and hypomethylating agents (HMA). **Methods:** Out of 620 newly diagnosed AML pts treated between 2007 and 2014, 169 with intermediate risk cytogenetics and known NPM1/FLT3 were analyzed. **Results:** Estimated 3-yr overall survival (OS) according to age, NPM1/FLT3 status, and treatments are shown in the table. Among adults and elderly treated with chemotherapy alone, those with NPM1+/FLT3- had a superior OS compared to those without this mutational status (P=0.004 and 0.0008, respectively). Adults without NPM1+/FLT3- had a significantly improved OS when treated with HCT in addition to chemotherapy (P<0.0001), and a comparable OS to those with NPM1+/FLT3- (P=0.43), when treated with chemotherapy alone. Similarly, elderly without NPM1+/FLT3- had a superior OS when treated with chemotherapy followed by HCT (P=0.028), and a comparable OS to those with NPM1+/FLT3- (P=0.83), when treated with chemotherapy alone. Among elderly pts without NPM1+/FLT3-, those treated with HMA alone (n=12) had a similar OS to those treated with chemotherapy without HCT (P=0.86). **Conclusions:** Combined NPM1+/FLT3- is associated with a favorable prognosis, irrespective of age, in newly diagnosed AML pts with intermediate risk cytogenetics, treated with chemotherapy. In pts without NPM1+/FLT3-, the OS improves with the addition of HCT to standard chemotherapy, irrespective of age. HMA seems to be comparable to chemotherapy alone in elderly pts without NPM1+/FLT3-.

Elderly (>60 yrs.) N=84*				Adults (18-60 yrs.) N=85			
Chemo alone N=51		Chemo + HCT N=12		Chemo alone N=37		Chemo + HCT N=48	
NPM1+/FLT3- N=17	Otherwise N=34	NPM1+/ FLT3- N=1	Otherwise N=11	NPM1+/ FLT3- N=13	Otherwise N=24	NPM1+/ FLT3- N=5	Otherwise N=43
Estimated 3-yr OS							
59%	20%	-	40%	64%	16%	-	51%
P=0.005				P<0.0001			

*Other treatments: N=21.

7065 Poster Session (Board #54), Sun, 8:00 AM-11:30 AM

Infectious complications in AML patients treated with induction vs. hypomethylating therapy. *First Author: Marla M Jalbut, Massachusetts General Hospital, Boston, MA*

Background: Infectious complications are common during AML treatment, partly related to cytopenias during standard induction. It is less clear whether the same degree of infectious complications occur with hypomethylating agents (HMAs), especially early in therapy. We compared incident infectious events, as well as death due to infection, among AML patients treated with HMAs vs. induction chemotherapy. **Methods:** We evaluated consecutive cases of newly diagnosed AML at Massachusetts General Hospital from 2010-2014, and identified 47 patients given upfront therapy with HMAs, and 126 given induction, typically "7+3." The cumulative incidence of infectious events, including related death, was calculated by the method of Fine and Gray, with death/non-infectious death as a competing risk, as appropriate. Incidence rate ratios were calculated between groups. Survival was compared by the method of Kaplan and Meier and log-rank test. **Results:** Median follow-up was 596 days. Induction patients were younger (62 vs 76 y.o., $p < 0.0001$), and fewer had secondary AML (33% vs. 62%, $p = 0.001$). Patients given induction had improved CR/CRi rates (83% vs. 38%) and 1-year OS (64.2% vs. 35.3%) compared to HMAs. The 30-day cumulative incidence of febrile neutropenia (82.5% vs. 34.4%, $p < 0.0001$), bacteremia (23% vs. 8.6%, $p = 0.0021$), and colitis (18.3% vs. 4.4%, $p = 0.0028$) was higher with induction vs. HMA therapy, while incident cellulitis was lower (4.8% vs. 17.2%, $p = 0.028$). Induction patients also had an increased incidence rate of febrile neutropenia (IRR 7.07, $p < 0.0001$), and lower rate of cellulitis and UTI (IRR 0.26, $p = 0.0006$, and IRR 0.30, $p = 0.0020$, respectively). There was no significant difference in fungemia, pneumonia, non-invasive candida infection, nor the cumulative incidence of death due to infection at 120 days (4.0% induction vs. 4.3% HMA, $p = 0.57$). **Conclusions:** AML patients treated with induction had greater rates of febrile neutropenia, bacteremia, and colitis compared to those treated with HMA therapy, but lower rates of cellulitis and UTI. In spite of the marked increase in early infectious events during induction vs. HMA therapy, there was no significant difference in the cumulative incidence of death due to infection.

7066 Poster Session (Board #55), Sun, 8:00 AM-11:30 AM

Digital *Fusion-Gene* expression profiling in acute leukemia (AL): Clinical validation of throughput molecular technology in laboratory medicine. *First Author: Ariz Akhter, University of Calgary, Calgary, AB, Canada*

Background: AL is a heterogenous and aggressive disease with dismal prognosis. Chromosomal translocations constitute the basis of current WHO classification and are central to AL pathogenesis. FISH technique is utilized to detect variable translocations for patient prognosis and therapy selection. It is a labor intensive and expensive technique, which may not support rapidly expanding scope of additional translocations of clinical importance in AL patients. Hence, throughput automated technologies may play a critical in the management of AL patients. **Methods:** Nanostring platform utilizes a novel digital color-coded automated technology that is based on direct multiplexed measurement of gene expression. The "*nCounter Leukemia Fusion Gene Expression Assay Kit"* allows profiling a comprehensive set of 25 fusion genes that result from balanced translocations in AL. It also includes probes for 12 clinically proven AL-related biomarkers. RNA extracted from FFPE tissue from 50 AL patients with known balanced chromosomal translocations and validated the fusion gene expression on this platform. **Results:** We observed highly significant concordance between Nanostring fusion gene results with FISH data in various translocation such as t(9;22) (BCR-ABL); t(15;17) PML-RARA; t(8;21) (AML-ETO); t(4;11) (MLL-AF4) and Inv(16) (CBFB-MYH11) ($P < 0.05$). Nanostring technology failed to validate fusion gene transcript in patients with t(12;21) (TEL-AML). High expression of BAALC, a prognostic biomarker associated with poor outcome in AL patients was noted in t(9;22) (58%), t(15;17) (12%), t(4;11) (50%), t(12, 21) (20%), t(8;21) (20%) and Inv(16) (63%). **Conclusions:** We have validated the application of automated throughput technology for AL patients in a clinical laboratory. Our study provides an efficient, viable and economical solution for the rapidly expanding molecular repertoire of laboratory testing for AL patients, which is critical to determine prognosis and select effective therapy. This approach also provides a promise to seamlessly incorporate newly discovered (up to 800) targets of diagnostic and prognostic importance on this digital platform.

7067 Poster Session (Board #56), Sun, 8:00 AM-11:30 AM

Construction and characterization of novel CD33/CD3 tandem diabodies (TandAbs) for the treatment of acute myeloid leukemia (AML). *First Author: Uwe Reusch, Affimed GmbH, Heidelberg, Germany*

Background: CD33 had been validated as an AML target in randomized studies of the antibody-drug conjugate, gemtuzumab ozogamicin (GO) in a subset of patients, but currently explored CD33-targeted therapeutics are ineffective in many patients. Here, we explored the potential therapeutic activity in AML of a series of novel CD33/CD3-directed tandem diabodies (TandAbs). These tetravalent bispecific antibodies comprised of single chain antibody variable fragments (scFv) have avidity due to two binding sites for each antigen and attractive pharmacokinetics due to a molecular size that is larger than the renal clearance threshold. **Methods:** CD33/CD3 TandAbs were generated from humananti-CD33 and anti-CD3 scFv domains and expressed in CHO cells. Binding affinities of purified TandAbs were determined via flow cytometry. T-cell activation was assessed via quantitation of CD25 and CD69 on T-cells. Cytotoxic properties of TandAbs against CD33+ AML cell lines and primary specimens from adults with AML, selected across the entire cytogenetic/molecular disease spectrum, were determined in 48-hour assays in the presence of healthy donor T-cells. **Results:** Our studies demonstrated that CD33/CD3 TandAbs induced potent cytolysis of CD33+ AML cell lines and patient-derived AML specimens at pM concentrations. Their cytotoxic effect required the presence of T-cells and was quantitatively dependent on the concentration of the TandAb as well as the effector-to-target (E:T) cell ratio. In a series of 29 primary AML specimens, high-affinity CD33/CD3-directed TandAbs were broadly active *in vitro*, even in leukemias with low CD33 expression, with similar activity profiles in specimens from patients with newly diagnosed AML and those with relapsed or refractory disease. **Conclusions:** CD33/CD3 TandAbs have potent and selective cytotoxicity for CD33+ AML cells that is independent of disease stage. Our findings identified several TandAbs that merit further study as targeted AML therapeutics.

7068 Poster Session (Board #57), Sun, 8:00 AM-11:30 AM

Long-term bosutinib (BOS) for Philadelphia Chromosome–Positive (Ph+) advanced (ADV) chronic myeloid leukemia (CML) after prior tyrosine kinase inhibitor (TKI) failure. *First Author: Carlo Gambacorti-Passerini, University of Milano-Bicocca, Monza, Italy*

Background: ADV Ph+ CML pts have worse outcomes vs chronic CML pts. In this first report of BOS activity in this cohort as fully enrolled, we evaluate long-term efficacy and safety of BOS in ADV pts ≥4 vs ≥1 y from last enrolled pt. **Methods:** Ongoing phase 1/2 BOS study in 79 accelerated (AP) and 64 blast phase (BP) pts with prior TKI failure **Results:** For AP and BP pts, 18% and 3% remained on BOS at 4 y (vs 48%; 13% at 1 y; 1 y = 48 wk); 57% and 28% newly attained or maintained baseline overall hematologic response (OHR) by 4 y (most by 12 mo); 40% and 37% attained/maintained major cytogenetic response (MCyR) by 4 y (most by 12 mo). Kaplan-Meier (KM) probabilities of maintaining OHR in responders at 4 vs 1 y were 49% vs 78% (AP) and 19% vs 28% (BP); KM MCyR probabilities at 4 vs 1 y were 49% vs 65% (AP) and 21% vs 21% (BP). AP and BP pts were treated for median 10.2 (range, 0.1–88.6); 2.8 (0.03–55.9) mo. Most common AEs were gastrointestinal (AP, 96%; BP, 83%), primarily diarrhea (85%; 64%), which was typically low grade (grade 1/2: 96%; 93%), transient (median duration/any grade AE: 2 [range, 1–910] d; 2 [1–211] d); no pt discontinued due to this AE. Newly occurring AEs arose mostly in y1; new cardiac/vascular AEs occurring in y4 were pericardial effusion, sinus bradycardia/1st degree atrioventricular block (same pt), and hypertension (all n=1); those in y1 (>2 pts either cohort) were pericardial effusion (AP, n=4; BP, n=1), tachycardia (n=2; n=4), hypertension (n=3; n=2; Table). Serious AEs occurred in 56% AP and 58% BP pts, most commonly pneumonia (n=9; n=5). 11 AP and 13 BP pts died within 30 d of last dose; 2 BOS-related (AP). Treatment discontinuations were mostly due to PD (AP, ≤1/>1 y, n=10/13; BP, n=29/3) and AEs in AP (n=16/5); death (n=6/0) and symptomatic deterioration (n=6/0) in BP. **Conclusions:** Durable response was seen in ~50% AP responders (~25% BP responders at y1, for whom BOS may be bridge to transplant); toxicity was manageable with long-term treatment. Clinical trial information: NCT00261846.

Newly Occurring AEs*.

	Y1		Y2		Y3		Y4	
n	AP n=79	BP n=64	AP n=34	BP n=5	AP n=19	BP n=3	AP n=15	BP n=2
Diarrhea	67	41	0	0	0	0	0	0
Cardiac	12	7	1	1	1	1	2	0
Vascular	4	7	4	0	1	0	1	0

*Not experienced by same pt previously (denominator=pts on treatment each y [1 y = 52 wk]).

7069 Poster Session (Board #58), Sun, 8:00 AM-11:30 AM

Clinical activity, safety profile, and hepatotoxicity of TGR-1202, a novel once daily PI3Kδ inhibitor, in patients with CLL and B-cell lymphoma. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: TGR-1202 is a novel, next generation PI3Kδ inhibitor which lacks the hepatotoxicity associated with other PI3Kδ inhibitors and is active in patients (pts) with advanced heme malignancies (ASH 2014). Herein we present updated safety and efficacy results from a Ph I study of TGR-1202 in pts with rel/ref CLL and B-cell lymphoma. **Methods**: TGR-1202 is administered orally once-daily following a 3+3 dose escalation design. Eligible pts have rel/ref B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), or other B-cell malignancy and an ECOG PS ≤ 2. Endpoints: safety, PK/PD, and efficacy. **Results**: As of Feb 2015, 58 pts evaluable for safety including CLL, FL, Hodgkin's (HL), DLBCL, MCL, and MZL. Median age 63 yo (range: 22-85), 72% male, ECOG 0/1/2: 19/38/1, median prior Tx: 3 (range: 1-14), 48% refractory to prior Tx. Safety: The only Gr ≥ 3 AE in ≥ 10% of pts was neutropenia (10%). AEs (all grades, all causality) in > 20% of pts were limited to diarrhea (34%), fatigue (31%), nausea (29%), and cough (26%). All diarrhea events Gr1/2, except one Gr3 event occurring in a pt in Cyc 1, which persisted for 2 days and resolved without dose interruption. Notably, in contrast to similar agents, no drug-related hepatotoxicity or colitis has been observed to date (ave time on study 7 Cyc). 2 episodes of Gr3 fatigue at 1800 mg of a new micronized formulation met the criteria for DLT. Expansion cohorts are open at 800 mg (CLL) and 1200 mg (NHL). Efficacy: A strong exposure-response relationship has been observed. Of 14 evaluable CLL pts, 13 (93%) achieved a nodal PR (median nodal ↓ of 76%), of which 7 (50%) achieved a PR per Hallek 2008 criteria. Responses have been limited in pts with aggressive lymphoma and HL. Of the 12 evaluable FL pts, 8 (67%) remain on study progression-free (range 7 - 99+ weeks), with 3 achieving a PR, notably being the 3 pts exhibiting the highest TGR-1202 plasma concentrations. **Conclusions**: TGR-1202 is well tolerated in pts with rel/ref heme malignancies with no reported hepatotoxicity or colitis (41% of pts on study 6+ Cyc) and promising activity in CLL and NHL. Enrollment continues in expansion cohorts. Clinical trial information: 01767766.

7070 Poster Session (Board #59), Sun, 8:00 AM-11:30 AM

A phase I trial of the human double minute 2 inhibitor (MK-8242) in patients with refractory/recurrent acute myelogenous leukemia (AML). *First Author: Farhad Ravandi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Human double minute 2 (HDM2) binds to and inhibits wild-type (WT) p53, thereby promoting oncogenesis. MK-8242 is a potent, orally bioavailable, small-molecule inhibitor of the HDM2:p53 protein-protein interaction being developed as a novel cancer therapy. **Methods:** This multi-center, non-randomized, open-label, 2-arm (A/monotherapy and B/combination therapy), 2-part (dose escalation and confirmation) study was designed to evaluate the safety/tolerability, pharmacokinetics (PK) and recommended phase 2 dose (RP2D) of MK-8242 +/- cytarabine in p53 WT patients (pts) with refractory/recurrent AML. The study was terminated for reasons unrelated to safety; only the monotherapy dose-escalation phase was completed. In Arm A, MK-8242 was initially dosed p.o. either QD (30 mg-250 mg) or BID (120 mg-250 mg) for 7 days on/7 days off (7on/7off) in a 28-day cycle The dosing schedule was later modified to 7on/14off in a 21-day cycle (210 mg or 300 mg BID) to improve the safety profile of the drug. **Results:** 26 pts enrolled (24 evaluable for response). Median age was 66 yrs (range: 29-81). All pts had ≥ 1 AE with 5 (19%) discontinuing due to AEs. There were 7 deaths (3 pneumonia-related; 2 AML progression; 1 sepsis; 1 respiratory failure); only 1 death (fungal pneumonia due to marrow aplasia) was deemed drug-related. With the initial 7on/7off regimen, DLTs occurred only in the 250 mg BID group in 2 pts (bone marrow failure, G1 and G4). After switching to the 7on/14off schedule, no DLTs were observed for the 210 mg BID or 300 mg BID groups (doses above 300 mg not tested). Across all dosing schedules, best responses were: 1/24 PR observed after 11 wks (120 mg QD, 7on/7off); 1/24 CRi observed after 2 wks (210 mg BID, 7on/14off); and 1/24 morphologic leukemia-free state after 4 wks (250 mg BID, 7on/7off). Plasma PK analysis on day 7 at the 210 mg BID dose revealed $AUC_{0\text{-}12hr}$ of 8.7 μM*hr, C_{max} of 1.5 μM (n = 5, T_{max}, 2-6 hr) and $T_{1/2}$ of 7.9 hr. **Conclusions:** The modified 7on/14off regimen showed a more favorable safety profile than the 7on/7off schedule, and a MTD for this regimen was not established. Clinical activity was seen at 210 mg BID (7on/14off), providing impetus for further study of HDM2 inhibitors in pts with AML. Clinical trial information: NCT01451437.

7071 Poster Session (Board #60), Sun, 8:00 AM-11:30 AM

Development of a bispecific tetravalent CD33/CD3 TandAb for the treatment of AML. *First Author: Uwe Reusch, Affimed GmbH, Heidelberg, Germany*

Background: Acute Myeloid Leukemia (AML) is a hematologic malignancy with dire prognosis; immunotherapy may offer a much needed alternative to cytotoxic chemotherapy. TandAbs are tetravalent, bispecific diabodies that exceed renal clearance limits, providing both avidity and pharmacokinetic advantages over monovalent bispecific constructs. To identify a potential immunotherapeutic for AML and other $CD33^+$ hematologic malignancies, fully human T-cell recruiting, CD33-directed bispecific TandAbs were constructed and profiled for manufacturability, stability and pharmacologic activity. **Methods:** Anti-CD33 scFv with high affinity to both human and cynomolgus CD33 were selected from fully human scFv libraries using phage display. Stable anti-CD33 scFv were formatted into TandAbs; linker length and domain order/topology were also varied. Expression levels in stably transfected CHO cells, purification properties, and stability were evaluated. Mechanism-based functional assays measured CD33/CD3 TandAb-mediated cytotoxicity towards CD33+ target cells. T cell activation and proliferation in the presence and absence of target cells were also studied. *In vitro* safety assessments of specificity and cytokine release from T cells without target cells were performed. CD33/CD3 TandAbs were studied in prophylactic and established HL-60 xenograft models. **Results:** CD33/CD3 TandAbs with excellent production and stability profiles also had potent cytotoxic activity towards CD33+ target cells (EC50 < 10 pM). TandAbs demonstrated equivalent binding affinity and potency for human and cyno antigens, facilitating toxicity studies. T cell activation, proliferation and cytotoxicity were strictly linked to the presence of CD33+ target cells. CD33/CD3 TandAbs did not elicit cytokine release from T cells without target cells. Potent anti-tumor activity of CD33/CD3 TandAbs was observed *in vivo*. **Conclusions:** A human CD33/CD3 TandAb therapeutic candidate with a promising activity and safety profile to date warrants clinical development as a potential treatment for AML. Preclinical development is ongoing.

7072 Poster Session (Board #61), Sun, 8:00 AM-11:30 AM

Serum chemokines and cytokines in CLL patients treated with duvelisib, a PI3K-δ,γ inhibitor. *First Author: Mark Douglas, Infinity Pharmaceuticals, Cambridge, MA*

Background: PI3K-δ and PI3K-γ play complementary roles in malignant B-cells and the tumor microenvironment (TME). Inhibition of PI3K-δ blocks cytokine-mediated CLL proliferation, while inhibition of PI3K-γ blocks M2 macrophage polarization and T-cell migration in vitro. Duvelisib, an oral PI3K-δ,γ inhibitor, has shown clinical activity in a phase 1 study in patients (pts) with advanced hematologic malignancies (Study IPI-145-02), including pts with relapsed/refractory (R/R) CLL (O'Brien, ASH 2014). **Methods:** Serum from 52 pts with R/R CLL and 30 healthy subjects (HS) was analyzed for 72 analytes (cytokines, chemokines, and matrix metalloproteinases) using Luminex xMAP technology at baseline, Cycle 1 Day 8 (C1D8), C2D1, and C3D1. Median change from baseline was analyzed for statistical significance using a paired t-test with Bonferroni correction for multiple hypotheses; threshold for reduction was ≤ 50% of baseline and for increase was ≥ 150% of baseline. Comparison between CLL and HS utilized a 2-sample t-test with Bonferroni correction. **Results:** Following treatment with duvelisib, the median serum levels of 12 analytes decreased to ≤ 50% of baseline ($p < 0.0002$) by C1D8. These included CCL1, CCL3, CCL4, CCL17, CCL22, CXCL10, CXCL13, IL-6, IL-10, IL-12p40, MMP-9 & TNFα. All of these were significantly elevated ($p < 0.0042$) at baseline in CLL pts compared to HS and reduced towards normal range following duvelisib treatment. In addition, MMP1 was the only analyte for which median serum levels increased above the threshold of ≥ 150% of baseline ($p < 0.0002$). Together, these 13 analytes were further explored for potential associations with clinical efficacy. TNFα was significantly elevated ($p < 0.0013$) at C2D1 & C3D1 in pts who did not exhibit a nodal response. **Conclusions:** Most of the analytes reduced following duvelisib treatment are known to be involved in the communication between CLL cells and the TME. Furthermore, one of these analytes (TNFα) exhibited elevated levels at C2D1 and C3D1 in pts who did not achieve a nodal response. Together, these data indicate that modulation of the TME via PI3K-δ,γ inhibition may be an important mechanism of action in supporting clinical activity of duvelisib in patients with CLL. Clinical trial information: NCT01476657.

7073 Poster Session (Board #62), Sun, 8:00 AM-11:30 AM

The dual SRC-ABL inhibitors in Ph+ acute lymphoblastic leukemia to enhance synergy between targeted BCR-ABL and BCL-2 inhibitors. *First Author: Jessica Taft Leonard, Oregon Health and Sci Univ, Portland, OR*

Background: Outcomes in adult Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph^+ALL) remain poor with a 5 year overall survival of less than 40%. Addition of the targeted BCR-ABL inhibitors (TKI) to standard cytotoxic therapy has greatly improved upfront treatment, yet relapse remains common with a median survival of just 4.5 months. Therefore identification of targeted agents that could enhance the activity of TKIs is urgently needed. ABT 199 is a BCL-2 inhibitor which has shown pre-clinical activity against a variety of B cell malignancies. Here we evaluate the combination of ABT199 across a panel of TKIs to explore potential mechanisms of synergy in hopes to better define the optimal combination for future clinical studies. **Methods:** Drug efficacy *in vitro* was determined using the Ph^+ALL cell line SupB15. Cells were incubated with varying concentrations of dasatinib, imatinib, nilotinib or ponatinib in combination with ABT199 for 72 hours. Cell viability was assessed using a colorimetric MTS assay, and cell apoptosis was assessed with annexin V staining. Combination effects were calculated using Calculsyn software. Standard immunoblots were used to assess inhibition of downstream pathways. **Results:** The combination index (CI) values for each of the TKIs with ABT199 ranged between 0.13 – 1.4 for Imatinib, 0.4 – 1.05 for Nilotinib, 0.06 – 0.33 for Ponatinib, and 0.07 – 0.64 for Dasatinib, where $CI < 1$ predicted synergy. As a single agent, ABT199 induced the highest degree of apoptosis, enhanced preferentially by dasatinib and ponatinib. Evaluation of key phosphorylated kinases showed that all four TKIs effectively inhibited the downstream ABL1 target pCRKL. In addition, both dasatinib and ponatinib inhibited pLYN while dasatinib also inhibited pBTK. **Conclusions:** Combination of BCL-2 and BCR-ABL targeting in Ph^+ALL is synergistic *in vitro*. The enhanced synergy seen with dasatinib and ponatinib may be due to the ability of these agents to target additional pathways active in leukemic cells. The addition of ABT-199 as part of TKI therapy for adult Ph^+ALL warrants further clinical investigation, particularly in patients with relapsed or refractory disease.

7074 Poster Session (Board #63), Sun, 8:00 AM-11:30 AM

Early clinical activity and pharmacodynamic effects of duvelisib, a PI3K-δ,γ inhibitor, in patients with treatment-naïve CLL. *First Author: Manish R. Patel, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL*

Background: Signaling via PI3K-δ and PI3K-γ has distinct and complementary effects on malignant B-cells and nonmalignant immune cells in chronic lymphocytic leukemia (CLL). Duvelisib, an oral PI3K-δ,γ inhibitor, has shown clinical activity in a phase 1 study, IPI-145-02. The activity of duvelisib monotherapy in pts with treatment-naïve (TN) CLL from this study are reported here. **Methods:** Following dose escalation, an expansion cohort of TN CLL pts was enrolled ($n = 18$). Response was based on iwCLL (2008) criteria. Safety included AEs and laboratory assessments. Pharmacodynamic assessments included peripheral blood (PB) flow cytometry for phospho-S473 AKT (pAKT) and Ki67, and measurement of serum chemokines and cytokines. Numbers of PB T-cell subsets were also monitored. **Results:** As of Oct 2014, 18 TN CLL pts received duvelisib 25 mg BID. The best ORR per iwCLL was 82% (PRs in 14/17 evaluable pts) with a median time on treatment of 53 weeks (range 8-69). Ten pts remain on treatment, while 8 discontinued, including 6 pts due to AEs. AEs overall were mostly Gr. 1 or 2. The most common ≥ Gr. 3 AEs were neutropenia (7/18) and ALT/AST increase (3/18). Inhibition of pAKT in CLL cells was rapid following a single dose and sustained through Cycle 2 Day 1 (C2D1). A reduction in the Ki67 proliferative fraction in both CLL and T-cells was also observed. The overall number of T-cells and T-cell subsets (CD4, CD8, memory cells) did not decrease through C3D1. Duvelisib also resulted in reductions in the median serum levels of CCL3, CCL4, CCL17, CCL22, CXCL10, CXCL13, IL-10, IL-12p40, MMP-9, IL-16, and TNFα to ≤ 50% of baseline at C1D8 and/or C2D1 ($p < 0.01$). **Conclusions:** Duvelisib 25 mg BID shows clinical activity in TN CLL pts.The inhibition of pAKT and Ki67 in CLL cells suggests duvelisib inhibits the PI3K pathway and suppresses malignant cell proliferation in TN CLL pts. In addition, the effect of duvelisib on serum chemokines, cytokines, and T-cell proliferation suggests that modulation of the tumor microenvironment may contribute to the observed early clinical activity of duvelisib in pts with TN CLL. These data support the further development of duvelisib in TN CLL, including combinations with other targeted therapies. Clinical trial information: NCT01476657.

7075 Poster Session (Board #64), Sun, 8:00 AM-11:30 AM

CDA status as predictive marker of aplasia duration and clinical outcome in AML patients receiving cytarabine based chemotherapy. *First Author: Cedric Mercier, La Conception University Hospital of Marseille, Marseille, France*

Background: Cytarabine is mainstays for treating hematological malignancies. As most nucleosidic analogs, cytarabine is metabolized in the liver by an exclusive enzymatic pathway driven by cytidine deaminase (CDA). CDA is highly polymorphic and dysregulations have been repeatedly associated with poor clinical outcome in patients treated with gemcitabine. **Methods:** We have used a test to determine, on a phenotype basis, CDA status in patients. This test was used in a subset of 42 adult patients (18F, 24M, mean age 60 years), all treated with a cytarabine-containing regimen. Response and treatment-related toxicities were monitored following current standards (CTC). This was a retrospective and prospective observational single-center study. All patients requiring a first induction chemotherapy for AML (AML de novo or secondary to myelodysplastic syndrome) and consolidation phase. The objective was to determine the relationship between the CDA status and clinical outcome. **Results:** In patients, mean CDA activity was 2.85 U/mg (min: 1, max: 14.8 U/mg). Ten out of 41 patients (i.e., 24%) showed low CDA activities and were considered as poor metabolizer (PM). Conversely, 4 patients (i.e., 9.75%) displayed particularly elevated (i.e., > 6U/mg) CDA activities and were considered as ultra-rapid metabolizer (UM). During first induction chemotherapy, the duration of aplasia was 30 days vs 22 days in low CDA activities group and normal or elevated CDA activities respectively ($p < 0.05$). During consolidation chemotherapy, the duration of aplasia was 21 days vs 9 days in low CDA activities group and normal or elevated CDA activities respectively ($p < 0.001$). Of note, PM patients all showed severe toxicities, including three toxic-deaths. Conversely, UM patients showed little efficacy. **Conclusions**: Overall this study strongly suggests that CDA status could be a relevant marker for predicting clinical outcome in patients treated with cytarabine. CDA status is significantly related with duration of aplasia, it could be further used as a covariate to tailor drug dosage so as to ensure an optimal efficacy/toxicity balance in patients with hematological malignancies.

7076 Poster Session (Board #65), Sun, 8:00 AM-11:30 AM

Long-term bosutinib (BOS) in patients (pt) with chronic phase (CP) chronic myeloid leukemia (CML) after prior imatinib (IM) failure. *First Author: Jeffrey Howard Lipton, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: BOS is a Src/Abl tyrosine kinase inhibitor for adults with Ph+ CML resistant/intolerant to prior therapy. We assess long-term efficacy/tolerability of BOS after ≥5 y vs ≥2 y follow-up from last enrolled pt. **Methods:** Data were from an ongoing phase 1/2 study in CP CML pts on 2nd-line BOS (500 mg/d start dose) after IM failure (n = 284). **Results:** 41% of pts remained on BOS at 5 y vs 54% at 2 y (1 y = 48 wk); 60% and 50% had newly attained or maintained baseline major cytogenetic response (MCyR) or complete cytogenetic response (CCyR) (most in ≤2 y). Kaplan-Meier (KM) probability of maintaining MCyR or CCyR in responders was similar at 5 y (71%, 71%) and 2 y (76%, 79%); 6 and 7 pts lost response > 2 y. Cumulative incidence of on-treatment transformation to AP/BP CML at 5 y was 4%; 55% discontinued without transformation < y5. 1/153 pts on-treatment > 2 y transformed to AP in y3–5. KM overall survival was 84% at 5 y vs 91% at 2 y (40% censored < y5). Median treatment duration was 25.6 (range 0.2–94.9) mo; follow-up: 51.4 (0.6–96.3) mo. 37 pts discontinued BOS y3-5 (vs 131 ≤2 y), mostly for disease progression (n = 11), AE (n = 7, y3: coronary artery disease, scleroderma, renal failure; y4: ascites and serositis [same pt], blood creatinine increased, pulmonary hypertension; y5: thrombocytopenia), and unsatisfactory efficacy (n = 7). Common newly occurring AEs (in > 5 pts) in y3 were cough (n = 7), blood creatinine increased (n = 7), pyrexia (n = 6), and blood creatine phosphokinase increased (n = 6); y4: blood creatinine increased (n = 6), pleural effusion (n = 6); y5, none in > 5 pts. Newly occurring AEs of interest (**Table**) were most common in y1–2; vascular AEs > y2 were primarily hypertension (y3, n = 5; y4, n = 3; y5, n = 2). 4 on-treatment deaths occurred y3–5, none BOS-related. **Conclusions:** BOS showed durable efficacy and manageable toxicity; a large proportion of CP CML pts with prior IM failure remained successfully treated at 5 y. Clinical trial information: NCT00261846.

Newly Occurring AEs*

n (%)	Y1 n = 284	Y2 n = 189	Y3 n = 148	Y4 n = 130	Y5 n = 124
Diarrhea	239 (84)	3 (2)	0	1 (1)	0
Cardiac	23 (8)	7 (4)	8 (5)	7 (5)	4 (3)
Vascular	11 (4)	8 (4)	5 (3)	4 (3)	5 (4)
Renal	14 (5)	4 (2)	8 (5)	7 (5)	5 (4)

*Not experienced by same pt previously (denominator = pts on treatment each y; 1 y = 52 wk)

7077 Poster Session (Board #66), Sun, 8:00 AM-11:30 AM

First report of a phase I/II study of DFP-10917, a nucleoside analog, given by continuous infusion (CI) in patients (pts) with relapsed or refractory acute leukemia. *First Author: Hagop M. Kantarjian, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: DFP-10917 has a unique mechanism of action upon prolonged administration at a low dose. Under such administration, DFP-10917 is converted to its nucleotide form and then incorporated into DNA in tumors to cause DNA strand breaks resulting in G2/M phase-arrest by cell-checkpoint regulators and ultimately the apoptosis of tumor cells. **Methods:** In phase I, DFP-10917 was administered by 7-day CI followed by 21 days rest (stage 1) or 14-day CI followed by 14 days rest (stage 2) in pts with relapsed or refractory acute leukemia in order to determine the maximum tolerated dose (MTD), recommended phase II dose (RP2D) and dose-limiting toxicity (DLT) of CI DFP-10917. **Results:** In stage 1, 27 pts received a 7-day CI of DFP-10917 at 8 escalating doses ranging from 4 to 35 mg/m^2/day. At the 35 mg/m^2 dose level, one patient experienced a DLT of grade 3 diarrhea during cycle 1. Two other pts treated at the 35 mg/m^2 dose level completed cycle 1 study treatment without DLT. The starting dose for stage 2 was calculated as 2/3rds the cumulative 7-day DFP-10917 dose at the MTD of 30 mg/m^2/day divided by 14-day resulting in a dose of 10 mg/m^2/day x 14 days. In stage 2 of phase I, 4 pts received 10 mg/m^2/day x 14-day CI DFP-10917 with DLTs of prolonged hypo-cellularity in 2 pts. At the 6 mg/m^2/day x 14-day dose level, 1 of 6 evaluable pts in a cohort experienced a DLT of prolonged hypo-cellularity, and the MTD/RD was defined as 6 mg/m^2/day x 14-day CI. Initial efficacy assessments include leukemia responses observed in 7 of 10 pts (70%) receiving the 14-day DFP-10917 CI; three were bone marrow complete responses, and four were partial response. Patients have received up to 7 cycles of DFP-10917 CI to date with ongoing responses. **Conclusions:** The MTD/RP2D of DFP-10917 in relapsed AML was established for 14-day CI at 6 mg/m^2/day, and the phase II study was initiated based on an acceptable safety profile. In phase II, the therapeutic efficacy of the DFP-10917 will be evaluated in relapsed or refractory acute myeloid leukemia (AML), or pts aged ≥ 60 years with newly diagnosed AML. Enrollment of the phase II study is ongoing.Clinical trial information: NCT01702155. Clinical trial information: NCT01702155.

7078 Poster Session (Board #67), Sun, 8:00 AM-11:30 AM

A phase (Ph) 1/2 trial of rituximab (RX), imprime PGG (IP), and alemtuzumab (AL) in the early treatment of patients (Pts) with high risk chronic lymphocytic leukemia (CLL). *First Author: Nandita Bose, Biothera, Inc., Eagan, MN*

Background: IP, a beta 1,3/1,6 glucan, can prime innate immune cells via complement receptors to kill antibody (Ab)-targeted, complement-opsonized tumor cells. Endogenous anti-beta glucan Abs (ABA) are required for IP binding and activation of innate immune cells. In stage IV NSCLC, serum ABA levels correlate with response to IP-containing therapy. Results from the Ph 1 portion of this study showed that IP in combination with RX and AL was well tolerated and associated with 73% complete response (CR) rate (Blood 120: abstr 1792, 2013). Here, we report clinical and translational results at the end of Ph 2. **Methods:** Primary endpoint of Ph 2 was % pts with CR 3 mos after completing 5 wks of IP + RX + AL. Eligible pts (n = 14) had CLL (per standard IWCLL criteria), high risk molecular features, no prior treatment, no standard indication for treatment initiation, adequate performance status and organ function. Planned enrollment was up to 39 pts. The study was terminated early due to slow accrual. Translational studies evaluated baseline serum ABA levels and in vitro IP binding to healthy donor whole blood immune cell subsets. **Results:** Among 14 pts enrolled, 6 (43%), 5 (36%) and 3 (21%) had Rai Stage 0, 1 and 2, respectively. CLL risk factors were 17p13- (21%), 11q22- (36%), and unmutated IGHV or VH3-21 use with ZAP70 and/or CD38 (43%). Grade 3/4 AEs were diarrhea, transaminase increase, dehydration, gastritis, hypertension, hyponatremia, neutropenia and febrile neutropenia. 13 (93%) pts responded to therapy (7 CR, 2 CR w/incomplete marrow recovery, 1 nodular PR and 3 PR by IWCLL-NCI 2008 criteria). As of 9/23/14 cutoff, median (med) f/u was 18.0 mo (range 9.5 - 28.0). Overall med duration of response was not reached: only 5/13 responders had progressed (med 5.6 mo; range 2.9 - 8.5); 8 are progression-free after med 10.2 mo (range 5.8 - 21.0). There were no deaths. ABA correlated with IP binding to neutrophils, monocytes and B-cells but not clinical response. Macrophage Ab-dependent cellular phagocytosis was enhanced *in vitro*and may contribute to anti-tumor mechanisms. **Conclusions:** IP in combination with RX and AL was safe and well tolerated, with high response rates. Clinical trial information: NCT01269385.

7079 Poster Session (Board #68), Sun, 8:00 AM-11:30 AM

Moxetumomab pasudotox and minimal residual disease in hairy cell leukemia. *First Author: Robert J. Kreitman, Laboratory of Molecular Biology, NCI, NIH, Bethesda, MD*

Background: Moxetumomab pasudotox is a recombinant immunotoxin containing truncated Pseudomonas exotoxin fused to an anti-CD22 Fv, reported to achieve 46% complete remissions in 28 relapsed/refractory hairy cell leukemia (HCL) patients treated with 5-50 ug/Kg every other day for 3 doses (QOD x3) per cycle. As a secondary endpoint of this phase I study, minimal residual disease (MRD) was studied in the original cohort and in an additional 21 patients enrolled at the highest dose level, amounting to 33 patients at 50 ug/Kg QOD x3. **Methods:** MRD studies included immunohistochemistry (IHC) of bone marrow biopsy (BMBx) and flow cytometry (FC) of blood and bone marrow aspirate (BMA). Real-time quantitative (RQ)-PCR, previously reported to detect 1 HCL cell in 10^6normal, used immunoglobulin rearrangement (IgH)-specific primers, when patient HCL IgH sequencing was possible. **Results:** Elimination of MRD by BMA FC, BMBx IHC and blood FC was achieved in 13 of 46 evaluable patients, 12 (36%) of 33 at 50 ug/Kg x3 and 1 (33%) of 3 at 40 ug/Kg QOD x3, vs 0 of 10 at lower doses (p = 0.04). Of 36 patients at 40-50 ug/Kg, those MRD-negative included 5 by blood FC, 1 by BMBx IHC, 5 by both blood FC and BMBx IHC, and 13 by all 3 studies. The median time to resolution of MRD in these 13 patients was 84 days, just prior to cycle 4. Of these 13 MRD-free patients, 11 (85%) remain MRD-free for 28-72 (median 45) months, and all 13 remain MRD-free in blood. In contrast, 7 of 10 patients MRD-free by blood but not BMA FC eventually became MRD+ in blood (p = 0.0005). RQ-PCR was more sensitive than BMA FC; of 19 patients evaluable for RQ-PCR, 5 of 6 MRD-free by BMA FC were also MRD-free by BMA RQ-PCR. **Conclusions:** Moxetumomab pasudotox can eradicate MRD in multiply relapsed HCL patients. We are aware of no other non-chemotherapy option with documented multi-year MRD-free BMA FC in a significant fraction of HCL patients. BMA MRD eradication is associated with lack of HCL progression in blood. Additional testing with RQ-PCR will determine if this more sensitive test is associated with outcome and can be used to help determine the optimal number of cycles. This study of investigator reported data was sponsored by MedImmune and supported by NCI's Intramural Research Program and the Hairy Cell Leukemia Foundation. Clinical trial information: NCT00462189.

7080 Poster Session (Board #69), Sun, 8:00 AM-11:30 AM

Correlation of genomic analysis by MyAML with chemotherapy drug sensitivity. *First Author: Pamela S. Becker, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Whole genome sequencing has demonstrated tremendous heterogeneity in the mutations and chromosomal translocations associated with acute myeloid leukemia (AML), yet we remain quite limited in our ability to predict outcomes of treatment. Most patients with AML cannot be cured with chemotherapy, and the overall survival remains poor. Thus, new approaches are needed to better tailor treatment for individual patients. **Methods:** MyAML uses next generation sequencing to analyze the coding regions and gene fusion genomic breakpoints of 194 genes associated with AML. Fragmented genomic DNA is captured with a customized probe design, and sequenced with 300bp paired end reads on an Illumina MiSeq instrument to an average depth of coverage $>$ 1000x. Using a custom bioinformatics pipeline, MyInformatics, single nucleotide variants (SNVs), indels, inversions and translocations are identified and annotated. High throughput drug sensitivity testing was performed against a panel of 160 drugs, of which 56 are FDA approved. De-identified samples from 12 patients with de novo AML and 12 patients with relapsed AML were analyzed. For 2 patient samples, Duplex Sequencing was also performed to detect sub-clonal mutations below the detection limit of conventional next-generation sequencing. Pearson's correlation was used to examine all possible pairs of missense mutations and the in vitro cytotoxicity response across the sample set. **Results:** From the 24 patient samples analyzed to date, an average of 129 missense mutations were identified in each sample with an allelic frequency $>$ 5%. These samples also contained an average of over 12 coding indels (~5 frameshift and 7 inframe indels) per sample. In addition, MyAML identified 3 samples with inv(16) and 6 samples with translocations, including the cryptic *NUP98-NSD1*t(5;11) that were not detected by karyotyping. For 2 of the samples, Duplex Sequencing was performed at a depth of $>$ 6000x. The FLT3 D835 tyrosine kinase domain (TKD) was identified in 2 patients not previously known to have this mutation. **Conclusions:** Data from disease focused genomics and in vitro chemotherapy sensitivity testing of individual patient samples will likely lead to innovations in treatment and improved outcomes in AML.

7081 Poster Session (Board #70), Sun, 8:00 AM-11:30 AM

Phase II trial of the combination of subcutaneous bortezomib (Bortez) and pegylated liposomal doxorubicin (PLD) for the treatment of patients with acute myelogenous leukemia (AML). *First Author: Ben Kent Tomlinson, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: The proteasome inhibitor Bortez has activity in AML, both as a single agent and in combination with standard induction. Bortez inhibits NF-κB signaling, and NF-κB activity promotes anthracycline resistance. The combination of Bortez and PLD was well tolerated in trials for multiple myeloma. **Methods:** We performed a phase II trial of Bortez and PLD in subjects at least 18 years old with relapsed/refractory AML or treatment naïve AML unfit for or who refused standard therapy. Bortez 1.5mg/m^2 was given subcutaneously on days 1, 4, 8, and 11, and PLD 40mg/m^{2}was given IV on day 4. Cycles were 21 days long. The primary endpoint was objective response rate (ORR), defined as complete remission (CR) plus partial remission (PR). **Results:** Fifteen subjects (53% male) were enrolled. Median age was 70 years (range 32-83). Four had relapsed, five had refractory, and six had untreated AML. Subjects had a median of two prior lines of therapy (range 0-7), including two with prior allogeneic transplantation. No subjects achieved a CR and three achieved a PR for an ORR of 20%. Two of the subjects achieving PR were treatment naïve. There were 12 patients that did not meet response criteria, and all three subjects with a PR progressed after cycle 2. The median number of completed cycles was 1 (range 0-2). Of 14 subjects with circulating blasts, eleven (79%) had a decrease in circulating blasts after the first cycle. Four subjects died from disease-related complications during cycle 1. The most common grade 3-4 adverse events were hematologic and infectious, occurring in 93% and 60% of subjects respectively. Two subjects (13%) had grade 3 peripheral sensory neuropathy. **Conclusions:** The combination of Bortez and PLD demonstrates modest anti-AML activity in a cohort of AML patients that includes heavily pretreated patients. The combination was well tolerated. Given the modest response rate and short duration of response, outcomes could be improved with modification of the current dosing schedule and/or inclusion of additional agent(s). Responses seen in older treatment naïve subjects suggest that this regimen should be studied further in this patient population. Clinical trial information: NCT01736943.

7082 Poster Session (Board #71), Sun, 8:00 AM-11:30 AM

Lenalidomide added to bendamustine-rituximab for untreated chronic lymphocytic leukemia (CLL): A phase 1 study. *First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Lenalidomide is an immunomodulator with activity in CLL. Bendamustine-rituximab (BR) is a widely used upfront regimen. We conducted a phase I trial combining lenalidomide (len) with BR. **Methods:** Patients had untreated CLL with an indication for therapy; ANC $\geq$ 1000, platelets $\geq$ 50000; and adequate organ function. A 3+3 design was used with 10 additional patients at the MTD. Escalating doses of len were added to standard dose BR, with bendamustine dosed at 90mg/m^2. Len was given on d8-22 in c1, and d1-21 in subsequent cycles. The starting dose level for len was 2.5mg. Level 2 was 2.5mg for c1 and escalated to 5mg with c2. Level 3 was 5mg for c1, then 10mg with c2. Patients could receive up to 6 cycles. All patients received allopurinol, aspirin and pegfilgrastim support. DLT was assessed during c1 of dose level 1, and c1-2 of subsequent dose levels. **Results:** Twenty-three patients were accrued. Median age was 64 (range 43-85). Thirty-five percent of patients had Rai stage 3/4, 52% had unmutated *IGHV*, and 26% had 11q deletion. Dose level 2 had one DLT of pulmonary embolism (PE). Dose level 3 was declared the MTD. Eleven subjects completed 6 cycles; median number of cycles was 5 ($<$ 1-6). Reasons for discontinuation were neutropenia (3), PE (2), rash (2), zoster (1), thrombocytopenia (1), Hodgkin lymphoma transformation(1), withdrawal of consent (1), and physician decision (1). Most common toxicities of any grade were rash (n = 14), fatigue (13), nausea (11), fever (10), anemia (9), thrombocytopenia (6), cough (5), and diarrhea (5). Five patients were suspected of tumor flare, 4 of whom were treated with steroids and the other spontaneously remitted. No tumor lysis syndrome was seen. Grade 3-4 toxicities occurring in $>$ 1 patient were rash (6), neutropenia (4), febrile neutropenia (3), anemia (2), and pneumonitis (2). One subject developed CMV reactivation. Dose reductions were required in 9/13 subjects at the MTD due to neutropenia (6), rash (3) and anemia (1). The ORR was 87% and CRR was 39%. **Conclusions:** Len-BR results in increased toxicity compared to what would be expected from BR alone, though efficacy was high. Given the rate of toxicities after the DLT assessment period, the 10mg len dose may be too high for most patients. Clinical trial information: NCT01400685.

7083 Poster Session (Board #72), Sun, 8:00 AM-11:30 AM

Clinical outcome of adult acute lymphoblastic leukemia based on Philadelphia chromosome status and socioeconomic status. *First Author: Bao Duy Dao, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) often relapse with chemotherapy alone. Many undergo allogeneic stem cell transplant (alloSCT) in first complete remission (CR1). Use of tyrosine kinase inhibitors (TKI) with chemotherapy improves outcomes although the standard of care for Ph+ALL remains undefined. **Methods:** 105 consecutive adult patients with ALL were treated at UT Southwestern Medical Center and its county affiliate Parkland Hospital from 2004-2014. Associations between alloSCT, socioeconomic status, and overall survival (OS) were evaluated using Cox regression methods and Kaplan-Meier analysis. **Results:** 34 patients had Ph+ALL. Median age was 49 years. 26 patients received chemotherapy + TKI alone. 8 patients underwent alloSCT after initial chemotherapy + TKI. 82.4% of Ph+ALL patients achieved CR1. At median follow up of 18 months, 61.5% of Ph+ALL patients who did not undergo alloSCT were alive compared to 50.0% of patients who did. AlloSCT was not significantly associated with OS (p = 0.74). Survival was not significantly differed between Ph+ALL and Ph-ALL (p = 0.58). Impact of socioeconomic status on OS within the Ph+ALL group was limited by small sample size. Within the entire cohort of ALL patients, about half of patients had an indigent care plan and were treated at the county hospital. These patients had an OS of 15.5 months compared to 49 months among privately insured patients (p = 0.008). OS improved from 17.9 months for patients treated at the county hospital to 78 months for individuals treated at our university facility (p = 0.0052). In univariate analysis, OS was significantly associated with insurance type (HR = 2.09; 95% CI 1.20-3.64) and treating facility (HR 2.24; 95% CI 1.25-4.00). In multivariate analysis, this association was no longer significant. **Conclusions:** In the advent of TKI, alloSCT did not significantly influence OS in Ph+ALL patients. Administration of chemotherapy + TKI alone may be a viable alternative given the increased morbidity associated with alloSCT. Socioeconomically disadvantaged patients appear to have inferior survival, but this needs further investigation in a larger cohort.

7084 Poster Session (Board #73), Sun, 8:00 AM-11:30 AM

Prognostic impact of renal insufficiency (RI) at diagnosis in patients with chronic lymphocytic leukemia (CLL). *First Author: Paolo Strati, Mayo Clinic, Rochester, MN*

Background: Renal function has a well-established prognostic role in patients with some hematological malignancies, such as multiple myeloma. However, its impact on survival in patients with CLL hasn't been explored. **Methods:** We used the Mayo Clinic CLL database to identify all patients diagnosed with CLL between 01/1995 and 11/2014 using the 2009 iwCLL criteria and seen at our center prior to treatment. Patients for whom we could not calculate a baseline creatinine clearance (Cr-Cl) due to missing creatinine/weight or who were missing baseline complete blood count (CBC) (n = 466) were excluded from final analysis. Renal insufficiency (RI) was defined as Cr-Cl < 45 mL/min calculated with the Cockroft-Gault equation. Logistic regression was used to determine which factors predicted RI. Fisher's exact test was used to compare treatment types by RI. The Kaplan-Meier method was used for the survival analyses. **Results:** The final analysis included 1268 patients. Of these, 87 (7%) had RI at diagnosis. Factors significantly associated with RI on univariate analysis (UVA) were age > 65 years, female sex, hypertension (HTN), hemoglobin < 11 g/dL, and Rai stage III-IV. Factors associated with RI on multivariate analysis (MVA) were age > 65 years, female sex, HTN, and advanced Rai stage. Of the 506 patients who required treatment, 25 had RI. Type of first treatment differed between patients with and without RI ($p < 0.001$); patients with RI were more likely to receive alkylator-based therapy (48% vs 15%) and less likely to receive purine analogue-based CIT (8% vs 44%). Median overall survival (OS) was 124 months, 59 months for those with RI, 132 months for those without RI ($p < 0.001$). Baseline characteristics (age, sex, HTN, diabetes, CBC, CD49d, CD38, ZAP70, *IGHV* mutation status and FISH) as well as RI were associated with OS on UVA. **Conclusions:** RI is relatively frequent at time of CLL diagnosis (7% of cases) and has a profound influence on therapy selection among patients requiring treatment. RI at time of CLL diagnosis is associated with overall survival.

7085 Poster Session (Board #74), Sun, 8:00 AM-11:30 AM

Effect of grade (G) 3 fibrosis on clinical outcome of patients (Pts) with myelodysplastic syndromes (MDS): Mayo Clinic Experience. *First Author: Naveed Cheema, Mayo Clinic, Rochester, MN*

Background: There have been renewed attempts at characterizing the clinicopathological findings of MDS with fibrosis (MDS-F) in order to determine if it warrants a distinct entity. Most of these studies were small while few studied clinical outcome of MDS-F. **Aim:** To studyclinical outcomes of patients with MDS-F. **Methods:** A retrospective, single-institution study of MDS cases per WHO classification from 1993-2014 was done. Bone marrow biopsy (BMB) fibrosis was identified as G 1, 2, or 3 on reticulin stain. Wilcoxon, Pearson tests, Kaplan Meier, multivariant analysis were done via JMP. **Results:** Initial screen of our database revealed 108 (13%) of 835 pts with MDS as MDS-F. On follow up, 49/108 (45%) had subsequent BMB. In 33/49 (67%) pts, diagnosis changed (median time 7 months, m) into AML,RAEB,RCMD in 17 (52%), 10 (30%), and 2 (6%) pts. A second change was in 5/14 pts. Final diagnoses in 49 pts were AML/RAEB/RCMD in 18 (37%), 15 (31%), and 8 (17%) (rest were atypical/ CMML/MDS MPN/RARS/MDS-F). Comparison between fibrosis (n = 108) and non-fibrosis groups (n = 727) showed no statistically significant difference in survival or time to AML. Statistically significant variables between the groups were age ($p = 0.0002$), platelet ($p < 0.0001$), multilineage dysplasia ($p < 0.0001$), dysmegakaryopoiesis ($p < 0.0001$), peripheral blasts ($p = 0.01$), cellularity ($p < 0.0001$) and IPSS-R group ($p = 0.01$). There was a statistically significant difference in mOS across all grades of fibrosis (33 in G1, 39 in G2, 8 m in G3, $p = 0.001$). Pts with G3 fibrosis vs all others had a statistically significant lower mOS of 8 vs 29 m ($p < 0.0001$). In multivariate analysis, only age ($p < 0.0001$), IPSS-R ($p < 0.0001$) and G3 fibrosis ($p = 0.018$) were found to have a statistically significant effect on mOS (but not blast or gender). JAK2 status and CD34 clustering had no significance on survival amongst the fibrosis group. **Conclusions:** MDS-F is a small entity with distinct lab and BMB findings. Only G3 fibrosis had a significant negative impact on mOS. On follow up, 55% progressed into AML or RAEB. Age, IPSS-R and G3 fibrosis were the only significant contributors to mOS. Our finding needs to be further investigated within larger sets of MDS pts.

7086 Poster Session (Board #75), Sun, 8:00 AM-11:30 AM

Up-regulation of CALR in patients with essential thrombocythemia independent from CALR mutations. *First Author: Ciro Roberto Rinaldi, University of Lincoln, Lincoln, United Kingdom*

Background: Somatic mutations in the exon 9 of calreticulin (CALR) gene were recently discovered in patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF) lacking JAK2 and MPL mutations, and absent in patient with polycythemia vera (PV). Among patients with ET or PMF with un-mutated JAK2 or MPL, CALR mutations were detected in 67% of those with ET and 88% of those with primary PMF. Over expression of the most frequent CALR deletion caused cytokine-independent growth in vitro owing to the activation of signal transducer and activator of transcription 5 (STAT5) by means of an unknown mechanism. Patients with myeloproliferative neoplasms carrying CALR mutations presented with higher platelet counts and lower hemoglobin levels than patients with mutated JAK2, but also a lower risk of thrombosis and longer overall survival than patients with mutated JAK2. **Methods:** We analyzed by Real Time PCR, CALR expression in peripheral blood (PB) of 38 patients affected by ET, 17 JAK2 mutated (45 %), 4 CALR (10.5%) mutated, 1 MPL mutated (3%) and 14 with no molecular abnormalities, and compared with a cohort of healthy volunteers. **Results:** We found a significant over expression of CALR (median 5.15; range 1.13-270.08) comparing with controls (median 0.38, range 0.18-1).No significant difference was found comparing CALR expression in CALR mutated (median 4.9, range 1.51-37.14) and CALR/JAK2 un-mutated patients (4.68, range 1.51-28.71). CALR up-regulation is not mutually exclusive with JAK2 mutations, there was, in fact, no difference in CALR mRNA between JAK2 mutated (median 5.09, range 1.13-270) and wild type ET patients (median 5.08, range 1.51-37). There was no significant difference when we correlated CALR expression with PLT counts, spleen size or type of cytoreductive therapy. **Conclusions:** CALR mRNA expression is independent from the CALR mutational status and more interestingly is up-regulated also in JAK2 mutated patients. A larger cohort of patients is required to confirm these preliminary findings.

7087 Poster Session (Board #76), Sun, 8:00 AM-11:30 AM

Ruxolitinib in polycythemia vera: Follow-up from the RESPONSE trial. *First Author: Srdan Verstovsek, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The RESPONSE trial is a multicenter, open-label phase 3 study evaluating the efficacy and safety of ruxolitinib (Rux) compared with best available therapy (BAT) in patients (pts) with polycythemia vera resistant to or intolerant of hydroxyurea. Results from the primary analysis, 48 wks from last pt first treatment (LPFT), were published (Vannucchi, NEJM 2015). **Methods:** This was a second preplanned analysis 80 wks after LPFT. The primary response was defined as achieving both hematocrit (HCT) control without phlebotomy (PBT) through wk 32 and a ≥ 35% reduction in spleen volume (SV) by imaging at wk 32. Durability of the primary response, HCT control, spleen volume reduction, and complete hematologic remission (CHR), as well as long-term safety, were evaluated. **Results:** At data cutoff, 91 (82.7%) pts randomized to Rux (Rux arm) were receiving treatment (median exposure, 111 wks), compared to 93 (84.5%) at the wk 48 analysis (median exposure, 81 wks). No pts remained on BAT, compared to 3 pts at the wk 48 analysis. Of the 23 (21%) pts in the Rux arm who achieved the primary response at wk 32, only 1 lost this response. For the 60% of pts in the Rux arm who achieved HCT control at wk 32, the probability of maintaining this response for 80 wks from time of initial response was 89%. Of the 98 pts on Rux at wk 32, 90% did not have a PBT from wk 32 to 80. A ≥ 35% SV reduction at wk 32 was achieved in 38% of Rux pts; all maintained their response. CHR at wk 32 was achieved in 24% of Rux pts; the probability of maintaining CHR for 80 wks was 69%. The Pruritus Symptoms Impact Scale was "very much improved" for 5 of 10 pts in the Rux arm at their end of study visit. The most common nonhematologic adverse events in the Rux arm were headache (21.8% at the wk 80 analysis [ie, entire follow-up] vs 20.9% at the wk 48 analysis), diarrhea (20.0% vs 19.1%), pruritus (20.0% vs 17.3%), and fatigue (17.3% vs 17.3%); most were grade 1 or 2. Grade 3 or 4 anemia and thrombocytopenia occurred in 1.8% and 5.5% of pts, respectively (no increase from wk 48 analysis). The rate of treatment discontinuation in the Rux arm due to adverse events remained low (4.5%). **Conclusions:** In RESPONSE, Rux responses were durable and treatment remained generally well tolerated, with 83% still receiving Rux at a median exposure of 111 wks. Clinical trial information: NCT01243944.

7088 Poster Session (Board #77), Sun, 8:00 AM-11:30 AM

Case series of hypomethylating agents (HMA) effect on myelodysplastic/myeloproliferative neoplasm unclassified (MDS/MPN-U): Mayo Clinic experience. *First Author: Ahmed K. Abou Hussein, Mayo Clinic, Rochester, MN*

Background: MDS/MPN-U is a rare myeloid disorder that has both dysplastic and proliferative features, but cannot be parsimoniously classified as either MDS or MPN. There is currently no standard treatment algorithm for MDS/MPN-U and is either based on MPN or MDS best available therapies. **Methods:** A retrospective, single-institution study between 1993-2014 of WHO-defined MDS/MPN-U cases was carried after getting appropriate IRB approval. Patients with diagnosis of chronic myelomonocytic leukemia and refractory anemia with ring sideroblasts were excluded. Wilcoxon, Pearson tests, Kaplan Meier, multivariant analysis were done via JMP 10. **Results:** A total of 63 patients with MDS/MPN-U were identified, 10 of whom were treated with HMA. The indication for treatment was thrombocytopenia in 50%, anemia in 30%, and symptomatic splenomegaly in 20%. Median age was 67.5 years (56-82), with 80% of the patients were males. Median platelet count was 101 $x10^9$ (14-184), hemoglobin (Hg) of 9.4 g/dL (6.9-16.3), white blood cell (WBC) count of 8.3 $x10^9$(1.8-90.7), peripheral blood blasts of 1% (0-6); bone marrow blasts of 5% (3-20). Cytogenetics were diploid in 70%, while splenomegaly was found in 30%. Two HMAs were used, with decitabine in 60% and azacitidine in the other 40%. There was no statistical significance on overall survival (OS) between the two HMAs ($p = 0.2$). The median number of treatment cycles was 5 (1-20), with achievement of complete response (CR) in 20%, partial response (PR) in 10%, stable disease in 40%, and progressive disease in 30%. Transformation to AML was seen in 40%, with a median time of 372 days (248-929). Bone marrow transplant was performed in one patient. Median OS was 15 months. Multivariate analysis revealed bone marrow blasts ($p = 0.01$) as the only statistically significant factor on OS (but not WBC, Hg or platelets). **Conclusions:** MDS/MPN-U is a rare entity with no standard treatment algorithm available at present. HMAs yielded an overall response (CR+PR) of 30%, with a median OS of 15 months. On a multivariate analysis only bone marrow blasts had an impact on mOS. Larger studies are needed to confirm our findings in this rare disease.

7089 Poster Session (Board #78), Sun, 8:00 AM-11:30 AM

Outpatient allogeneic hematopoietic cell transplant following alemtuzumab based reduced intensity conditioning in patients with advanced mycosis fungoides/Sezary syndrome. *First Author: Enkhtsetseg Purev, National Institutes of Health, Bethesda, MD*

Background: Advanced mycosis fungoides/Sezari syndrome (MF/SS) is associated with poor prognosis and is incurable with conventional chemotherapeutic approaches. We describe a novel transplant approach that enables outpatient administration and monitoring, provides a measure of disease control prior to engraftment, and reduces the incidence of GHVD. **Methods:** Subjects with advanced MF received a G-CSF mobilized PBSC allograft from an HLA identical sibling following alemtuzumab, and fludarabine conditioning regimen. CSA was used as GVHD prophylaxis to supplement alemtuzumab-induced *in-vivo* T-cell depletion. Donor lymphocyte infusions (DLI) were used as required to promote transition to full donor chimerism and/or promote a graft-vs-tumor effect. Conditioning and as well as stem cell infusions were carried out largely in an outpatient setting. **Results:** 5 subjects with stage IIb-IV MF/SS were enrolled. The conditioning was well tolerated with no serious adverse events. None of the subjects had profound and prolonged neutropenia and thrombocytopenia. Median time to calculated donor neutrophil recovery was 45 d (range 15 d to 6 mo). 4/5 subjects achieved full and sustained donor T-cell and myeloid chimerism, which occurred at a median 9 mo and 6 mo post-transplant, respectively. Among those at risk, 2/4 developed CMV reactivation. None of the subjects developed PTLD. At a median follow-up of 3 yrs, 1 subject developed aGVHD and 1 subject developed cGVHD. 3 subjects achieved complete remission at a median of 7 mo post-transplant mediated by a potent graft-versus-tumor effect. 3 subjects are alive at 10 yrs, 8 yrs, and 6 mo after transplant. 1 subject died 3 yrs post-transplant from a second malignancy while SS was in complete remission, 1 subject died 6 mo post-transplant from grade IV GI GVHD. **Conclusions:** The outpatient based reduced intensity transplant approach described here is well tolerated and associated with prolonged, GVT-induced complete remissions in patients with advanced stage MF/SS. The trial is ongoing and efforts are underway to permit enrollment of patients with available HLA-matched unrelated donors. Clinical trial information: NCT00047060.

7090 Poster Session (Board #79), Sun, 8:00 AM-11:30 AM

Hepatitis C virus infection in patients undergoing hematopoietic cell transplantation in the era of direct-acting antiviral agents. *First Author: Andreas Kyvernitakis, Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There is paucity of literature regarding hepatitis C virus (HCV) infection in hematopoietic cell transplant (HCT) recipients. In the study described herein, we aimed to evaluate several aspects of HCV infection in HCT recipients, including the yield of HCV antibody testing, impact of this infection on cancer status, morbidity and mortality, along with the role of antiviral treatment (AVT). **Methods:** The medical records of cancer patients with chronic HCV infection seen at MD Anderson Cancer Center from 8/2009-12/2014 were reviewed. Those seen from 8/2009-10/2012, were reviewed retrospectively, whereas those seen from 11/2012-12/2014, were analyzed prospectively in an observational study. Diffuse large B-cell, mantle cell and follicular lymphomas were considered HCV-associated non-Hodgkin lymphomas (NHLs), as reported previously. We treated patients with different AVT regimens, including pegylated IFN, pegylated IFN plus ribavirin (PR), sofosbuvir plus PR, sofosbuvir plus ribavirin, and sofosbuvir plus simeprevir. **Results:** Of 434 HCV-infected cancer patients evaluated, 59 underwent 64 HCTs. The majority (80%) underwent autologous transplantation. Thirteen percent of them became HCV-seronegative post-HCT. Acute exacerbation and reactivation occurred in 28% and 10% of HCTs, respectively. Compared to patients who did not receive AVT, treated patients had fewer relapses of HCV-associated NHL (83% versus 20%; P = .04), slower progression to cirrhosis (323 days versus 2242 days; P = .05), and a higher 5-year survival rate (50% versus 82%; P = .01). AVT discontinuation rates post-HCT were 71% in those receiving IFN-containing regimens versus none in those receiving IFN-free regimens (P = .02). AVT was effective in 28% of those given IFN-containing treatment and 100% of those given direct-acting antivirals. **Conclusions:** HCV seropositivity can be lost post-HCT, posing a diagnostic challenge. HCV treatment should be offered to all HCT recipients, as it improves both hepatic but also oncologic outcomes. HCV infection in HCT recipients can be successfully treated with selected direct-acting antivirals.

7091 Poster Session (Board #80), Sun, 8:00 AM-11:30 AM

Influence of variant allele frequency (VAF) on the phenotypic penetrance of TP53 mutations in myeloid malignancies. *First Author: David Andrew Sallman, Moffitt Cancer Center, Tampa, FL*

Background: The clinical implementation of next generation sequencing (NGS) has allowed for the quantitative detection of clinically significant somatic mutations in myeloid malignancies. However, the clinical relevance of the VAF in these mutations is unknown. Here we investigate the role of *TP53* VAF in MDS and AML which is a recognized adverse prognostic feature associated with a complex karyotype. **Methods***:* A training set of NGS profiled MDS or AML cases were retrospectively identified from the Moffitt Cancer Center MDS database. A validation set was obtained from WHO defined MDS cases profiled at Genoptix. Clinical variables and outcomes of MDS patients were characterized at the time of sample procurement. Fisher's exact and t-tests were used for comparative analyses. Kaplan-Meier estimates were used to estimate overall survival and analyzed from the date of mutation identification. **Results***:* From May 2013 to October 2014, 43 patients of 252 screened cases were identified in our training set with a *TP53* mutation. The mean VAF across duplicate libraries was 39.8%. As previously reported, *TP53* mutation was strongly associated with complex karyotype (70% vs 6%, $p < .0001$). When parsed by VAF, 100% of *TP53* mutated patients with a VAF $> 40\%$ had complex cytogenetics in comparison to 50% of patients with a VAF $< 20\%$ ($p = .0016$). Further, patients with complex cytogenetics had a significantly increased VAF (median 49% vs 18%, $p = .0009$). MDS patients with a *TP53* VAF $> 40\%$ had a median overall survival (OS) of 102 days versus an OS that was not reached in patients with lower VAF ($p = .04$). The validation set ($n = 150$) confirmed the training set findings ($p < .0001$). Additionally, *RUNX1*mutations were associated with thrombocytopenia ($p < .0001$) and VAF more strongly predicted the presence of thrombocytopenia ($p = .04$), suggesting that allelic burden influences phenotype penetration across multiple genes. **Conclusions***:* Consideration of *TP53* VAF improves prognostic precision compared to binary mutational analysis alone. This study supports inclusion of VAF at point of care for *TP53* and other recurrent mutations.

7092 Poster Session (Board #81), Sun, 8:00 AM-11:30 AM

Prognostic and predictive value of IPSS-R in assessing overall survival (OS) in a phase III study of rigosertib in second-line higher-risk (HR) MDS patients. *First Author: Lewis R. Silverman, Mount Sinai Medical Center, New York, NY*

Background: ONTIME was a randomized (2:1) study of rigosertib (RIG) vs best supportive care (BSC) in 299 pts with HR-MDS who had relapsed after, failed to respond to, or progressed during hypomethylating agents (HMAs). This study showed a trend favoring RIG in the overall ITT analysis and a significant effect of RIG in the subgroup of patients with very high risk (VHR) per the IPSS-R. **Methods:** We examined the utility of the IPSS-R and the correlation between baseline disease characteristics and OS in 93 RIG and 41 BSC pts with IPSS-R VHR. Results*:* This first clinical study using IPSS-R in 2nd-line HR-MDS pts showed an effect ($p < 0.001$) of RIG on median OS vs BSC in not only the overall group of pts with IPSS-R VHR, but also in several subgroups defined by baseline disease characteristics (see table). Overall, adverse events (AEs) were reported in 100% of RIG pts and 95% of BSC pts with IPSS-R VHR. AEs ≥ Grade 3 in ≥ 10% of pts were: anaemia (RIG 24%, BSC 11%), thrombocytopenia (21%, 11%), febrile neutropenia (17%, 11%), neutropenia (15%, 13%), pneumonia (12%, 13%). Conclusions*:* IPSS-R is a useful prognostic tool for 2nd-line MDS pts. After HMA failure, MDS pts with IPSS-R VHR and certain subgroups identified by baseline disease characteristics showed an OS advantage when treated with RIG compared to BSC. Such characteristics should be considered in the design of future 2nd-line studies in MDS patients with IPSS-R VHR. Clinical trial information: NCT01241500.

Median (months) OS by baseline disease characteristics in pts with IPSS-R VHR.

Characteristic	RIG N	RIG OS	BSC N	BSC OS	Log-rank p-value	Hazard ratio (RIG/BSC) (95% CI)
All patients with IPSS-R VHR	93	7.6	41	3.2	0.0050	0.56 (0.37-0.84)
Primary HMA failure*	55	8.1	21	2.6	0.0055	0.48 (0.28-0.81)
FAB classification of RAEB-t	23	5.8	9	3.4	0.0031	0.26 (0.10-0.68)
ECOG performance status 0 or1	79	8.9	30	3.6	0.0006	0.44 (0.28-0.71)
Bone marrow blast 20-30%	24	5.9	9	3.4	0.0020	0.25 (0.10-0.64)
Hemoglobin < 9 g/dL	63	6.9	21	2.3	< 0.0001	0.30 (0.17-0.54)
Platelet count ≥ 40 $\times 10^9$/L	37	10.1	13	4.4	0.0009	0.27 (0.12-0.62)
Neutrophil count ≥ 0.8 $\times 10^9$/L	24	8.5	12	2.7	0.0038	0.29 (0.12-0.70)
FAB classification of CMML	1	9.2	5	4.7	< 0.0001	--

*Failed to respond to or progressed during HMA treatment (Prebet 2011)

7093 Poster Session (Board #82), Sun, 8:00 AM-11:30 AM

Use of dual donor T-cell chimerism to predict prognosis after double cord blood allogeneic transplantation. *First Author: Muhamed Baljevic, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Double cord blood transplantation (dCBT) is an important strategy to overcome dose limitation of single CBT. By day 21, over 80% of patients (pts) have single unit dominance maintaining long-term hematopoiesis. However, outcomes of pts who have persistence of both CB units after dCBT is unknown. **Methods:** We retrospectively analyzed 105 pts who engrafted after dCBT between 2003 through 2014 and had donor T cell chimerism (TCC) of at least 10% from each CB unit at day 100 +/- 30 after transplant (dCTT). Pts alive and free of disease progression at day 100 were evaluable. **Results:** Of 105 pts, 10 (9.5%) had dTCC. Median age was 43 (range; 1-73). Disease diagnosis was AML in 57.1% and ALL in 21.9%. Disease status at dCBT was 1st or 2nd complete remission in 67.6% and active disease in 32.4%. Conditioning was myeloablative in 73.3% and reduced intensity in 26.7%. Immunosuppressive therapy included mycophenolate mofetil and tacrolimus; all pts received anti-thymocyte globulin. One of the CB units were manipulated by ex-vivo expansion in mesenchymal stem cell co-culture in 72.4% of the pts. The median dose of $CD34^+$ and total nucleated cells infused was $0.36x10^6$/kg (0.12-5.35) and $0.51x10^7$/kg (0.3-1.29), respectively. Singe TCC (sTCC) and dTCC pts were comparable except for more frequent ≥ 4/6 HLA matching between 2 CB units (66.3% vs. 90%, $p = 0.1$), and less use of CB manipulation in dTCCC (74.7% vs. 50%, $p = 0.1$). Transplant outcomes were similar between groups with 3-year (yr) overall survival and progression free survival of 40% vs. 41.4% and 40% vs. 32.3%, respectively. Seven of 10 pts with dTCC were evaluable for long-term assessment [> 6 months (mo)]: 1 pt had autologous recovery with progression after 6 mo of dCBT. Unit dominance was observed in 4 pts, within 4 to 20 mo after dCBT; 1 of them progressed 5 mo after unit dominance and another died of fungal infection at 15 mo. Two AML pts had long-term dTCC with units contributing 58%/42% and 84%/16% at 4 and 3.2 yrs after dCBT. Both were alive in remission at last follow-up. **Conclusions:** The unique situation of TCC from both CB units around day 100 is not associated with worse transplant outcomes in pts receiving dCBT. These provocative results need to be confirmed in larger studies.

TPS7094 Poster Session (Board #83a), Sun, 8:00 AM-11:30 AM

A phase II, randomized trial of standard of care with or without midostaurin to prevent relapse following allogeneic stem cell transplantation in patients with FLT3-ITD mutated acute myeloid leukemia. *First Author: Richard T. Maziarz, Oregon Health and Sci Univ, Portland, OR*

Background: Midostaurin, an orally administered multitarget kinase inhibitor, potently inhibits the FLT3 and c-Kit tyrosine kinases. Prior phase 1/2 and 1b clinical trials of the drug have demonstrated tolerable safety profiles and clinical activity in pts with AML (Fischer, *J Clin Oncol*, 2010; Stone, *Leukemia*, 2012), and it is currently in development in advanced mastocytosis (phase 2; Gotlib, ASH 2014) and AML (phase 3; Stone, ASCO 2011). In the phase 3 randomized trial in pts with newly diagnosed, *FLT3*-mutated AML aged < 60 years, midostaurin 50 mg BID or placebo was administered sequentially with standard induction and consolidation therapy, followed by 1 year of maintenance. Results are pending from this primary therapy trial (RATIFY; NCT00651261). Overall, pts with *FLT3*-ITD–mutated AML have a poor prognosis and are generally considered for curative alloHSCT in first clinical remission (CR1). However, an EBMT retrospective analysis of outcomes for pts who underwent alloHSCT in CR1 demonstrated a high rate of early relapse, with very poor long-term survival (Brunet, *J Clin Oncol*, 2012). There is interest in the use of post-transplant adjuvant maintenance therapy with hypomethylating agents or TKIs in pts with high-risk AML to potentially increase long-term relapse-free and overall survival (OS). **Methods:** This randomized, open-label phase 2 study is investigating the efficacy and safety of midostaurin 50 mg BID in pts with *FLT3*-ITD–mutated AML who underwent alloHSCT in CR1 to determine whether the addition of study drug will reduce relapse at 18 mo post-HSCT. Secondary endpoints are disease-free survival, nonrelapse mortality, OS, safety, and pharmacokinetics. Key inclusion criteria include a documented *FLT3*-ITD mutation, age 18 to 60 years, 8/8 or single-allele mismatch 7/8 donor, and CR1 status. Pts may enroll after the date of engraftment and hematologic recovery to an ANC > 1000/μL and platelets ≥ 20,000/μL without platelet transfusion. **Status:** The trial is open at 18 centers, and 22 of the planned 60 pts have been enrolled. ClinicalTrials.gov no. NCT01883362. Clinical trial information: NCT01883362.

TPS7095 Poster Session (Board #83b), Sun, 8:00 AM-11:30 AM

Randomized, multicenter, open-label, phase 3 study of the BTK inhibitor ibrutinib in combination with obinutuzumab vs. chlorambucil in combination with obinutuzumab in patients with treatment-naïve CLL/SLL (PCYC-1130): iLLUMINATE. *First Author: Ian Flinn, Sarah Cannon Research Institute, Nashville, TN*

Background: There are limited safe and effective first-line options for CLL patients (pts) who have comorbidities, are older, and are not candidates for fludarabine-based regimens. The combination of chlorambucil with obinutuzumab is a recently approved treatment option for these pts. In a recent trial in treatment-naïve (TN) pts with CLL (median age 71 y), single-agent ibrutinib resulted in an ORR of 71% (CR, 13%), PR with lymphocytosis of 13%, and an estimated 22-month PFS of 96% and OS of 96% (O'Brien, 2014). Ibrutinib was effective even in pts with poor prognostic factors. This randomized, multicenter, open-label, phase 3 trial compares the chemotherapy-free combination of ibrutinib and obinutuzumab to chlorambucil/obinutuzumab, in TN pts with CLL not appropriate for fludarabine-based chemoimmunotherapy due to comorbidity, age, or presence of del17p. **Methods**: In iLLUMINATE, an ongoing trial of TN pts who have active disease requiring therapy, approximately 212 TN CLL/SLL pts will be randomized if they meet 1 of the following criteria: CIRS > 6, estimated CrCL ≥ 30 but < 70 mL/min, del17p or TP53 mutation, or are ≥ 65 years of age. Pts will be randomized to ibrutinib (420 mg per day continuously) or oral chlorambucil (0.5 mg/kg D1 and D15 of each 28-day cycle for 6 cycles). All pts will be given 6 cycles of IV obinutuzumab according to the product label. Key exclusion criteria include any prior treatment for CLL, evidence of CNS involvement, or Richter's transformation. Treatment will be administered up to the specified maximum number of cycles, or until PD or unacceptable toxicity. The primary endpoint is PFS, assessed by Independent Review Committee (IRC). Secondary endpoints include ORR, MRD-negative response rate, OS, hematologic improvement, patient-reported outcomes, safety, and tolerability. Pts on the chlorambucil/obinutuzumab arm may cross over to ibrutinib after IRC-confirmed PD if they meet treatment criteria. Enrollment has initiated and is planned in approximately 16 countries including the US, EU, and Australia (NCT02264574). Clinical trial information: NCT02264574.

TPS7096 **Poster Session (Board #84a), Sun, 8:00 AM-11:30 AM**

A multicenter, open-label phase 2a study of ibrutinib with or without cytarabine in patients with acute myeloid leukemia (PCYC-1131). *First Author: Jorge E. Cortes, Department of Leukemia, MD Anderson Cancer Center, Houston, TX*

Background: Therapeutic options in patients with acute myeloid leukemia (AML) who are elderly, unfit, or who relapse after induction therapy remain an unmet need. Studies with primary AML samples and cell lines suggest a role for Bruton's tyrosine kinase (BTK) as a therapeutic target in AML (Rushworth, 2014). Expression and increased phosphorylation of BTK were detected in AML cells, and treatment with ibrutinib (an oral, covalent inhibitor of BTK) resulted in down-regulation of cell growth, decreased adhesion to the bone marrow stromal cells and cell migration induced by a CXCR4 ligand, SDF1 (Zeitseva, 2014). As such, ibrutinib may have a dual anti-AML effect by (1) a direct anti-proliferative/cytotoxic activity and (2) mobilizing cells from the protective bone marrow microenvironment. In addition, ibrutinib augmented the cytotoxicity of cytarabine and daunorubicin in patient derived AML cells. **Methods**: PCYC-1131 (NCT02351037) is a phase 2, open-label, non-randomized study of ibrutinib ± low-dose cytarabine (LD-AraC) in patients with AML. The study will enroll approximately 67 patients with pathologically documented AML that has failed standard treatment, or patients without prior therapy who declined standard treatment. Initially, the safety of the combination will be assessed in 6–9 patients receiving oral ibrutinib 560 mg once daily continuously + LD-AraC at 20 mg twice daily subcutaneously for 10 days per 28-day cycle. Dose limiting toxicities (DLTs) will be assessed during the first treatment cycle. If less than 33% of patients experience DLTs, additional patients will be assigned at investigator discretion to receive ibrutinib monotherapy (n = 33), or ibrutinib + LD-AraC (n = 34). Patients on ibrutinib monotherapy who experience treatment-failure or relapse will be permitted to add LD-AraC. The primary endpoints are overall remission rate, safety, and tolerability. Additional endpoints include relapse-free survival, event-free survival, overall survival, clinical benefit rate, pharmacokinetics of ibrutinib ± LD-AraC, and evaluation of prognostic and predictive biomarkers. Safety data will be summarized descriptively. Clinical trial information: NCT02351037.

TPS7097 **Poster Session (Board #84b), Sun, 8:00 AM-11:30 AM**

An international phase 3 randomized, placebo-controlled study of CC-486 (oral azacitidine) maintenance therapy in patients with acute myeloid leukemia (AML) in complete remission (CR): The Quazar AML maintenance trial. *First Author: Gail J. Roboz, Weill Medical College of Cornell University and the New York Presbyterian Hospital, New York, NY*

Background: Few inroads have been made in the past 30 years to improve overall survival (OS) in older patients (pts) with AML. While induction chemotherapy (IC) can induce CR in 40-50% of older pts, most relapse within 3-18 months. Post-remission therapy (Tx) is required to prevent relapse. Parenteral azacitidine (AZA) prolonged OS in older pts with AML vs conventional care regimens (10.4 vs 6.5 months, *P*= 0.1009) (Dombret, *Haematologica*, 2014:LB2433). CC-486 is an oral formulation of AZA in development for use in hematologic malignancies. An oral formulation allows delivery of AZA at lower systemic doses over a more prolonged schedule than is practical with SC AZA. CC-486 taken at home is convenient for pts, eliminates injection- and catheter-site reactions, and avoids resource utilization costs of hospital/clinic visits. Thus, CC-486 may offer a relapse-free survival (RFS) advantage and improve quality of life. The Quazar phase 3 AML Maintenance trial (clinicaltrials.gov NCT01757535) is designed to assess whether CC-486 is an effective low-intensity maintenance Tx that can extend OS in older pts with AML. **Methods:** Pts aged ≥ 55 yrs with *de novo* AML or AML secondary to MDS in first CR or CRi (IWG 2003) after IC, with or without consolidation, are randomized 1:1 to 300 mg QD CC-486 or placebo for 14 days of 28-day treatment cycles. Randomization is stratified by age (55-64 / ≥ 65 yrs) and cytogenetic risk (Intermediate / Poor) at induction, prior MDS, and post-remission consolidation Tx. All pts can receive supportive care. The primary endpoint is OS. Secondary endpoints include RFS, time to relapse, time to discontinuation, and safety. Exploratory analyses assess molecular and cellular markers of minimal residual disease during maintenance Tx that may be predictive of clinical outcomes. Enrollment began in May 2013, with a target of 460 pts from 150 global sites. Accrual is designed to allow enough events for ≥ 90% power to detect a statistically significant treatment effect on OS (n = 330 deaths; expected duration 60 months). By Jan 2015, 168 pts had been randomized. Study enrollment continues through 2016. Clinical trial information: NCT01757535.

TPS7098 **Poster Session (Board #85a), Sun, 8:00 AM-11:30 AM**

First-in-human study of FLX925, an orally administered FLT3/CDK4/CDK6 inhibitor, in subjects with relapsed or refractory acute myeloid leukemia (AML). *First Author: Naval Guastad Daver, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Acquired mutations in oncogenic kinases remains an obstacle between valid therapeutic hypotheses and meaningful patient benefit. The inhibition of FLT3 can be efficacious in AML patients, particularly in FLT3-ITD mutated cancers. However, relapse is common and frequently associated with the acquisition of secondary resistance mutations in FLT3. FLX925 is a next-generation kinase inhibitor that was prospectively designed to address or avoid common mechanisms of resistance to earlier FLT3 inhibitors, with its unique binding mode and potent activity against CDK4/CDK6 (Keegan et al, Mol Cancer Ther, 2014). FLX925 retains its cellular potency against clinically relevant secondary resistance mutations in FLT3 that occur with quizartinib or sorafenib treatment. In addition, FLX925 potently inhibits CDK4/CDK6, central components of the cell cycle machinery. This unique profile may reduce the emergence of resistant clones and extend the therapeutic potential of FLX925 to other malignancies dependent on these pathways (e.g., MCL). These data suggest the unique profile of FLX925 makes it an ideal inhibitor for the treatment of cancers driven by FLT3 signaling, such as AML. **Methods:** This open label, sequential-group, dose escalation and cohort expansion study includes adult patients diagnosed with relapsed or refractory AML. Eligible patients need to have failed prior induction therapy or relapsed within 12 months of prior therapy. During cohort expansion, at the RP2D, patients will be enrolled into 3 cohorts: subjects with a FLT3 ITD or kinase domain mutation with (Cohort A) or without (Cohort B) prior FLT3 inhibitor treatment, or patients without a FLT3 mutation at screening (Cohort C). The primary objectives of the study are to characterize the safety and tolerability of twice-daily, oral FLX925. Key secondary objectives are to evaluate the pharmacokinetic (PK) profile, pharmacodynamics (PD) effects, and the magnitude and duration of antitumor activity with FLX925, using standard criteria. A Simon 2-stage mini-max approach will be used to test the null hypothesis based on the CRc rate. This trial (NCT02335814) is currently enrolling patients. Clinical trial information: NCT02335814.

TPS7099 **Poster Session (Board #85b), Sun, 8:00 AM-11:30 AM**

GRASPA-AML 2012-01 study (NCT01810705): A multicenter, open, randomized phase 2b trial evaluating ERY001 (L-asparaginase encapsulated in red blood cells) plus low-dose cytarabine vs low-dose cytarabine alone, in treatment of newly diagnosed acute myeloid leukemia (AML) elderly patients, unfit for intensive chemotherapy. *First Author: Xavier G. Thomas, Centre Hospitalier Lyon Sud, Cedex, France*

Background: Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic progenitor cells and the most common malignant myeloid disorder in adults, with a median age of 65 years at diagnosis. There is unmet medical need for elderly patient with AML unfit for intensive chemotherapy. L-asparaginase (L-ASP) plays a key role in all treatment phases for Acute Lymphoblastic Leukemia (ALL). Some leukemic cells, with asparagine synthetase deficiency, need plasmatic L-asparagine for protein synthesis. L-ASP hydrolyses L-asparagine leading to depletion of this amino acid. Normal cells are resistant to L-asparaginase because they can synthesize asparagine using asparagine synthetase. Several clinical studies and case reports showed a potential benefit of L-ASP in certain AML cell lines or mixed lineage leukemia. ERY001 is a novel platform of RBC encapsulation of L-asparaginase. Antitumor activity of ERY001 as well as any L-ASP is based on depletion in plasmatic asparagine, which is an essential amino acid for cells survival in almost all lymphoblastic cells. **Methods:** GRASPA-AML 2012-01 is an international multicenter, open label, randomized, phase 2b trial evaluating clinical activity and tolerability of ERY001 plus low-dose cytarabine (LDAC) vs LDAC alone, in treatment of elderly patients (65-85 years), with newly diagnosed AML and who are unfit for intensive chemotherapy. The primary objective is progression free survival (PFS). The key secondary objectives are: response to treatment, event free survival, overall survival, quality of life, pharmacokinetic and pharmacodynamics profiles, and immunogenicity. Patients are randomized 2:1 to: Arm A: LDAC only (40 mg daily for 10 consecutive days, every 28 days); Arm B, ERY001 (100 IU/kg) in combination with subcutaneous LDAC, for up to 24 months. Patients are assessed every 4-5 days during each cycle. The study is currently in recruiting phase. Seventy-three patients were recruited to date. Clinical trial information: NCT01810705.

TPS7100 Poster Session (Board #86a), Sun, 8:00 AM-11:30 AM

A phase 1b trial of duvelisib, a PI3K-δ,γ inhibitor, in combination with obinutuzumab in patients with CLL/SLL previously treated with a Bruton's tyrosine kinase inhibitor (BTKi). *First Author: James Stewart Blachly, Ohio State University Medical Center, Columbus, OH*

Background: Abrogating B-cell receptor pathway signaling through BTK inhibition is an effective treatment strategy for CLL. However, some patients (pts) do not respond, or progress despite BTK inhibitor (BTKi) treatment. Duvelisib, an oral inhibitor of PI3K-δ and PI3K-γ, can reduce downstream PI3K signaling even in the setting of BTK C481S mutation, thus providing an alternative for attenuating CLL growth and survival signaling. Early clinical activity observed in a Phase 1 study of duvelisib monotherapy in a subset of pts previously treated with a BTKi, suggest further evaluation is warranted (Porcu, ASH 2014). Combining duvelisib with obinutuzumab may augment clinical benefit through both cell intrinsic and extrinsic mechanisms. This study (IPI-145-18; ClinicalTrials.gov: NCT02292225) was designed to identify a tolerable dose of duvelisib combined with obinutuzumab, and to evaluate the safety and efficacy of the combination in relapsed/refractory CLL/SLL pts previously treated with a BTKi. **Methods:** This is a Phase 1b, open-label, dose escalation, safety and tolerability study of duvelisib in combination with obinutuzumab in pts with CLL/SLL whose disease is refractory to or has relapsed while receiving a BTKi therapy. Dose escalation (DE) Cohort 1 will receive duvelisib 25 mg BID in combination with obinutuzumab at its approved dose and schedule. Dose escalation of duvelisib to 50 mg BID or 75 mg BID may occur based on evaluation of dose limiting toxicities. Sequenced administration may be explored if the DE of duvelisib cannot progress when treatments are administered concurrently. An expansion phase is planned to explore the optimal dosing regimen of duvelisib in combination with obinutuzumab. Approximately 64 pts will be enrolled at 5-6 US sites. The primary endpoints are dose-limiting toxicities (DE phase only), AEs, and safety laboratory changes. Secondary endpoints are overall response rate, duration of response, progression-free survival, overall survival, BTK mutation status, and pharmacokinetics. Response will be evaluated according to the modified IWCLL 2008 response criteria. Clinical trial information: NCT02292225.

TPS7101 Poster Session (Board #86b), Sun, 8:00 AM-11:30 AM

Phase III randomized, double-blind, active-controlled study of momelotinib versus ruxolitinib in patients with myelofibrosis. *First Author: Elliott F. Winton, Emory Univ School of Medcn, Atlanta, GA*

Background: Momelotinib (MMB) is a JAK1/2 inhibitor that displays potent *in vitro* inhibitory activity against cells dependent on JAK2, including cells with the JAK2V617F mutation. In a completed phase I/II study of MMB which enrolled 166 subjects with myelofibrosis (MF) (CCLO9101), the rate of spleen response was 39%, and the rate of anemia response was 53% (Pardanani et al, Blood 2013). Assessment at 3 months showed improvement of constitutional symptoms. Most common treatment-related adverse events were thrombocytopenia (46%), peripheral neuropathy (44%), diarrhea (25%), dizziness (24%), and nausea (22%). Dizziness is believed to be part of the first-dose effect of MMB. **Methods:** 420 subjects with primary (PMF), post-polycythemia vera (PPV-MF), or post-essential thrombocythemia MF (PET-MF) will be randomized in a 1:1 manner to receive either MMB plus ruxolitinib (RUX) placebo, or RUX plus MMB placebo in this double-blind, active-controlled study for 24 weeks, with the option for eligible subjects to subsequently continue open-label MMB treatment for up to an additional 168 weeks. Key inclusion criteria include palpable splenomegaly $\geq$ 5 cm, high risk or intermediate-2 risk MF, or intermediate-1 risk MF with symptoms, and platelet count $\geq 50 \times 10^9$/L. Prior use of a JAK inhibitor is not allowed. The primary endpoint is Splenic Response Rate at Week 24, defined as the proportion of subjects achieving $\geq$ 35% reduction in spleen volume at Week 24 as measured by MRI or CT scan. Secondary endpoints include Response Rate in Total Symptom Score at Week 24 defined as the proportion of subjects who achieves $\geq$ 50% reduction from baseline in total symptom score to Week 24 as measured by the modified MPNSAF TSS diary. The Data Monitoring Committee last reviewed the trial in November 2014 and recommended that the trial continue as planned. Clinical trial registry number: NCT01969838. Clinical trial information: NCT01969838.

TPS7102 Poster Session (Board #87a), Sun, 8:00 AM-11:30 AM

Phase III randomized, open-label, active-controlled study of momelotinib versus best available therapy in ruxolitinib-treated patients with myelofibrosis. *First Author: Vikas Gupta, Princess Margaret Cancer Center, Toronto, ON, Canada*

Background: Momelotinib (MMB) is a JAK1/2 inhibitor, and displays potent *in vitro* inhibitory activity against cells dependent on JAK2 including cells with the JAK2V617F mutation. Dosing of ruxolitinib (RUX), the first JAK inhibitor approved for myelofibrosis (MF), is based on platelet count, with dose reduction indicated for various degrees of hematologic toxicity. In the phase III study of RUX versus placebo (PBO) in MF (COMFORT-1), 70% of subjects in the RUX arm experienced thrombocytopenia of any grade compared to 31% of subjects in the PBO arm, with rates of Grade 3 and 4 thrombocytopenia of 13% and 1% on the RUX and PBO arms, respectively. Grade 3 and 4 anemia rates were 45% and 19% for the RUX and PBO arms, respectively (Verstovsek et al, NEJM 2012). For those patients who experience significant hematologic toxicities while on RUX, no approved alternative JAK inhibitor therapy is currently available. **Methods:** 150 subjects with primary, post-polycythemia vera, or post-essential thrombocythemia MF will be randomized in a 2:1 manner to receive either MMB or best available therapy (BAT) for 24 weeks, with the option for eligible subjects to continue open-label MMB in an extended treatment phase for up to an additional 168 weeks. Treatment on the BAT arm may include RUX. Key inclusion criteria are palpable splenomegaly $\geq$ 5 cm, currently or previously treated with RUX and characterized by either requirement for red blood cell transfusion while on RUX, or dose adjustment of RUX to $<$ 20 mg twice daily at start of or during RUX treatment plus either $\geq$ Grade 3 thrombocytopenia, $\geq$ Grade 3 anemia, and/or $\geq$ Grade 3 hemorrhage. The primary endpoint is Splenic Response Rate at Week 24, defined as the proportion of subjects who achieve $\geq$ 35% reduction in spleen volume from baseline at Week 24, as measured by MRI or CT scan. Secondary endpoints include Response Rate in Total Symptom Score, defined as the proportion of subjects who achieve $\geq$ 50% reduction in total symptom score from baseline to Week 24 as measured by the modified MPNSAF TSS diary. The DMC last reviewed the trial in Nov 2014 and recommended that the trial continue as planned. Clinical trial registry number: NCT02101268. Clinical trial information: NCT02101268.

TPS7103 Poster Session (Board #87b), Sun, 8:00 AM-11:30 AM

Phase 1 study to evaluate the safety and tolerability of MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody, in myelodysplastic syndrome (MDS) after treatment with hypomethylating agents. *First Author: Guillermo Garcia-Manero, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Myelodysplastic syndrome (MDS) is a group of clonal bone marrow disorders associated with an increased risk of transformation to acute myeloid leukemia (AML). Despite recent progress in the treatment of MDS, therapeutic options are still limited, particularly for patients who fail to respond or relapse during treatment with hypomethylating agents and thus have poor survival rates. The programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway is an important checkpoint used by tumor cells to block antitumor responses. PD-L1 is present on myeloblasts during progression from MDS to AML, and its expression is enhanced by hypomethylating agents, providing the rationale for targeting PD-L1 in MDS. MEDI4736 is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity. **Methods:** This Phase 1, multicenter, open-label, dose-escalation, and dose-expansion study (NCT02117219) evaluates the safety/tolerability of IV MEDI4736 in patients with pathologically confirmed MDS and Eastern Cooperative Oncology Group performance status of 0-2 who failed to respond, relapsed after an initial response, or were unable to tolerate hypomethylating agents. The primary objective is to assess the safety and tolerability of MEDI4736. Secondary objectives include: evaluation of clinical outcome in patients with MDS (International Working Group 2006 MDS response criteria), analysis of pharmacokinetics and immunogenicity of MEDI4736, and effect on patient-reported outcomes. Recruitment is ongoing, with a target enrollment of approximately 70 patients across 11 centers (United States, Germany, and United Kingdom). Clinical trial information: NCT02117219.

7500 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Bevacizumab 15mg/kg plus cisplatin-pemetrexed (CP) triplet versus CP doublet in Malignant Pleural Mesothelioma (MPM): Results of the IFCT-GFPC-0701 MAPS randomized phase 3 trial. *First Author: Gerard Zalcman, Caen Univ Hosp, Caen, France*

Background: MPM median overall survival (OS) did not exceed 13 months with pemetrexed-platinum doublet, with virtually no surviving patients at 5 years. Vascular endothelial growth factor is a potent mitogen for MPM cells. **Methods:** In this French multicenter randomized phase 3 trial, eligible patients had unresectable, histologically proved MPM, age < 76, no prior chemo, PS 0-2, no thrombosis, nor bleeding. Randomized patients (1:1) received pem 500 mg/m^2, CDDP 75 mg/m^2 at D1, with (arm B) or without bevacizumab (arm A), 15 mg/kg Q21D, for 6 cycles. Arm B non-progressive patients received bevacizumab maintenance therapy until progression or toxicity. Primary endpoint was OS. 445 patients were to be randomized, and 385 events observed, to show a significant OS improvement, with 80% statistical power, 5% a-risk. **Results:** From Feb. 2008 to Jan. 2014, 448 patients were included in 73 centers. Males: 75.4%, median age: 65.7 years (range 34.7-75.9), PS 0-1: 96.7%. The IDMC recommended a second interim analysis after 85% of events. On 01-Jan-2015, the duration since last news was < 30 days in 105 out of 106 still living patients. Overall survival was significantly longer in the experimental arm (median: 18.8 months, 95%CI[15.9-22.6] *vs.* 16.1 months, 95%CI[14.0-17.9] for the reference arm, (adj.HR = 0.76, 95%CI[0.61; 0.94], p = 0.012). With only 46/448 non-progressive patients at the date of analysis, median PFS was 9.6 months, 95%CI[8.5-10.6] in bevacizumab arm *vs.* 7.5 months, 95%CI[6.8-8.1] (adj.HR = 0.62, 95%CI[0.50-0.75], p < 0.0001). G3-4 hematological toxicities did not significantly differ in the two arms (49.5% *vs.* 47.3%). Significantly more G3 proteinuria (0.0 *vs.* 3.1%), G3 hypertension (0.0 *vs.* 23%), G3-4 arterial thrombotic events (0.0 *vs.* 2.7%) were observed in bevacizumab arm. QOL and exploratory biomarkers studies will be also presented at time of the meeting. **Conclusions:** Bevacizumab addition to pemetrexed/cis-platin provides a significantly longer survival in pts with MPM, with acceptable toxicity, making this triplet a new treatment paradigm. Clinical trial information: NCT00651456.

7501 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Phase III trial (NGR015) with NGR-hTNF plus best investigator choice (BIC) versus placebo plus BIC in previously treated patients with advanced malignant pleural mesothelioma (MPM). *First Author: Rabab M. Gaafar, National Cancer Institute, Cairo University, Cairo, Egypt*

Background: Currently, there are no standard options for MPM patients who failed a pemetrexed-based chemotherapy (CT). NGR-hTNF, a tumor-targeted antivascular agent, displays antitumor activity through a vessel normalization that improves intratumor CT uptake and T-cell infiltration. **Methods:** MPM patients who progressed on or after a front-line pemetrexed-based regimen, stratified for performance status (PS) and CT agent, were randomly assigned to receive weekly NGR-hTNF 0.8 μg/m^2 (arm A; n = 200) or placebo (arm B; n = 200), both given with BIC (gemcitabine [G], vinorelbine [V], doxorubicin [D] or supportive care). Primary endpoint was overall survival (OS). Hypothesis testing: hazard ratio (HR) = 0.72, 1-β = 0.80, α = 0.05. **Results:** Baseline characteristics were balanced between arms (A vs B): median age (65 vs 67 years); men (76% vs 74%); PS $\geq$ 1 (72% vs 69%); nonepithelial histology (15% vs 19%); poor EORTC score (30% vs 23%); prior treatment-free interval (TFI) $<$ median of 4.8 months (47% vs 53%). Investigator-selected CT (n = 381, 95%): G 55%, V 42%, D 3%. Patients completing six CT cycles: 41% vs 32% (p = 0.08). Most common grade 3/4 toxicity: neutropenia (17% vs 19%) and fatigue (5% vs 8%). After a median follow-up of 18.9 months, OS did not differ significantly between arms in ITT analysis (median 8.4 vs 7.9 months; HR = 0.94 p = 0.61). By predefined OS analyses, there was a significant interaction only between treatment group and TFI (p = 0.008). In 198 patients with TFI shorter than 4.8 months after first-line therapy, median OS for NGR-hTNF vs placebo was 9.0 vs 6.3 months and 1-year OS was 39% vs 23%, respectively (HR = 0.69 p = 0.02; stratified HR = 0.65 p = 0.01). By CT agent, median OS for NGR-hTNF plus G vs placebo plus G was 9.0 vs 6.2 months and for NGR-hTNF plus V vs placebo plus V was 9.7 vs 6.9 months. A significant treatment-by-TFI interaction was also observed for PFS (p = 0.009), with 6-month rates in the short TFI subset of 25% for NGR-hTNF and 12% for placebo (HR = 0.71 p = 0.03). **Conclusions:** Though the primary endpoint was not met, OS and PFS benefit reported with NGR-hTNF plus CT in patients with short TFI deserves a confirmatory first-line phase III trial. Clinical trial information: NCT01098266.

7502 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028. *First Author: Patrick Alexander Ott, Dana-Farber Cancer Institute, Boston, MA*

Background: Treatment options for pts with SCLC that progresses on platinum-based chemotherapy are limited. Pembrolizumab, an anti–PD-1 monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2, has shown antitumor activity in multiple advanced malignancies, including non-small cell lung cancer. We assessed the safety and efficacy of pembrolizumab in pts with PD-L1$^+$SCLC. **Methods:** KEYNOTE-028 (ClinicalTrials.gov, NCT02054806) is an ongoing multicohort, phase Ib study of pembrolizumab in pts with PD-L1$^+$ advanced solid tumors. Key eligibility criteria for the SCLC cohort include: confirmed, measurable disease; PD-L1 expression in $\geq$ 1% of cells in tumor nests or PD-L1$^+$ bands in stroma as assessed by IHC at a central laboratory; failure of standard therapy; and absence of autoimmune disease or interstitial lung disease. Pembrolizumab 10 mg/kg is given every 2 wk for up to 2 y or until confirmed progression or unacceptable toxicity. Primary end points are safety, tolerability, and response assessed per RECIST v1.1 by investigator review every 8 wk for the first 6 mo and every 12 wk thereafter. **Results:** Of the 135 pts with SCLC screened, 37 (27%) had PD-L1$^+$ tumors. Seventeen pts were enrolled from March 2014 through January 2015 (59% men; median age, 62 y; 59% ECOG PS 1). One pt was misenrolled and did not receive pembrolizumab. All 16 treated pts received prior platinum and etoposide. 9 pts (53%) experienced a drug-related AE (DRAE); only 1 pt had a grade $\geq$ 3 DRAE. There were no treatment-related deaths or discontinuations due to DRAEs. Four of 16 (25%) evaluable pts had a partial response. One (7%) pt had stable disease, resulting in a disease control rate of 31%. Six (37%) pts had progressive disease as their best response, and 5 pts had no assessment at the time of analysis. Responses are durable, with all responders on treatment for 16+ wks with ongoing response. **Conclusions:** Pembrolizumab is generally well tolerated and has promising antitumor activity in pts with PD-L1$^+$ SCLC who have progressed on prior platinum-based therapy. Enrollment in the SCLC cohort of KEYNOTE-028 is ongoing. Clinical trial information: NCT02054806.

7503 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. *First Author: Scott Joseph Antonia, Moffitt Cancer Center, Tampa, FL*

Background: Patients (pts) with SCLC respond to initial platinum (PLT) based chemotherapy (CT), but rapidly progress. Combined blockade of PD-1 and CTLA-4 immune checkpoint pathways has anti-tumor activity with a manageable safety profile. Nivolumab (NIVO) is a fully human IgG4 PD-1 immune checkpoint inhibitor approved in the US & Japan. Interim safety and efficacy of NIVO +\- ipilimumab (IPI), a CTLA-4 checkpoint inhibitor, in pretreated SCLC pts are reported. **Methods:** Pts who were PLT sensitive or refractory and had progressive disease were enrolled regardless of tumor PD-L1 status or number of prior CT regimens. This open-label study randomized pts to NIVO 3 mg/kg IV Q2W or NIVO+IPI (1 + 1 mg/kg, 1 + 3 mg/kg or 3 + 1 mg/kg) IV Q3W for 4 cycles followed by NIVO 3 mg/kg Q2W. Primary objective was overall response rate (ORR). Other objectives were safety, PFS, OS and biomarker analysis. **Results:** Seventy-five pts were enrolled (NIVO, n = 40; NIVO+IPI, n = 35); 59% had $\geq$ 2 prior regimens. Drug-related adverse events (DrAEs) in $\geq$ 10% were fatigue (18%), diarrhea (13%), nausea (10%), and decreased appetite (10%) with NIVO; and fatigue (29%), diarrhea (17%), pruritus (14%), nausea, endocrine disorders and rash (11% each) with NIVO+IPI. Gr 3/4 DrAE in $\geq$ 5% included diarrhea and rash (6% each; NIVO+IPI). Drug-related pneumonitis occurred in 2 pts (1 per arm). One pt experienced a drug-related SAE of myasthenia gravis on study which was fatal. Of 40 evaluable NIVO pts, partial response (PR) was seen in 6, 15% (duration of ongoing responses [DOR] 80-251+ days); stable disease (SD) in 9, 22.5%; and progressive disease (PD) in 25, 62.5%. In 20 evaluable NIVO+IPI pts, 1 had complete response (CR), 5% (DOR 322+ days); 4 had a PR, 20% (DOR 41-83+ days); 6 had SD, 30%, and 9 had PD, 45%. In the NIVO+IPI arm, 12 pts had not reached first tumor assessment and 3 were not evaluable. Nine pts (23%) continue treatment with NIVO and 19 (54%) with NIVO+IPI. **Conclusions:** In this PD-L1 unselected SCLC population with progression post-PLT, NIVO alone or combined with IPI was tolerable. ORR was 15% (NIVO) and 25% (NIVO+IPI) for evaluable pts; durable responses were noted. Updated safety, clinical activity and biomarker analysis will be presented. Clinical trial information: NCT1928394.

7504 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Results from a randomized study of carboplatin and etoposide (CE) with or without palifosfamide (Pa) in extensive stage small cell lung cancer (ES-SCLC): The MATISSE study. *First Author: Shadia Ibrahim Jalal, Indiana University School of Medicine, Indianapolis, IN*

Background: Extensive stage small cell lung cancer (ES-SCLC) is a disease with high mortality. SCLC is initially exquisitely sensitive to chemotherapy with carboplatin and etoposide (CE), considered the standard first-line regimen in ES-SCLC in the US. In a previous phase III trial, the combination of cisplatin, etoposide, and ifosfamide (VIP) improved overall survival (OS) as compared to cisplatin and etoposide in ES-SCLC but with increased toxicity (JCO 13: 2594-2599,1995). Palifosfamide (Pa), a bi-functional DNA alkylator is the active metabolite of Ifosfamide that does not generate toxic metabolites facilitating its combination with CE. This trial was therefore pursued comparing CE with or without Pa in ES SCLC. **Methods:** This was a multi-center, open-label trial in chemotherapy-naive patients (pts) with ES SCLC with planned enrollment of 548 pts. Pts were randomized 1:1 to receive CE (C at AUC 5mg/mL/min day 1 with E 100mg/m^2/day days 1-3) or PaCE (Pa at 130mg/m2/day, E at 100mg/m^2/day both on days 1-3 and C at AUC 4mg/mL/min day 1). The primary endpoint was overall survival (OS). The secondary endpoints included progression-free survival, objective response rate, and quality of life assessment. Pts were stratified based on age, gender, and Eastern Cooperative Oncology Group (ECOG) performance status. **Results:** The MATISSE trial closed prematurely in light of the negative phase III trial evaluating the addition of Pa to doxorubicin in sarcoma (PICASSO). ES-SCLC pts (N = 188) were randomized to CE (n = 94) or PaCE (n = 94). Pt characteristics were well balanced with median age of 61 and the majority of pts having an ECOG PS of 0-1. Median OS in the Intent to treat population was 10.0 months (95% CI: 7.7-10.5) with PaCE and 10.4 months (95% CI: 8.7-13.4) with CE (p value 0.096). Serious treatment-related adverse events were observed in 28.3% pts receiving PaCE and 27.5% pts receiving CE with febrile neutropenia occurring in 4.3% of pts on PaCE arm and 5.5% of pts on CE arm. **Conclusions:** The addition of Pa to CE did not improve survival in ES-SCLC. The safety profile was as anticipated and the addition of Pa did not lead to increased toxicity. Clinical trial information: NCT01555710.

7505 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

A multicenter, randomised, phase III trial comparing fixed dose versus toxicity-adjusted dose of cisplatin + etoposide in advanced SCLC patients. The STAD-1 trial. *First Author: Alessandro Morabito, National Cancer Institute of Naples, San Nicola La Strada Caserta, Italy*

Background: Classic dosing of chemotherapy does not account for pts' variability and some pts could be underdosed. We tested whether toxicity-adjusted dosing of chemotherapy was more active than classic dosing in advanced SCLC pts. (ClinicalTrials.gov NCT00526396). **Methods:** Advanced chemonaïve SCLC pts, aged $\leq$ 75, ECOG PS $<$ 2, were randomised to either control (fixed-dose cisplatin/etoposide: C 80mg/m2, d1 + E 100mg/m2,d1-3, q3w) or experimental arm (toxicity-adjusted CE where, in absence of toxicity, dose of both agents were escalated according to the table). Primary endpoint was the objective response rate (ORR) according to RECIST 1.0. 160 pts were required based on 80% power, 2-sided $\alpha = 0.05$; $\geq$ 80% ORR in the experimental vs $\leq$ 60% ORR in the standard arm. **Results:** 161 patients were randomly assigned either to standard (n = 81) or experimental arm (n = 80). Two patients withdrew the consent immediately after the randomisation, one in each arm, and were excluded from the analysis. Median age was 64, most of the patients were males (72%), had PS1 (55%), had not been pre-treated with RT (89%) and did not show brain metastases (75%). A median number of 6 chemotherapy cycles was administered in both the arms. The ORR was 54% and 57% in the control and the experimental arms (p = 0.75). With 44 mos of median follow up, median PFS was 6.0 mos in the control arm and 5.6 mos in the experimental arm (HR = 1.02; 95% CI: 0.73-1.43, p = 0.90), whilst median OS was 9.6 mos and 9.2 mos in the control and experimental arm (HR = 1.01, 95% CI: 0.71-1.42; p = 0.97). Six patients died while on treatment, one in the control arm and 5 in the experimental one. Among grade 3-4 toxicities, neutropenia (p = 0.005) and fatigue (p = 0.04) were significantly more frequent in the experimental arm. **Conclusions:** As expected, toxicity-adjusted dosing increases side-effects. However, it does not improve the ORR, nor does prolong PFS or OS in advanced SCLC patients. Clinical trial information: NCT00526396.

	C (mg/m^2)	E (mg/m^2)
Level –2	stop	stop
Level –1	60 (-25%)	80 (-25%)
Level 0 (starting dose)	80	100
Level +1	100 (+20%)	120 (+20%)
Level +2	110 (+10%)	120 (-)
Level +3	110 (-)	135 (+12.5%)
Level +4	120 (+9%)	135 (-)
Level +5	120(-)	150 (+11%)

7506 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC). *First Author: Suresh Senan, VU University Medical Center, Amsterdam, Netherlands*

Background: Efficacy and safety of concurrent Pem+Cis and TRT followed by consolidation Pem vs other CTX regimens were evaluated; interim safety results (concurrent phase) were presented previously (Vokes et al. 2013). **Methods:** Five hundred and ninety-eight patients (pts) with stage III unresectable nsNSCLC were randomized 1:1 to Pem+Cis (Pem 500 mg/m^2+Cis 75 mg/m^2, intravenously, plus vitamins) plus concurrent TRT (66.0 Gy) every 21 days (q21d) x 3 cycles followed by Pem consolidation q21d x 4 cycles vs the control arm Eto+Cis (Eto 50 mg/m^2+Cis 50 mg/m^2, intravenously) plus concurrent TRT (66.0 Gy) q28d x 2 cycles followed by 2 cycles of a consolidation CTX of choice: Cis+Eto, Cis+vinorelbine, or paclitaxel+carboplatin. The primary objective was OS. Progression-free survival (PFS), objective response rate (ORR), and safety were key secondary objectives. This superiority trial was designed to achieve 80% power, assuming an OS HR of 0.74 with 355 events at 0.05 α (two-sided) using a log-rank test. **Results:** Five hundred and fifty-five pts were treated: 283 Pem+Cis, 272 Eto+Cis. Baseline characteristics were balanced between arms (Pem+Cis/Eto+Cis): median age, 59.5/58.7; female, 41.2%/40.1%; stage IIIB, 53.5%/51.2%; positron emission tomography scans, 83.1%/81.1%; and Eastern Cooperative Oncology Group performance status 1, 50.5%/50.2%. Pem+Cis vs Eto+Cis median OS was 26.8 vs 25.0 mos (HR 0.98; 95% CI: 0.79, 1.20; p = 0.831) and median PFS was 11.4 vs 9.8 mos (HR 0.86; 95% CI: 0.71, 1.04; p = 0.130). Pem+Cis/Eto+Cis ORR was 35.9%/33.0% (p = 0.458) and disease control rate was 80.7%/70.7% (p = 0.004). Possibly related grade (G) 3/4 toxicities (Pem+Cis vs Eto+Cis) occurred in 64.0% vs 76.8% of pts (p = 0.001). The Pem+Cis arm had a lower incidence of possibly related G3/4 neutropenia/granulocytopenia vs the Eto+Cis arm: 24.4% vs 44.5% of pts (p $<$ 0.001). Pem+Cis vs Eto+Cis rates of G3/4 pneumonitis/pulmonary infiltrates and esophagitis were 1.8% vs 2.6% and 15.5% vs 20.6%, respectively. **Conclusions:** The Pem+Cis arm did not improve OS vs the control arm, but did have a better safety profile than the Eto+Cis arm. Clinical trial information: NCT00686959.

7507 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Randomized phase III trial of customized adjuvant chemotherapy (CT) according BRCA-1 expression levels in patients with node positive resected non-small cell lung cancer (NSCLS) SCAT: A Spanish Lung Cancer Group trial (Eudract:2007-000067-15; NCTgov: 00478699). *First Author: Bartomeu Massuti, Alicante University Hospital, Alicante, Spain*

Background: Postop platinum-based CT improves outcomes in resected NSCLC with N+ (St II-IIIA). Analysis of expression of genes involved in DNA repair could be used to individualize optimal CT. BRCA1 may act as a differential regulator of response to cisplatin (Cis) and antimicrotubule agents. **Methods:** Phase III multicenter trial. After surgery, patients (p) with St II and III were random 1:3 to control arm (Cis-Docetaxel) or to experimental arm with treatm. according BRCA1 express. levels (low : Cis-Gemcitabine; intermediate : Cis-Doc; high: Doc alone). Stratification factors: N1 vs N2; age $<$ or $>$ 65 y; non-squamous vs squamous (Sq) ; lobectomy vs pneumonectomy). Planned PORT in N2. Primary end-point OS. Secondary: DFS, toxicity, compliance, recurrence pattern. Statistical hypothesis: 20% increase 5y surv. control group (45%). **Results:** From June 2007 to May 2013, 591 p were screened and 500 of them were random: 108 in control, 392 experimental (110 p Cis-Gem, 127 Cis-Doc and 110 Doc alone). No disbalance between arm for prognostic factors: Median age 64 y; 79% males, 21% females; 43% Sq, 49% Adeno; pneumonectomy 26%; N1 58%, N2 48%; smoking habit: 57% former, 32% current, 11% never. Median tumor size 4.4 cm (0.8-15.5). Median mRNA BRCA1 levels 15.78 (0.73-132). Mean BRCA1 levels 6.95 Adeno vs 20.29 Sq (p $<$ 0.001). Median f-u 30 months (0-79 m). With a cut-off of March 15th median survival has not reached both arms and no significant diffs. have been seen for OS with HR 0.866 (p = 0.45) or DFS (HR 1). In exper. group HR for OS was 0.842 (NS) comparing low with high-BRCA1 levels. In p with high-BRCA1 levels control treatm. (Cis-Doc) was superior to exper. (Doc) with HR 1.24 (NS). For p receiving all planned treatm. HR is 0.63 with p = 0.043 compared with p not able to complete treatm. P with Sq histology showed a longer DFS (HR 0.73; p = 0.05) but without diff. in OR (HR 1). **Conclusions:** BRCA1 based adjuvant CT does not improve OS. In p with high-BRCA1 levels Doc alone is inferior to Cis-Doc. Full dose of planned treatm. confers a survival advantage, however, longer follow-up is still warranted. Clinical trial information: 00478699.

7508 Poster Discussion Session; Displayed in Poster Session (Board #255), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Final results of phase Ib of tarextumab (TRXT, OMP-59R5, anti-Notch2/3) in combination with etoposide and platinum (EP) in patients (pts) with untreated extensive-stage small-cell lung cancer (ED-SCLC). *First Author: Maria Catherine Pietanza, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Notch signaling is implicated in cancer stem cell self-renewal and proliferation; thus being an appealing target in the treatment of SCLC. Tarextumab (TRXT), a fully human IgG2 antibody targeting Notch2 and 3 receptors, has shown preclinical efficacy in SCLC models with cisplatin. This Phase Ib study explores the MTD, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of TRXT with EP in chemo-naive ED-SCLC. **Methods:** Notch signaling is implicated in cancer stem cell self-renewal and proliferation; thus being an appealing target in the treatment of SCLC. Tarextumab (TRXT), a fully human IgG2 antibody targeting Notch2 and 3 receptors, has shown preclinical efficacy in SCLC models with cisplatin. This Phase Ib study explores the MTD, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of TRXT with EP in chemo-naive ED-SCLC. **Results:** By November 18, 2014, 27 pts were treated with TRXT at dose range from 5 mg/kg to 15 mg/kg. The MTD was not reached and TRXT 15 mg/kg was determined to be the Phase 2 dose. One DLT of Grade 3 nausea and vomiting was reported in the 10 mg/kg dose cohort. Frequently reported ($\geq$ 15%) TRXT-related adverse events were: diarrhea (59.3%), fatigue (44.4%), nausea (40.7%), anemia (25.9%), decreased appetite (25.9%) and vomiting (25.9%); most were Grade 1 or 2 and managed with supportive care. The overall response rate was 84%. The median duration of treatment was 128 days (6 cycles) with mPFS and mOS of 124 and 228 days, respectively. The median follow-up for PFS and OS was of 86 and 107 days respectively. **Conclusions:** TRXT with EP is well tolerated. Encouraging anti-tumor activity has been observed. Final safety, efficacy, PK, immunogenicity and predictive biomarker results will be presented. TRXT at a dose of 15 mg/kg has been selected for the phase 2 randomized, placebo-controlled portion of the study, which is ongoing. Clinical trial information: NCT01859741.

7509 Poster Discussion Session; Displayed in Poster Session (Board #256), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Lurbinectedin (PM01183) with doxorubicin (DOX), an active treatment as second-line therapy in small cell lung cancer (SCLC). *First Author: Martin Forster, University College London, London, United Kingdom*

Background: PM01183 inhibits transactivated transcription and acts on the tumor microenvironment. It lacks cross-resistance with platinum. PM01183 and DOX are synergistic *in vitro*. Recommended dose (RD): 4 mg (or 2 mg/m^2) + 50 mg/m^2, respectively, both on day (D) 1 every 3 weeks. Compelling activity was observed earlier in 2nd line SCLC patients (pts), leading to a cohort expansion. The historical response rate (RR) of DOX-based combinations is around 20%. **Methods**: SCLC pts $\leq$ 75 years with ECOG PS 0-1, adequate organ function and 1 prior chemotherapy-containing line were included. Stable asymptomatic brain metastases were allowed. DOX was discontinued before reaching 450 mg/m^2, non-progressing pts could continue on PM01183 alone. CSF prophylaxis was not mandatory. **Results:** 21 pts were treated and evaluable for efficacy [response rate (RR) by RECIST v1.1]. Male: 76%; median age: 62 y (r, 48-73); ECOG PS = 0/1 in 43%/57%; 29% had brain metastases, 62% had bulky disease and 81% responded to 1st line, 5% CRs. Median chemotherapy-free interval (CTFI) was 3.1 months; 48% were resistant (R = CTFI $\leq$ 90 d). Confirmed RR was 67% (95%CI: 43-85%), including ~10% CRs. CTFI was predictive of RR (100% *vs.* 30% in R pts; p = 0.001). Grade (G) 4 neutropenia, thrombocytopenia or anemia occurred in 86%/19%/5%, respectively and febrile neutropenia (G3/4) in 29%. Other toxicities were generally mild: fatigue (G3 = 14%), anorexia, nausea/vomiting, alopecia, stomatitis (G3 = 10%), dysgeusia, constipation and pneumonia (10%). Three pts discontinued due to toxicity (myelosuppression in 2), no cardiac toxicity or G5 events occurred. As of January 2015, 5 pts (24%) are still ongoing. Progression-free survival (PFS) is 4.7 months (95%CI: 3.5-not reached). **Conclusions:** The PM01183 and DOX combination showed compelling clinical activity as 2nd line treatment in SCLC. RR could be comparable to those achieved in 1st line. Reversible myelosuppression was the most frequent and expected side effect; DOX dose adjustment and/or CSF prophylaxis might be appropriate to improve tolerance. A randomized study is planned to help define the role of this combination in relapsed SCLC pts. Updated results will be presented. Clinical trial information: NCT01970540.

7510 Poster Discussion Session; Displayed in Poster Session (Board #257), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Pazopanib (P) or placebo in completely resected stage I NSCLC patients: Survival results of the phase II trial IFCT-0703. *First Author: Benjamin Besse, Gustave Roussy, Villejuif, France*

Background: P is an anti-angiogenic agent approved in metastatic renal cell carcinoma and sarcoma. We have previously reported compliance of adjuvant P (*i.e.* % of patients (pts) able to receive at least 3 months (m.) of P, whatever the dose) in stage I NSCLC. Compliance has already been reported (WCLC 2013) and has been found adequate at the dose 400 mg/d (69% [95%CI 50-84] (p = 0.027, compared to 38% in P 800 mg/d) vs 93% [95%CI 77-99] in placebo. Here we report survival data. **Methods:** In this double-blind non-comparative randomized multicenter phase II trial, 143 pts with resected stage I NSCLC (7thTNM edition) were randomized to receive placebo or P 800 mg/d during 6 m. The Fleming's two-stage primary endpoint was compliance. After 64 pts included (interim analysis), IDMC recommended to start with P 400 mg/d because of initial insufficient compliance. A one-step Fleming design was used with the new dose. Here, we present survival data for which the intent to treat analysis was performed in 142 pts (1 consent withdrawal). **Results:** Between Mar 2009 and Aug 2012, 71 pts were enrolled in each arm. Most pts were male (61%) and smokers (91%), median age was 60. Pathological stage was IA in 103 pts (72%) and 16% were squamous cell carcinomas. No toxic deaths were observed. 2 pts had grade (G) 4 toxicities in P800 (fatigue in P arm, GGT in the placebo arm). Most common G3 toxicities in P800 were diarrhea (9%), hypertension (13%), and increased transaminases (16% vs. 0% in P400); in P400 gastro-intestinal disorders (16%, 6% diarrhea) and hypertension (6%). Median follow-up was 47 m. The number of events for disease free survival (DFS) is 17 in the P arm and 13 in the placebo arm: 3 yrs DFS rates were 77% [95%CI 67%-87%] and 83% [95%CI 74%-92%] respectively (Hazard Ratio (HR) = 1.3 [95%CI 0.6-2.8], p = 0.53). Among the 14 deaths, 9 occurred in the P arm and 5 in the placebo arm. All deaths were secondary to tumor recurrence but 2, related to cardiac events (1 in each arm). 5 yrs overall survival rates were 83% [95%CI 72-94] in the P arm and 94% [95%CI 88-100] in the placebo arm (HR = 1.9 [95%CI 0.6-5.5], p = 0.27, unplanned analysis). **Conclusions:** Although comparison of survival was unplanned in this phase II, our results do not support a phase III trial. Clinical trial information: NCT00775307.

7511 Poster Discussion Session; Displayed in Poster Session (Board #258), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

ARQ 197 in patients with previously-treated malignant mesothelioma (MM): A phase II trial from the University of Chicago Phase II Consortium. *First Author: Steven Brad Maron, University of Chicago, Chicago, IL*

Background: The MET receptor tyrosine kinase plays a key role in MM biology. MET and its ligand, hepatocyte growth factor (HGF), are each over-expressed in ~80% of MM; MET is mutated and/or amplified in ~10% of MM. Cancers with MET over-expression or mutation are potentially more sensitive to MET inhibitors, such as ARQ 197 (tivantinib), which inhibits MM growth and proliferation in preclinical models. **Methods:** We conducted a multicenter phase II trial of ARQ 197 in previously-treated pts with histologically-confirmed pleural (PL) or peritoneal (PER) MM, measurable disease, PS 0-1, and $\leq$ 2 prior chemotherapies. Primary endpoint: response. ARQ 197 360mg was given orally BID. CT scans were obtained Q8 weeks. A Simon, optimal, 2-stage design required 2 responses in 16 pts to proceed to a 2nd stage. Correlatives: MET mutation, gene amplification, IHC, and serum HGF. **Results:** 18 pts enrolled at 4 centers between 2/13 and 12/13. Male 61%; median age 66 (range 19-81); PS 0: 50%; epithelial/biphasic/sarcomatoid histology: 89%/5%/5%; PL/PER: 61%/39%; Median # cycles: 3 (range 2-14). There were no objective responses. Stable disease (SD): 50% (33% PL pts, 71% PER pts). 3 PER pts had SD for 9.7, 11, and 15.2 months, respectively. Median PFS: 1.9 mo (95% CI: 1.8-5.4); PL/PER 1.8/3.8 mo (95% CI: 1.8-5.4/1.8-11). Median OS 12.2 mo (95% CI: 7.1-22.2); PL/PER: 8.0/22.2 mo (95% CI: 4.6-12.2/7.1-NR). Grade 3/4 toxicities: leukopenia, lymphopenia, abdominal pain, fatigue, infection 6% each. Correlatives: N = 16. IHC expression (0/1+/2+/3+): c-MET (38%/31%/19%/13%), p-MET (0%/0%/31%/69%,) and p-AKT (0%/13%/31%/56%). One pt had a T1101 mutation in the MET juxtamembrane domain. There was no correlation between MET pathway IHC expression or mutation and PFS or OS upon preliminary analysis. **Conclusions:** The trial did not meet its pre-specified response endpoint. However, 43% of peritoneal pts had SD for > 9 months. Though p-MET expression was high, MET IHC expression or mutation did not correlate with disease control. Alternative biomarkers predictive of the activity of ARQ 197 in PER MM pts should be evaluated. Funded by NCI N01-CM-2011-0071C.

7512 Poster Discussion Session; Displayed in Poster Session (Board #259), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

A randomized phase II study of TS-1 plus cisplatin versus vinorelbine plus cisplatin with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC): WJOG 5008L. *First Author: Takashi Seto, National Kyushu Cancer Center, Fukuoka, Japan*

Background: Cisplatin-based chemotherapy and concurrent radiotherapy is the standard treatments for LA-NSCLC. Thistrial evaluated two experimental regimens of chemotherapy with concurrent radiotherapy. **Methods:** Eligible patients with unresectable stage III NSCLC, 20 to 74 years of age, and ECOG PS of 0–1 were randomized to either Arm SP, S-1 (40 mg/m^2/dose per oral, b.i.d, on days 1-14) and cisplatin (60 mg/m^2 on day 1) repeated every 4 weeks or Arm VP, vinorelbine (20mg/m^2 on day 1, 8) and cisplatin (80 mg/m^{2}on day) repeated every 4 weeks with early concurrent thoracic radiotherapy of 60 Gy at 2 Gy per daily fraction. The primary endpoint was overall survival rate at 2-year (2yr-OS). A pick-the-winner design was used to identify the treatment regimen most likely to be superior. The planned sample size was 55 patients per arm, assuming in each arm that the null hypothesis for 2yr- OS was 50% versus an alternative hypothesis for 65% with one-sided alpha of 0.10 and power of 80% (Study ID: UMIN000002420). **Results:** One hundred eleven patients were registered between Sep 2009 and Sep 2012. Of 108 patients for efficacy analysis, the 2yr-OS was 76% (95% CI, 62-85%) for SP and 69% (95% CI, 54-79%) for VP. The hazard ratio (HR) of death between the two arms was 0.85 (0.48-1.49). The median progression-free survival (PFS) was 14.8 months for SP and 12.3 months for VP with a HR of 0.92 (0.58-1.44). 80% and 48% of patients completed the protocol treatment in SP and VP, respectively. Common grade 3-4 toxicities in SP v VP were neutropenia 33.3% v 75.9%, platelets 9.3% v 3.7%, hemoglobin 1.9% v 27.8%, febrile neutropenia 9.3% v 16.7%, diarrhea 5.6% v 0%. There were 4 and 5 treatment-related deaths in SP and VP, respectively. **Conclusions:** Both arms rejected the null hypothesis for 2yr-OS. In this study Arm SP was declared the winner in terms of 2yr-OS, PFS, treatment completion, and toxicity. Clinical trial information: 000002420.

7513 Poster Discussion Session; Displayed in Poster Session (Board #260), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Survival following stereotactic body radiation therapy or conventionally fractionated radiation for definitive non-operative treatment of stage I non-small cell lung cancer: A review of the National Cancer Data Base. *First Author: Cliff Grant Robinson, Washington Univ in St Louis, St. Louis, MO*

Background: Despite a dramatic increase in utilization of stereotactic body radiation therapy (SBRT) for non-operative treatment of clinical stage I NSCLC over the last decade, there are no reported clinical trials or large scale comparisons with standard conventionally fractionated radiation (CFRT). We sought to compare overall survival (OS) between these modalities using the National Cancer Data Base (NCDB). **Methods:** Patients with clinical stage I (AJCC 6th edition T1-T2N0M0) NSCLC who underwent definitive non-operative treatment with either SBRT or CFRT from 1998 to 2010 were identified from the NCDB. Cox regression was used to assess the impact of patient and treatment variables on OS. Inverse probability adjusted Kaplan-Meier survival curves were calculated to assess differences in OS while adjusting for baseline imbalances between the treatment groups. **Results:** A total of 19373 patients met inclusion criteria (5944 SBRT, 13429 CFRT). Median follow-up was 18.7 months. On multivariable analysis, improved OS was independently correlated with younger age, female gender, non-Caucasian race, lower Charlson comorbidity score, smaller tumor size, use of chemotherapy, treatment at an academic facility, and was most strongly associated with use of SBRT (HR .775, 95% CI, .737 to .817). Chemotherapy was delivered in 32.9% of CFRT patients and 4.2% of SBRT patients. Chemotherapy was correlated with improved OS on multivariable analysis for CFRT but not SBRT. In an adjusted Kaplan-Meier comparison, SBRT was associated with a significant increase in median (29.8 v 26.2 months) and 3-year (42.3% *v* 36.4%) OS compared with CFRT ($P < .0001$). **Conclusions:** In a large population-based analysis of outcomes in a modern cohort of patients with clinical stage I NSCLC treated with definitive non-operative therapy, SBRT was associated with a significant improvement in OS compared with CFRT.

7514 Poster Discussion Session; Displayed in Poster Session (Board #261), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Trimodality therapy in the treatment of stage IIIA non-small cell lung cancer (NSCLC): Analysis of the National Cancer Database. *First Author: Madhusmita Behera, Winship Cancer Inst Emory Univ, Acworth, GA*

Background: Significant controversy remains regarding the care of patients (pts) with clinical stage IIIA NSCLC. While multi-modality therapy is an acceptable strategy in selected pts, the optimal approach is not firmly established. We analyzed outcomes and predictors associated with trimodality therapy (TT) in the National Cancer Database (NCDB). **Methods**: The NCDB was queried from 2003-2011 for NSCLC pts diagnosed with stage IIIA-N2 disease and treated with chemotherapy and radiation (CRT). Three cohorts of pts were studied - CRT only/no surgery (NS), CRT + lobectomy (L) and CRT + pneumonectomy(P). The univariate and multivariable analyses (MV) were conducted using Cox proportional hazards model and log rank tests. All analyses were performed using SAS Version 9.3. **Results**: A total of 29,584 pts were included in this analysis: NS-91.7%, L-7%, and P-1.5%. Pt characteristics: median age 66 years (yrs); males 56%; whites 86%; academic centers 27%; metro locations 78%; government insured 63%; Charlson/Deyo comorbidity score 0 in 66%. Pts $<$ 60 yrs were more likely to receive TT- L (47%), P (60%) vs. NS (29%); $p<$ 0.001. Pts in academic centers were more likely to get TT than NS (42% vs. 25%). On MV analysis, L and P had significantly better survival vs. NS: HR 0.43 (0.38-0.48) and HR 0.57 (0.46-0.71) respectively; $p <$ 0.001. The median survival of L, P and NS were 44.5 m vs. 25.6 m vs. 15.7 m ($p <$ 0.001) and 5- year survival rates (SR) were 44% vs. 33% vs. 14% respectively. 30-day mortality was higher in P vs. L [7% vs. 2.6%; OR 0.26(0.16-0.45); $p<$ 0.001]. Pts with $<$ 2 lymph nodes (LN) had better survival than pts with $>$ 2 LNs in L (50% vs. 37%; 60m vs. 38.8m) but worse in NS (13.8% vs.16.4%; 15.3m vs.18.5m). On MV analysis of LNs, L had better survival than NS: HR 0.4 (0.35-0.46) in $<$ 2 LN pts and HR 0.56 (0.46-0.69) in $\geq$ 2 LN pts; $p<$ 0.001. In pts with $<$ 2 LN, L had better survival than P (60m vs. 25.5m; $p<$ 0.0001). L and P had better SR than NS in all ages: 48% vs.37% vs. 19% in $\leq$ 60 yrs; 42% vs. 30% vs.14% in 61-70 yrs, 36% vs.19% vs. 10% in $>$ 70 yrs. **Conclusions**: TT was utilized in less than 10% of pts with stage IIIA-N2 disease, suggesting high degree of pt selection. In this selected group, TT was associated with favorable outcomes relative to CRT alone.

7515 Poster Discussion Session; Displayed in Poster Session (Board #262), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Programmed cell death 1 (PD-1) and its ligand (PD-L1) expression in thymic epithelial tumors (TETs): Impact on the treatment efficacy and alteration in expression after chemotherapy (C). *First Author: Yuki Katsuya, National Cancer Center Hospital, Tokyo, Japan*

Background: Recent studies have demonstrated the efficacy of anti-PD-1/L1 antibodies. To understand the clinical impact of PD-1/L1 expression in TETs, we evaluated the frequency of PD-1/L1 expression in pre- and post-C (Pre/Post) specimens and the correlation between PD-1/L1 expression and the treatment efficacy. **Methods:** The expression of PD-1/L1 was evaluated by immunohistochemistry in patients (pts) with thymoma (TM) or thymic carcinoma (TC) treated by chemotherapy between 2000 and 2014 at the National Cancer Center Hospital. Using formalin-fixed paraffin-embedded tissue samples and a validated PD-L1 antibody (E1L3N), the PD-L1 expression in TET cells was reported in terms of the H-score (0-300), with a score $\geq$ 1 being defined as positive. PD-1 expression in the tumor-infiltrating lymphocytes was evaluated based on the intensity (0–3) of staining using a PD-1 antibody (NAT105). The objective response rate (ORR), progression-free survival (PFS) and the difference in PD-1/L1 expression between the Pre/Post TM specimens were evaluated. **Results:** A total of 29 pts was included; TM/TC, 12/17; male/female, 14/15; median age 57; WHO histology (B1/B2/B3/Squamous/others), 1/7/3/12/6. Pre/Post serial specimens were available for 6 TMs. All pts received platinum-based C, and the ORR was 42% in TMs and 18% in TCs. Expression of PD-L1 was positive in 9 (75%) of the TMs and 8 (47%) of the TCs. In the PD-L1 positive population, ORR was 56% (5/9) in TMs and 13% (1/8) in TCs. In the PD-L1 negative population, ORR was 0% (0/3) in TMs and 22% (2/9) in TCs. There were no statistically significant differences in the PFS according to the PD-L1 expression status. Increase of the PD-L1 score and PD-1 staining intensity were observed after C in serial specimens of TM; mean Pre/Post PD-L1 score, 41.6/92.5 ($p = 0.058$); median Pre/Post PD-1 intensity, 0/2.5 ($p = 0.055$). **Conclusions:** Although there was no obvious correlation between PD-L1 expression and the efficacy of C in pts with TETs, increased expression of PD-1/L1 after C was observed in the TMs. Further efforts to develop novel therapies, including anti PD-1/L1 antibodies, are warranted.

7516 Poster Discussion Session; Displayed in Poster Session (Board #263), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Defining the immunologic phenotype of thymic epithelial tumors. *First Author: Jarushka Naidoo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Thymic epithelial tumors (TETs) are associated with immune dysfunction and are poorly responsive to conventional therapies. We aimed to characterize the immune microenvironment in TETs, to identify potential targets for immunotherapy. **Methods:** Tumor tissue from 24 TETS was identified. Tumor-infiltrating lymphocytes (TILs: CD3+ and CD8+ T-cells), PD-L1 expression on tumor cells (antibody: E1L3N), and a panel of co-stimulatory (CD137, GITR, OX40, ICOS) and co-inhibitory immune checkpoint molecules (PD-1, CTLA-4, TIM-3) on immune cells, was investigated by immunohistochemistry. PD-L1 positivity was defined as ≥ 25% of tumor cells with positive membranous staining. TILs and immune cell checkpoint molecule staining were semi-quantitatively scored as: low = 0-1, high = 2-3. Associations between clinicopathologic factors, immune checkpoint molecule expression and TILs, was evaluated. Overall survival (OS) was measured from the time of cancer diagnosis, assuming that immune markers do not change throughout the course of disease. Data was analyzed using Fisher's exact, Wilcoxon rank sum and log-rank tests, and Cox proportional hazards model. **Results:** Tumor tissue from B2/B3 thymomas (n = 12) and thymic carcinomas (n = 12) was evaluated. CD8+ TILs was seen in all tumors. Sixty-three percent of TETs (n = 15/24) were PD-L1+. PD-L1 positivity was more common in thymomas than thymic carcinomas (11/12 vs. 4/12, $p < 0.01$). When analyzed as a continuous variable, PD-L1 expression had an inverse correlation with risk of death ($p = 0.02$). Eighteen pts with TETs (n = 18/24, 75%) had high TIM-3 expression. Two immunologic parameters correlated with improved OS: PD-L1+ tumor cells ($p < 0.01$) and high TIM-3 expression ($p = 0.01$). There was a positive correlation between PD-L1+ tumor cells and CD8+ T-cells ($p = 0.02$), PD-L1+ tumor cells and high TIM-3 expression ($p = 0.03$), CD8+ T-cells and high TIM-3 expression ($p = 0.03$). **Conclusions:** TETs possess a robust TIL infiltrate. The majority of tumors have high expression of the co-inhibitory checkpoint molecule TIM-3, and are PD-L1+. These parameters may correlate with OS. These data support the immunotherapeutic targeting of the PD-1/PD-L1 and TIM-3 pathways in patients with TETs.

7517 Poster Discussion Session; Displayed in Poster Session (Board #264), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Evaluating causes of screen failure (SF) in non-small cell lung cancer (NSCLC) clinical trials requiring specific biomarker (BioM) results for enrollment. *First Author: Danielle J. Nameth, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*

Background: Trials for NSCLC have increasingly targeted specific molecular abnormalities. This approach has led to approval of multiple drugs based on results in specific BioM populations prior to completion of randomized trials. As a result, many trials now require evaluation of a fresh biopsy prior to enrollment. Implications of potentially increased duration of screening on interpretation of clinical outcomes have not been completely explored. **Methods**: We reviewed charts of patients (pts) with NSCLC consented to 26 trials between January 2012 and December 2014 through the UCLA Jonsson Comprehensive Cancer Center lung cancer program to assess factors associated with lack of enrollment. **Results**: 385 pts consented to participate in therapeutic clinical trials, 280 of whom signed consent for one of several trials requiring specific results from a recent biopsy with 139 pts ultimately enrolling in such trials. In treated pts in whom a new biopsy was required, median number of days from informed consent to biopsy was10 and from biopsy to first dose was 25**.** Of the 141 SF pts, 34 (24.1%) were eligible based on BioM status. Of these, SF was due to worsening performance status (PS) in 18 (52.9%), pursuing alternate therapy in 3 (8.8%), screening labs out-of-range in 3 (8.8%), withdrawal of consent in 2 (5.8%), and other reasons (prohibited medications, etc.) in 8 (23.5%). **Conclusions**: Approximately one-quarter of screened pts who did not enroll on trials requiring BioM interpretation from a recent biopsy were eligible based on BioM results, most of whom experienced SF based on worsening PS. Whether these patients would have enrolled if the clinical trial had a more traditional design cannot be known. Implications of these findings for accurately assessing trial efficacy should be assessed, as should the generalizability of our results. Whether the delay in enrollment based on the duration of screening either excludes pts who would have been more likely to experience early decline or enrolls pts who have become more ill during screening should be more fully explored.

7518 Poster Discussion Session; Displayed in Poster Session (Board #265), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Prospective molecular analysis of small cell lung cancer (SCLC) using next generation sequencing (NGS). *First Author: Maria Catherine Pietanza, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recent studies using NGS on resected SCLC have provided insights into the landscape of genetic alterations in this disease. We report our experience with prospective genomic profiling of SCLC patients using the biopsy specimens available in clinical practice and a targeted, hybrid capture-based, NGS assay, MSK-IMPACT. **Methods:** Utilizing an IRB approved protocol, we are evaluating SCLC tumors of patients in active treatment. FFPE surgical resections, core biopsies, and fine needle aspirates (FNA) are being evaluated by NGS to identify single nucleotide variants, indels, and copy number alterations in a common set of 222 cancer-associated genes shared by pre-clinical and clinical versions of MSK-IMPACT. Clinical data are collected (smoking status; stage [extensive (ES), limited (LS)]; treatment response). **Results:** Currently, 50 patient samples have undergone evaluation, 58% from core biopsies or FNA. The 50 SCLC patients include 4 never smokers, 58% with ES-SCLC, and 30% resistant to first line therapy. Alterations have been noted in 202 of 222 targeted genes. The median number of non-synonymous somatic mutations is 7. Of 526 total non-synonymous mutations, 5% are hotspot COSMIC mutations, 25% are loss-of-function, and 47% are G-to-T transversions, reflective of tobacco induced carcinogenesis. We observe frequent inactivation of RB1 (96%) and TP53 (92%). Other common genomic events include alterations in SOX2 (26%), EPHA5 (22%), CDKN2C (20%), MYCL1 (20%), and PIK3CA (18%). Tumors from the 4 never smokers (0 pk yrs) displayed a median of 3 mutations, of which none were G-to-T transversions, while those from moderate (< 20 pk yrs) and heavy (20+ pk yrs) smokers contained 4.5 and 8 mutations, respectively ($P < 0.05$). ES-SCLC patients had a lower median number of mutations (5/tumor) than LS-SCLC patients (9/tumor). Diverse amplifications, deletions, and mutations are noted in sensitive tumors, while homozygous deletions are more common in refractory tumors. **Conclusions:** Comprehensive molecular evaluation of SCLC is feasible on clinically available specimens using a targeted NGS assay. Prospective analyses allow us to fully characterize the molecular diversity of SCLC in the clinical setting.

7519 Poster Discussion Session; Displayed in Poster Session (Board #266), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Genomic profiling of large-cell neuroendocrine carcinoma of the lung. *First Author: Tomohiro Miyoshi, Division of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan*

Background: Large-cell neuroendocrine carcinoma (LCNEC) of the lung shares many clinical characteristics with small-cell lung cancer (SCLC). However, little is known about the molecular biology of LCNEC. We analyzed lung LCNECs for biologically relevant genomic alterations using a next-generation sequencing-based genomic profiling assay. **Methods:** Genomic DNAs extracted from surgically resected or biopsy samples were subjected to a 1.499 Mb custom target capturing panel including all exons of 244 cancer-related genes. Seventy eight LCNEC samples including 10 LCNECs combined with other non-small cell lung cancers (NSCLCs) were applied to the target sequencing. In the 10 combined LCNECs, both morphologic components of LCNEC and other NSCLCs (adenocarcinoma: 5, squamous cell carcinoma: 5) were analyzed separately. Frequencies of detected driver gene alterations were compared with those in previous reports regarding SCLC. **Results:** The demographics of the 78 patients were as follows: median age 70 years (range: 22-84); male 67 (86%); history of smoking 76 (97%); pathological stage I/II/III = 38/14/13 for 65 resected cases and clinical stage II/III/IV = 1/4/8 for 13 biopsy cases. We identified high prevalence of inactivating mutations in *TP53* (74%) and *RB1* (29%), and mutations of histone modifiers, *CREBBP* (10%) and *EP300* (4%), were detected as with the previous reports on SCLC. Genetic mutations in the PI3K/AKT/mTOR pathway were detected in 30 (40%) of the tumors: *PIK3CA* 3%, *PTEN* 6%, *AKT2* 1%, *AKT3* 1%, *TSC*1 5%, *TSC2* 3%, *RPTOR* 4%, *RICTOR* 10% and *mTOR* 5%. Other known activating mutations were also detected in *KIT* (1%), *KRAS* (4%) and *HRAS*(1%). In the combined cases, the concordance rate of types of genetic alterations between the two components was 87% (range: 50-97). **Conclusions:** The genomic profile of LCNEC was similar to that of SCLC. Genetic alterations of the individual components in combined LCNEC were closely concordant with each other despite their distinct histologic morphologies.

7520 Poster Session (Board #267), Mon, 8:00 AM-11:30 AM

Adjuvant chemotherapy for patients with T2N0M0 non-small cell lung cancer. *First Author: Daniel Morgensztern, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Adjuvant chemotherapy (CT) improves overall survival (OS) in patients with completely resected stage II and III non-small cell lung cancer (NSCLC). However, its role in patients with stage IB disease remains unclear. We therefore evaluated the role of adjuvant CT in patients with completely resected T2N0M0 NSCLC. **Methods:** Patients with pathologic stage T2N0M0 NSCLC who underwent complete (R0) resection from 2003 to 2010 were identified from the National Cancer Database (NCDB). Patients were grouped based on tumor size: 3-3.9 cm, 4-4.9 cm, 5-5.9 cm and 6-7 cm. Survival curves according to the CT status were estimated by the Kaplan-Meier product-limit method and compared by log-rank test. Cox proportional hazard model was used to evaluate whether adjuvant CT was an independent predictor for survival for each tumor size groups. **Results:** Among the 29,908 patients meeting inclusion criteria, there were 5,209 (17.4%) and 24,699 (82.6%) patients in the CT and observation groups respectively. Patients treated with CT were younger (median age 65 vs 71 years, $p < 0.001$), had smaller median tumor sizes (3.7 vs 4.1 cm, $p < 0.001$), and a lower incidence of sub-lobar resection (5.6% vs 8.2%, $p < 0.001$). Adjuvant CT improved median OS compared to observation for all tumor size groups in both univariate (UVA) and multivariate (MVA) analyses (Table). **Conclusions:** Adjuvant CT was associated with improved OS in all tumor size groups for patients with completely resected T2N0M0 NSCLC. Despite the biases inherent in a database study, the benefit from adjuvant CT in patients with tumors < 4 cm suggests a possible role in this patient population and the need for revisiting its current status as an exclusion criteria for adjuvant trials.

Adjuvant chemotherapy versus observation.

	Median OS (months)	5 year OS	UVA-HR(95% CI)	MVA-HR(95% CI)
All patients	95.6 vs 67.0	67.9 vs 54.6%	0.64 (0.61-0.68)	0.70 (0.66-0.74)
3-3.9cm	NR vs 71.3	70.5 vs 57.9%	0.66 (0.61-0.73)	0.75 (0.68-0.85)
4-4.9cm	90.7 vs 64.7	66.5 vs 52.7%	0.61 (0.55-0.68)	0.70 (0.63-0.77)
5-5.9cm	87.9 vs 58.8	65.9 vs 49.3%	0.60 (0.53-0.69)	0.68 (0.60-0.78)
6-7cm	86.9 vs 54.6	65.3 vs 46.8%	0.55 (0.47-0.64)	0.62 (0.53-0.72)

7521 Poster Session (Board #268), Mon, 8:00 AM-11:30 AM

Prognostic effect of single versus multiple somatic mutations in non-small cell lung cancer (NSCLC). *First Author: Kevin Jao, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Somatic mutations are becoming increasingly important biomarkers for treatment selection and outcome in patients with NSCLC. **Methods:** Tissue from 200 patients with NSCLC at the Princess Margaret Cancer Centre, were analyzed by next-generation genomic sequencing using Mi-SEQ or Sequenom multiplex platforms. *TP53* analysis was added for DNA sequenced by Sequenom. Mutation status was correlated with clinical and demographic data retrieved from patient records. **Results:** Somatic mutations were identified in 139 patients (70%): single (n = 67) and multiple (≥ 2, n = 72). The most common mutations were *TP53* (n = 70, 30%), *KRAS* (n = 48, 21%) and *EGFR* (n = 45, 20%). Multiple mutations were significantly associated with younger age (p = 0.02), but not with sex, histology, stage, ethnicity or smoking status. Multiple mutations occurred most frequently with *TP53* (n = 53, 32%), *EGFR* (n = 35, 21%) and *KRAS* (n = 25, 20%). Among multiple mutations, the most common co-mutations were *KRAS-TP53* (25%) and *EGFR-TP53* (19%); 10% of patients had 2 *EGFR* mutations. On univariate analysis, there was a trend for multiple mutations to be associated with poorer overall survival (OS) (HR 1.65, CI 0.95-2.87, p = 0.07) in the entire group, and significantly shorter OS in adenocarcinoma (n = 116) (HR 2.12, CI 1.47-2.01, p = 0.028). In the subgroup of 94 surgically resected stage I-III patients, multiple mutations (n = 49) were associated with shorter relapse-free survival (median 1.7 *v* 3.2 yrs, HR 1.92, CI 1.17-3.14, p = 0.008) and OS (median 5.8 v 7.8 yrs, HR 2.29, CI 1.06-4.94, p = 0.026). No OS difference was seen in advanced stage III/IV patients with single (n = 21) *v* multiple mutations (n = 23) (HR 0.93 CI 0.4-2.2, p = 0.88). No significant OS difference was seen in adenocarcinoma patients with *KRAS* mutation alone (n = 21) v *KRAS* with other mutations (n = 24) (HR 1.53, CI 0.61-3.86, p = 0.366). **Conclusions:** Multiple mutations are associated with poorer outcomes in resected NSCLC. The differences are both statistically significant and clinically relevant. Larger datasets are required to validate whether mutational status is an independent prognostic factor or predictive of a differential benefit from adjuvant chemotherapy in early stage NSCLC.

7522 Poster Session (Board #269), Mon, 8:00 AM-11:30 AM

Validation of a cell cycle progression score for 5-year mortality risk in patients with stage I non-small cell lung cancer. *First Author: Takashi Eguchi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The aim of this study was to validate a molecular expression signature [cell cycle progression (CCP) score] and a Prognostic Score [(PS) combination of CCP and pathological stage (IA or IB)] that identify stage I non-small cell lung cancer patients with a higher risk of cancer-related death after surgical resection. **Methods:** Formalin-fixed paraffin-embedded surgical tumor samples from 1200 patients diagnosed with stage I adenocarcinoma who underwent definitive surgical treatment without adjuvant chemotherapy were analyzed for 31 proliferation genes by quantitative RT-PCR. The prognostic discrimination of the CCP score and the PS were assessed by Cox proportional hazards regression using 5-year lung cancer death as primary outcome. **Results:** In a multivariate model the CCP score was a significant prognostic marker of 5-year lung cancer mortality [hazard ratio (HR) = 1.54 per interquartile range (95% confidence interval = 1.10–2.15; $p = 0.0110$)]. Other significant variables included age, tumor size, lymphatic invasion, morphology grade and type of surgery. Gender, smoking status, pathological stage, pleural invasion and vascular invasion were not significant. In a separate multivariate model the PS was a significant prognostic marker of 5-year lung cancer mortality [hazard ratio (HR) = 1.76 per interquartile range (95% confidence interval = 1.14–2.72; $p = 0.0112$)]. Using a previously established threshold (85^{th} percentile) of the PS, there was a significant difference in lung cancer survival between low-risk and high-risk patient groups ($p < 0.0001$). **Conclusions:** This study validates both the CCP score and PS as independent prognostic markers of lung cancer death in patients with Stage I lung adenocarcinoma treated with surgery alone. Significantly, in the Stage IB population, CCP and PS provide quantitative risk information above that captured by current NCCN high risk features. Patients with resected stage I lung adenocarcinoma and a high CCP and PS may be candidates for adjuvant therapy to reduce cancer related mortality.

7523 Poster Session (Board #270), Mon, 8:00 AM-11:30 AM

The effect of platinum based adjuvant chemotherapy on survival in the surgically resected lung adenocarcinoma according to the expression of EGFR mutation specific antibody and c-MET. *First Author: In-Ho Kim, Division of Oncology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea*

Background: To assess the role of mutant EGFR and C-MET in survival benefit obtained from platinum-based adjuvant chemotherapy (PBAC) among resected lung adenocarcinoma (RLADC) patients. **Methods:** From 2005 through 2013, the RLADC patients (stage IB-IIIA) receiving either PBAC (Paclitaxel/Carboplatin, Paclitaxel/Cisplatin, or Vinorelbine/Cisplatin) or to be observed were enrolled. We did immunohistochemistry (IHC) study with mutant EGFR-specific antibody (mutEGFR-sAb) and C-MET in tissue microarray with 301 cases. We assessed the effect of PBAC on survival according to the expression of mutEGFR-sAb and C-MET. **Results:** Until Oct. 2014, 85 patients experienced relapse and 65 patients died among 301 patients. The median follow-up period for survival was 22.4 months. 137 patients received PBAC. Clinical characteristics is as follows; F: M = 165:136, stage Ib 170, II 74, IIIa 47**.** The IHC were positive for mutEGFR-sAb in 78 cases (42 in exon 19, 36 in exon 21) and for C-MET in 136 cases. Compared with EGFR mutation by direct sequencing ,the specificity and sensitivity of mutEGFR-sAb were 99% and 88%, respectively. PBAC prolonged overall survival (OS) in mutEGFR-sAb (+) group of stage II,III patients with statistical significance (p = .040), not in mutEGFR-sAb (-) group (p = .460). Among all patients, PBAC was an independent prognostic factor for relapse free survival(RFS) (HR = 0.29, P = .034) and OS (HR = 0.17, P = .033) in mutEGFR-sAb (+) group. By contrast, in patients with mutEGFR-sAb (-), PBAC was not associated with RFS (HR = 0.63, p = .144) and OS (HR = 0.55, P = .091). Meanwhile, in C-MET (+) subgroup of stage II and IIIa patients, PBAC showed significantly longer survival (RFS; p = .088, OS; p = .015), not in C-MET (-) subgroup. (RFS; p = .979, OS; p = .839). The multivariate analysis indicated that PBAC may be an important factor for increased survival among C-MET(+) patients (RFS; HR = 0.53, p = .086, OS; HR = 0.34, p = .010) but not among C-MET (-) (RFS; HR = 0.74, p = .472, OS; HR = 0.77, p = .597). **Conclusions:** Taken together, our data suggests that overexpression of mutEGFR-sAb and C-MET may be favorable predictive biomarkers for PBAC among RLADC patients.

7524 Poster Session (Board #271), Mon, 8:00 AM-11:30 AM

Therapeutic Interventional Mapping System (TIMS): A novel strategy for the selection of tri-targeted therapy combinations for non-small cell lung cancer (NSCLC). *First Author: John Mendelsohn, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Combining three targeted therapies significantly improved outcomes in AIDS. A similar strategy could theoretically benefit patients with metastatic NSCLC, but a scientific method for rational selection of drug combinations is needed. **Methods:** We assessed genomics and the transcriptome (including miRNA), utilizing defined subsets of relevant genes/gene products, and scored information about the relationships between targeted drugs and genes, based in part on the biological hallmarks of cancer. Interventional points (genes/group of genes) that, when activated, could be blocked by a customized therapy combination, were identified. The underlying algorithm integrates and weighs the genomic (DNA sequencing) and transcriptomic data (mRNA and miRNA differential expression between tumor and normal -bronchial mucosa - tissues). **Results:** Key genes (N = 183) grouped in 24 interventional points forming the Therapeutic Interventional Mapping System (TIMS) were elucidated. Frequency and trends of co-activation derived from 121 NSCLC patients defined a list of candidate triple therapy combinations. The focus, in order to limit toxicity, was on the application of two small molecules (TKI) and an immune-modulator (anti-PD1L). Twenty-eight percent of NSCLC patients displayed the simultaneous activation of PD1L, Ras/Raf and mTor/PI3K interventional points. Overall, fifty two percent of NSCLC patients could be targeted by a triple combination that includes an anti-PD1L agent. Most individuals could benefit from two or even more triple combinations to overcome resistance. **Conclusions:** The TIMS's strategy enables conversion of thousands of genomic and transcriptomic measurements into a simple and actionable result (a 1 to 10 score) that may be usable by physicians to select triple drug therapy. Comparing tumor and normal tissue biopsies has proven feasible in the ongoing WINTHER trial (NCT01856296). This novel strategy may allow deployment of personalized tri-targeted therapies that will be prospectively tested in a clinical trial with the objective to significantly impact survival in advanced NSCLC and other malignancies.

7525 Poster Session (Board #272), Mon, 8:00 AM-11:30 AM

Prognostic value of cytokine profile on survival in non-small cell lung cancer patients treated with radiotherapy. *First Author: Shulian Wang, Department of Radiation Oncology, GRU Cancer Center and Medical College of Georgia, Augusta, GA*

Background: Immunomodulatory and inflammatory cytokines play an important role in cancer development and progression. This study is to investigate the prognostic value of cytokine profile on overall survival (OS) in non-small cell lung cancer (NSCLC) patients treated with radiotherapy (RT). **Methods:** The pre-RT plasma levels of 30 cytokines were measured by multiplex ELISA in 154 stage I-III NSCLC patients who were enrolled in prospective studies. Cox-regression analysis was performed to evaluate the prognostic values of cytokine levels, clinical factors on OS. **Results:** With a median follow up time of 21.3 months for patients alive, the 3- and 5-year OS was 38.3% and 18.5%, respectively. In univariate analysis, 6 out of 30 cytokines were identified as prognostic biomarkers for OS. Elevated level of TGFa ($p = 0.011$), IL-1b ($p = 0.000$), IL-4 ($p = 0.048$), IL-15 ($p = 0.005$), EGF ($p = 0.011$), sCD40L ($p = 0.020$) was significantly associated with inferior OS. Male ($p = 0.034$), older age ($p = 0.023$), poor ECOG performance status ($p = 0.002$), weight loss ($p = 0.036$), fatigue ($p = 0.005$), non-adenocarcinoma histology ($p = 0.004$), lower RT dose ($p = 0.046$) were significantly associated with inferior OS. In multivariate analysis, TGFa ($p = 0.041$), ECOG performance status ($p = 0.006$), fatigue ($p = 0.018$), histology ($p = 0.019$) were independent prognostic factors for OS. **Conclusions:** Elevated plasma level of TGFa before radiotherapy may represent an independent adverse biomarker for poor OS of NSCLC treated with RT. This result, if validated, will provide important additions to identify risk group of NSCLC patients and guide the development of new targeted therapies. [KFM1]

7526 Poster Session (Board #273), Mon, 8:00 AM-11:30 AM

Final overall survival (OS) analysis of a multicenter phase II study of concurrent high-dose (72Gy) three-dimensional conformal radiotherapy (3D-RT) without elective nodal irradiation with chemotherapy using cisplatin (CDDP) and vinorelbine (VNR) in patients with stage III non-small cell lung cancer (NSCLC). *First Author: Hidehito Horinouchi, Nantional Cancer Center Hospital, Tokyo, Japan*

Background: We previously reported the adverse events and objective responses in a multicenter phase II study of high-dose chemoradiotherapy. This is a final analysis of the pattern of recurrences, progression free survival (PFS) and OS. **Methods:** Patients with stage III NSCLC were eligible if they met the following key criteria: age between 20 and 74 years, PS 0-1 and $V_{20} \leq 30\%$. Participants received 3-4 cycles of CDDP (80 mg/m^2 day 1) and VNR (20 mg/m^{2}days 1 and 8) every 4 weeks. The 3D-RT was administered at a total dose of 72 Gy divided into 36 fractions from day 1 chemotherapy. The primary endpoint was the 2-year survival rate and the planned sample size was 60 to reject the rate of 45% under the expectation of 65% with a power of 90% and an alpha error of 5%. **Results:** Thirty-one patients were enrolled between 2009 and 2011. The median follow-up time (range) was 51.4 (28.8-65.6) months at the point of data cut-off. This trial was terminated early due to the slow accrual and appearance of grade 5 pulmonary toxicities in 2 patients. There were 25 men and 6 women with a median (range) age of 59 (32-72) years. Of the 25, 23 had adenocarcinoma and 21 had stage IIIA disease. The median (range) V_{20}value was 20 (9-30). Among the 20 patients showing disease progression, in-field failures were observed in 5 (25%) patients as the first relapse and a further 4 patients (9 [45%] patients in total) during the follow-up period. The 2-, 3-, and 5-year PFS rates (95% CI) were 44.9% (27.1-61.2), 34.6% (18.5-51.2), and 34.6% (18.5-51.2), respectively. The 2-, 3-, and 5-year OS rates (95% CI) were 64.5% (45.2-78.5), 51.2% (32.6-67.1), and 43.8% (25.8-60.5), respectively. The median PFS and median survival time were 17.1 months and 41.2 months, respectively. **Conclusions:** The higher TRT dose associated both with an unacceptable incidence of pulmonary toxicities and with relatively better long-term survival. Development of a better strategy is warranted to obtain both a better outcome and tolerable pulmonary toxicities. Clinical trial information: UMIN000001743.

7527 Poster Session (Board #274), Mon, 8:00 AM-11:30 AM

Incomplete non-small-cell lung cancer (NSCLC) resections in the National Cancer Data Base (NCDB): Predictors, prognosis and value of adjuvant therapy. *First Author: Raymond U Osarogiagbon, Baptist Cancer Center, Memphis, TN*

Background: Data are limited on the expected rate and survival impact of incomplete NSCLC resections, and the value of postoperative adjuvant therapy in this situation. **Methods:** We analyzed surgically treated stage I-IIIA NSCLC patients in the NCDB from 2004 to 2011 for clinical, sociodemographic and institutional factors associated with margin-positive resection using multivariate logistic regression models. We compared survival of patients with and without positive margins using proportional hazards (PH) models; and the impact of postoperative adjuvant therapy evaluated with multivariate PH models. **Results:** Of 113,007 resections over 8 years, 5338 (4.72%) had positive margins. Black race, age-based Medicare insurance and urban residence ($p < .01$) were associated with increased adjusted odds ratio (aOR) of resection with positive margins. Squamous histology, high tumor grade, tumor location in the main bronchus, and advancing pathologic stage were clinical factors associated with higher aOR ($p < .001$). Surgery performed at Community Cancer Programs, institutions with high proportions of underinsured patients, institutions at lower cancer resection volume quartiles, also had increased aOR ($p < .01$). The stage-adjusted 5-year survival rate of margin negative vs positive patients was 59% and 40%, respectively ($p < .0001$). After adjustment for stage and other significant factors, postoperative adjuvant therapy was associated with a lower 5-year mortality risk: adjusted hazard ratio 0.75 ($p < .0001$) for chemotherapy; 0.86 ($p < .002$) for radiotherapy; 0.75 ($p < .0001$) for chemoradiotherapy. **Conclusions:** Black race, urban residence, and certain facility characteristics (e.g., low resection volume and high percentage of underinsured patients) were independently associated with incomplete resection. Margin involvement significantly impairs survival after lung cancer resection, irrespective of stage. Contributory intra-institutional provider practices should be identified, to minimize this outcome disparity. Postoperative adjuvant therapy mitigates the mortality risk independently of stage, and should be offered to all patients.

7528 Poster Session (Board #275), Mon, 8:00 AM-11:30 AM

Phase II trial of neoadjuvant bevacizumab plus pemetrexed and carboplatin in patients with unresectable stage III lung adenocarcinoma (GASTO 1001). *First Author: Si-Yu Wang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Unresectable stage III non-small cell lung cancer is often treated with concurrent chemoradiotherapy. Bevacizumab has showed its efficacy in advanced non-squamous lung cancer. The aim of this phase II trial is to assess the efficacy and safety of induction bevacizumab (Bev) plus chemotherapy followed by surgery in unresectable stage III lung adenocarcinoma. **Methods:** This phase II trial investigated induction Bev (7.5 mg/kg) plus pemetrexed (500 mg/m^2) and carboplatin (AUC = 5) followed by surgery for patients with unresectable, stage III lung adenocarcinoma. Neoadjuvant therapy was administered every 3 weeks for 4 cycles. Surgery was scheduled 3-4 weeks after last neoadjuvant therapy and patients' resectability was assessed by a medical team, including thoracic surgeons, medical oncologists, and radiologists. The primary endpoint was resectability rate. **Results:** From April 2012 to April 2014, 42 patients were enrolled and received Bev plus pemetrexed and carboplatin (PC). Grade 3 or 4 neoadjuvant-related adverse events included fatigue in 5 patients, neutropenia in 4, hypertension in 1, anemia in 1 and thrombocytopenia in 1. The adverse events thought to be related to bevacizumab included epistaxis in 3 patients (grade 1, 2; grade 2, 1) and hypertension in 2 patients (grade 1, 1; grade 3, 1). Complete response was achieved in 1 patient, partial response in 22, stable disease in 17, and progressive disease in 2. After neoadjuvant therapy, 31 patients underwent surgery, with pneumonectomy in 11. R0 resection was achieved in 22 patients. Postoperative complications included pneumonia (4 patients), atelectasis (2), bronchial stump insufficiency (1), empyema (1), subcutaneous emphysema (2) and arrhythmia (1). No perioperative hemorrhage events, thromboembolic events and wound-healing problems were observed. No patient died in the perioperative period. The median event-free survival (EFS) was 15.4 months, and the 1-year EFS was 56.1%. **Conclusions:** The treatment modality of neoadjuvant Bev-PC followed by surgery appears to be feasible and safe in patients with unresectable stage III lung adenocarcinoma. Clinical trial information: NCT01588704. Clinical trial information: NCT01588704.

7529 Poster Session (Board #276), Mon, 8:00 AM-11:30 AM

Phase I study of bi-weekly *nab*-paclitaxel and carboplatin with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer. *First Author: Yukihiro Hasegawa, Aomori Prefectural Central Hospital, Aomori, Japan*

Background: Nanoparticle albumin-bound paclitaxel (*nab*-P) is a cremophor-free formulation of paclitaxel designed to improve solubility and intratumor delivery of active drug. A weekly paclitaxel and carboplatin during with concurrent thoracic radiotherapy (TRT) in non- small cell lugn cancer (NSCLC) is considered a standard regimen in Japan. For more efficiency and less toxicity, we conducted a phase I study of bi-weekly *nab*-P and carboplatin in combination with TRT for patients with unresectable stage III NSCLC. **Methods:** Patients (aged ≤ 75 years) with unresectable clinical stage III NSCLC and having performance status 0 or 1 and adequate organ function were eligible. They received radiotherapy (60 Gy in 30 fractions) once daily starting on day 1. Concurrent *nab*-P (day 1; 60 mg/m^2 at level 1, 80 mg/m^2 at Level 2, 100 mg/m^{2}at level 3) and C (day 1; AUC = 4 at levels 1-3) were administered every 2 weeks for 3 courses. Patients received 2 cycles of consolidation therapy with full dose nab-P (100 mg/m2 weekly for 3 weeks) and C (AUC 6 on day one of each cycle) every 3 weeks. Dose-limiting toxicity (DLT) was defined as grade 4 hematologic or grade 3 non-hematologic toxicity, and the following chemotherapy treatment delayed 15 days or more. **Results:** 18 patients were enrolled at Aomori Prefectural Central Hospital, including 17 males and one female with median age of 63 years (range: 42.4-74). Six patients have been treated at level 1, 2 and 3, respectively. At level 1, 1 to 6 patients showed DLT. At level 2, 2 to 6 patients showed DLTs. At level 3, 1 to 6 patients showed DLT. One of 4 DLTs was grade 3 pneumonitis. The other DLTs were chemotherapy treatment delays. Three patients had grade 3 leukocytopenia and one patient had grade 3 neutrocytopenia. No grade 4 hematologic toxicity was observed. One patient had grade 3 pneumonitis at level 2 but no patient had grade 3 esophagitis. Four patients achieved complete response, 12 had partial response, 1 had stable disease, and 1 had progression disease. **Conclusions:** The maximum tolerated dose was not reached, and the recommended dose was determined at level 3. Clinical trial information: UMIN000010480.

7530 Poster Session (Board #277), Mon, 8:00 AM-11:30 AM

Genomic heterogeneity of lung cancers and its potential clinical implications. *First Author: Jianjun Zhang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Substantial genomic heterogeneity of lung cancers between different patients, reflecting distinct genetic background and potentially different carcinogen exposures in different patients, has been well documented, particularly under t*he Cancer Genome Atlas* (*TCGA*) efforts. On the other hand, our recent study (Zhang, et al, Science, 2014, 346:256-9) and others (de Bruin, et al, Science, 2014, 346:251-6) have revealed limited intra-tumor heterogeneity (ITH) in localized lung adenocarcinomas (LUAD). Our more recent work on synchronous multifocal lung cancers (MSLC) has demonstrated distinct genomic profiles in different tumors within the same patients in spite of identical genetic background and exposure history (Liu and Zhang et al, submitted). **Methods:** We analyzed data from the two studies on ITH of LUAD (Zhang, et al, Science, 2014, 346:256-9 and de Bruin, et al, Science, 2014, 346:251-6), our MSLC study and data from TCGA LUAD study to assess the genomic heterogeneity of lung cancers under different clinical scenarios. We are currently conducting studies to assess the genomic heterogeneity of primary lung cancers versus distant metastases, versus relapsed diseases, and versus secondary primary lung cancers. **Results:** The percent mutations in a tumor sample that are identical to mutations from another tumor sample under different clinical scenarios are: 91% between different regions within the same tumors (n = 16); 80% between primary lung cancers and metastatic lymph nodes (n = 4); 0.12% between different independent tumors within the same patients (n = 6) and 0.05% from unrelated patients (n = 519). The data from primary lung cancers versus distant metastases, versus relapsed diseases and versus second primary cancers is pending. **Conclusions:** With the caveat of small sample size, our data suggests that in localized LUADs, metastases resemble matched primary tumor closely while multifocal primary cancers within the same patients have distinct genomic profiles in spite of identical genetic background and exposure history. Genomic profiling may be useful for identification of both synchronous and metachronous multifocal lung cancers.

7531 Poster Session (Board #278), Mon, 8:00 AM-11:30 AM

The impact of a *Bim* deletion polymorphism on the survival of patients with completely resected non-small cell lung cancer. *First Author: Jun Atsumi, Department of Thoracic and Visceral Surgery,Gunma University Graduate School of Medicine, Maebashi, Japan*

Background: A deletion polymorphism of the *Bim* gene is observed in the Asian population; this polymorphism has been reported to be a prognostic factor for non-small cell lung cancer (NSCLC) patients treated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and chemotherapy. We investigated the impact of the *Bim* deletion polymorphism on the survival of patients with completely resected NSCLC. **Methods:** Distribution of the *Bim* polymorphism was detected using polymerase chain reaction analysis from peripheral neutrophils in samples from 412 NSCLC patients who underwent complete resection. We measured overall survival (OS) and disease free survival (DFS) in all eligible patients, and post-recurrence survival (PRS) in 98 patients who developed recurrences and received anti-cancer therapy. **Results:** The *Bim* deletion polymorphism was detected in 63 (14.0%) patients. OS and DFS rates were significantly lower for patients with the *Bim* deletion polymorphism than those with wild type (OS, $P < .001$; DFS, $P = .006$). On multivariable analysis, *Bim* deletion polymorphism was identified as an independent prognostic factor for OS (hazard ratio [HR] = 1.99; 95% confidential interval [CI], 1.18 to 3.38; $P = .010$), but not for DFS (HR = 1.19; 95% CI, 0.78 to 1.98; $P = .367$). Among the 98 patients who developed recurrences and were treated with anticancer therapy, patients with the *Bim* deletion polymorphism had a significantly worse PRS than those with wild type (median 11.4 months vs 26.9 months, respectively, $P < .001$). This trend was consistent with subgroup analysis stratified by *EGFR* mutation status ($P = .001$ for *EGFR* mutant group; $P = .002$ for *EGFR* wild type group) or histology ($P = .012$ for adenocarcinomas; $P = .013$ for non-adenocarcinomas). A multivariate analysis suggested that the *Bim* deletion polymorphism is an independent predictor of PRS (HR = 2.99; 95% CI, 1.58 to 5.50; $P = .001$). **Conclusions:** The *Bim* deletion polymorphism is a novel indicator of shorter PRS among patients with recurrent NSCLC treated with anticancer therapy in the Asian population.

7532 Poster Session (Board #279), Mon, 8:00 AM-11:30 AM

Prognostic value of miRNAs in resected lung adenocarcinomas. *First Author: Sandra Gallach, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia, Spain*

Background: Adenocarcinoma (ADC) is one of the most common types of non-small cell lung cancer (NSCLC). Deregulated microRNAs (miRNA) in tumor were associated with poor prognosis. In this study, we analyzed the prognostic value of 22 deregulated miRNAs (identified by NGS in a previous study) in a group of early-stage ADCs. **Methods:** RNA was isolated from fresh-frozen lung ADC specimens (tumor and normal lung) (N = 78). Deregulated miRNA (miR-182, -29a, -19b-1, 34a, 339-5p, -590, -31, -188, -21, -135b, -199b, -224, -196b, -451a, -144, -195, -125a, -218, -145, -30a, -126, -139) were analyzed in paired tumor/normal samples by RTqPCR using TaqMan microRNA assays. Statistical analyses were considered significant at $p<0.05$. **Results:** For survival analysis, continuous variables were dichotomized using the median expression of each miRNA as a cutoff. Of the 22 miRNAs analyzed, high expression levels of miR-34a, miR-145, miR-19b-1, miR-29a, miR-339-5p, miR-21, miR-218 and miR-188 were associated with worse OS and/or PFS (Table 1). Furthermore, patients with combined high levels of miR-188 and miR-339-5p had significantly reduced OS and PFS ($p < 0.0001$ and $p = 0.001$, respectively). The multivariate analysis revealed that this combined variable (miR-188 & miR-339-5p) is an independent prognostic marker for PFS (HR 3.119 [1.500-6.487]; $p = 0.002$) and OS (HR 2.499 [1.003-6.224]; $p = 0.003$). **Conclusions:** Expression of miR-188 and miR-339-5p seems to have a prognostic role in resectable ADC, and the combination of both could be an independent prognostic biomarker in this type of patients. Supported by grants *RTICC (RD12/0036/0025), TRACE (TRA09-0132) and Beca Roche Oncohematología.*

miRNAs univariate analysis for OS and PFS.

	OS		PFS	
miR (high *vs* low)	Median (months)	p	Median (months)	p
miR-34a	46.43 *vs* NR	0.036	19.1 *vs* NR	0.009
miR-145	46.67 *vs* NR	0.039	19.23 *vs* 49.30	0.039
miR-19b-1	42.90 *vs* NR	0.007	23.00 *vs* 49.30	0.114
miR-29a	49.63 *vs* NR	0.056	21.13 *vs* 66.97	0.047
miR-339-5p	37.00 *vs* NR	0.013	19.13 *vs* 66.97	0.037
miR-218	42.90 *vs* NR	0.014	26.70 *vs* 37.80	0.099
miR-21	37.50 *vs* NR	0.052	19.10 *vs* 66.97	0.019
miR-188	34.43 *vs* NR	0.002	18.20 *vs* 66.97	0.009
Combined miRNAs ($miR\text{-}188^{high}$-$miR\text{-}339^{high}$ *vs* other combinations)	23.93 *vs* NR	<0.001	15.43 *vs* 66.97	0.001

7533 Poster Session (Board #280), Mon, 8:00 AM-11:30 AM

"The burden upon me": The complexity of healthcare utilization among Medicare patients undergoing curative lung cancer treatment. *First Author: Carolyn Jean Presley, Yale Cancer Center, Smilow Cancer Hospital, New Haven, CT*

Background: Due to new lung cancer CT-screening guidelines and the aging American population, the use of curative treatment for early-stage non-small cell lung cancer (NSCLC) will increase among older adults. Yet little is known about the treatment burden to the patient and Medicare system in terms of healthcare system encounters and number of providers seen. **Methods:** We used the SEER-Medicare database to study Medicare fee-for-service patients aged 67-94 years who were diagnosed with stage I NSCLC from 2007 through 2009 and received curative treatment with either sublobar resection, lobectomy, or stereotactic body radiotherapy (SBRT). We examined healthcare utilization in the 30 days before through 12 months after treatment initiation, determining the total number of days in contact with the healthcare system as well as the number of unique physicians seen. We described care received in the acute, outpatient, post-acute, home care, and hospice settings. **Results:** Of the 4,214 patients, 90.9% received surgery and 9.1% SBRT. During the first 100 days post-treatment, an average of 1 in 4 days was spent in contact with the healthcare system (mean: 25 encounter-days excluding home health visits). Among patients who survived the entire 13-month follow-up period, there was an average of 50 days with at least one encounter. Approximately 3% of patients had ≥ 10 acute care encounter-days, while 97.7% had ≥ 10 outpatient encounter-days and 23.5% had ≥ 10 homecare encounter-days. The median number of physicians seen was 22 (interquartile range 16-31). **Conclusions:** The burden of receiving healthcare for older patients with NSCLC is substantial in terms of frequency of encounters and number of providers seen. Interventions are needed to improve patient-centered, streamlined cancer care.

7534 Poster Session (Board #281), Mon, 8:00 AM-11:30 AM

Effects of obesity and smoking on survival in non-small cell lung cancer. *First Author: Damien Mikael Hansra, Oncology and Radiation Associates, Miami, FL*

Background: Obesity is an emerging leading cause of morbidity and mortality in the US & the relationship between obesity, tobacco, & survival in NSCLC is unclear. **Methods:** Data (n = 87,631) were obtained from linkage of the 1996-2007 FCDS & AHCA databases providing procedure and diagnoses codes. Survival time was calculated from date of diagnosis to date of death. Smoking status was categorized as never, current, and former. Obesity (yes/no) = ICD9 code BMI > 30kg/m2, cachexia = ICD9 code "wasting syndrome", & non-obese = non-obese & non cachectic. Cox proportional regression models used to predict survival; demographic, clinical, treatment factors, & comorbidities were included in adjusted models with smoking status and obesity as the main factors. **Results:** The majority of patients (pts) were either former (49%) or current (40%) smokers, & non-obese (88%). 6.8% of pts were obese & 4.8% of pts were cachectic. There were significant differences between survival curves & median survival (months) for obese vs. non-obese vs. cachectic pts. (20 vs. 10 vs. 7.9; $P < .001$). Former & current smokers had shorter median survival than never smokers (10.8 & 9.2 vs. 11.9; $P < .001$). Survival rates (%) at 1-yr (60.1 vs. 45.2 vs. 37.7; $P < .001$), 5-yr (30.3 vs. 15.4 vs. 9.5; $P < .001$), 10-yr (18.1 vs. 7.6 vs. 2.7; $P < .001$) were better for obese vs. non-obese & cachectic pts respectively. Independent predictor of worse survival in unadjusted model was former (HR 1.08; $P < .001$) & current (HR 1.20; $P < .001$) smokers compared to never. Obese & non-obese pts had better survival vs. cachexia pts(HR 0.52; $P < .001$ and HR 0.80, $p < .001$ respectively) & obese pts had better survival than non-obese pts (HR 0.65, $p < .001$). In the adjusted model, controlling for extensive variables & comorbidities, former (HR 1.11; $P < .001$) & current (HR 1.19; $P < .001$) smokers still had significantly worse survival vs. never smokers. Obese pts still had better survival (HR 0.87; $P < .001$, & HR 0.88, $p < .001$) vs. cachexia & non-obese pts respectively, survival rate is not significantly different comparing non-obese & cachexia pts. **Conclusions:** Our results show that being a former or current smoker worsens survival while obesity improved survival when compared with cachexia & non-obese pts.

7535 Poster Session (Board #282), Mon, 8:00 AM-11:30 AM

Association between the EGFR or KRAS mutation status and the FDG-PET findings in surgically resected lung adenocarcinoma. *First Author: Kazuya Takamochi, Juntendo Univ, Tokyo, Japan*

Background: ^{18}F-fluoro-2-deoxy-glucose (^{18}F-FDG) positron emission tomography (PET) is a functional imaging modality based on the glucose metabolism. The association between *EGFR* or *KRAS* mutations and the standardized uptake value (SUV) of ^{18}F-FDG has not yet been fully elucidated. **Methods:** Correlations between the *EGFR* or *KRAS* mutation status and clinicopathological factors including SUV_{max} were statistically analyzed in 734 surgically resected lung adenocarcinoma patients. A cap analysis of gene expression (CAGE), a method to determine and quantify the transcription initiation activities of mRNA across the genome reflecting gene expression levels by determining the 5' ends of capped RNA molecules using high-throughput sequencers, was done to examine the molecular basis between the SUV_{max} and mutations in 62 lung adenocarcinomas. **Results:** *EGFR* and *KRAS* mutations were detected in 334 (46%) and 83 (11%) of the 734 lung adenocarcinomas, respectively. Univariate analyses showed *EGFR* mutations to be more frequently observed in females, never-smokers, patients with normal CEA levels, tumors without lymph node involvement and blood vessel invasion, and tumors with lower SUV_{max} values. In multivariate analyses, the smoking status and the SUV_{max} were the significant predictors of *EGFR* mutations. In contrast, no relationship was seen between the *KRAS* mutation status and the SUV_{max}. Four genes associated with the glucose metabolism and five genes associated with the cell cycle showed a lower expression in the *EGFR* mutated tumors than the wild type tumors and a positive correlation with SUV_{max}. However, no such genes were found for *KRAS* mutations. **Conclusions:** Tumors with *EGFR* mutations show lower values of SUV_{max} than wild type ones.In contrast, no relationship was found between *KRAS* mutation and the $SUV_{max.}$ These results suggest that tumors with *EGFR* mutations are less aggressive with likely lower levels of glucose metabolism.

7536 Poster Session (Board #283), Mon, 8:00 AM-11:30 AM

Comparison of concurrent use of carboplatin-Paclitaxel versus cisplatin-etoposide with thoracic radiation for stage III NSCLC patients: A systematic review. *First Author: Conor Ernst Steuer, Emory Univ, Atlanta, GA*

Background: The two most commonly used chemotherapy regimens deployed concurrently with thoracic radiation (RT) for patients with unresectable IIIA and IIIB non-small cell lung cancer (NSCLC) are carboplatin/paclitaxel (CP) and cisplatin/etoposide (CE). Because there are no prospective comparisons of these two regimens in this setting, we conducted a systematic review of published trials to compare outcomes and toxicities between CE and CP. **Methods:** Studies which enrolled stage III patients receiving RT with CP or CE were identified using electronic databases (MEDLINE, EMBASE, and Cochrane library) and meeting abstracts. Trials were excluded if they were phase I, enrolled less than 10 pts, or included surgical resection. A systematic analysis of extracted data was performed using Comprehensive Meta Analysis (Version 2.2) software using random and fixed effect models. Clinical outcomes were compared using point estimates for weighted values of median overall survival (OS), progression free survival (PFS), response rate (RR) and toxicities. Two-tailed T-test with a significance level of 0.05 was used for all comparisons. **Results**: 3194 patients were included from 32 studies in the CE arm, and 3789 patients from 51 studies in CP. Baseline characteristics of patients on the CE arm versus CP arm were: median age 61 vs. 63 years, male 67.6% vs. 78%, squamous histology 39% vs. 40%, and median radiation dose 62 Gy vs. 63 Gy. There was no significant difference in response rates between CE and CP (65% vs. 56%, $p = 0.6$), respectively. There was no significant difference in median progression free survival (11.5m vs. 9.3m $p = 0.2$), overall survival (19.8m vs. 18.4m, $p = 0.48$), or 3-year survival rate (31% vs. 25%, $p = 0.4$) for CE vs. CP. CE was associated with higher grade 3/4 hematological toxicities than CP, such as neutropenia (53% vs. 23% $p < 0.0001$), as well as grade 3/4 nausea/vomiting (20% vs. 9% $p = 0.018$), while rates of grade 3/4 pneumonitis and esophagitis were similar. **Conclusions:** CE and CP regimens were associated with comparable efficacy when used with concurrent radiotherapy for stage III unresectable NSCLC pts. The toxicity profile favored the CP regimen.

7537 Poster Session (Board #284), Mon, 8:00 AM-11:30 AM

Pulmonary sarcomatoid carcinoma: An analysis of the National Cancer Database. *First Author: Conor Ernst Steuer, Emory Univ, Atlanta, GA*

Background: Pulmonary sarcomatoid carcinomas (SC) are a grouping of five rare non-small cell lung cancer (NSCLC) subtypes. Small case series suggest that these patients have a poor prognosis. We sought to better define the clinical characteristics and outcomes of SC utilizing the National Cancer Database (NCDB), an oncology outcomes database administered by the American College of Surgeons and the American Cancer Society. **Methods:** The NCDB lung cancer database was queried from 1998 to 2011 for SC using ICD-O-3 codes. Data were extracted on patient demographics, tumor pathology, treatments, and outcomes. Overall survival (OS) data were available for patients diagnosed from 1998-2006 and co-morbitity data from 2003-2011. The univariate association with covariates between SC and other forms of NSCLC was assessed using Chi-square test or ANOVA, where appropriate. The univariate (UV) and multivariable analysis (MV) with OS were conducted by Cox proportional hazards model and/or log-rank tests. All statistical analyses were conducted using SAS Version 9.3. **Results:** Of the 1,547,531 NSCLC patients in the NCDB, 7965 were diagnosed with SC (0.7%). SC patients had a median age of 70, 59% were male, 89% were Caucasian, and 61% had a Charlson/Deyo co-morbidity status of 0. At presentation, the median primary tumor size was 5 cm and 18% of SC patients were AJCC stage I, 10% stage II, 24 % stage III, and 48% stage IV. Patients were treated with surgical resection (38.5%), radiation (38.2%), and chemotherapy (38.6%). The median OS for stage I-II SC was 16.9 months (m), 5.8 m for stage III, and 5.4 m for stage IV. The 1-year and 5-year survival rates for metastatic SC were 30% and 14%. When compared to other forms of NSCLC in MV analysis, SC patients had a higher risk of death (hazard ratio (HR) 1.34 (95% CI 1.20-1.48) $p < .001$). A propensity scored matched analysis performed for SC vs. other NSCLC confirmed our findings with worse outcomes in the SC group (HR 1.34 (CI 1.15-1.56) $p < .001$). **Conclusions:** SC represents a rare histologic subtype of NSCLC accounting for 0.7% of all lung cancers. It is associated with aggressive clinical characteristics and an inferior outcome relative to other histological subtypes of NSCLC.

7538 Poster Session (Board #285), Mon, 8:00 AM-11:30 AM

Association between radiation dose and outcomes with postoperative radiotherapy for N0-N1 non-small-cell-lung cancer. *First Author: Elyn H. Wang, Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT*

Background: To review trends in the use of postoperative radiation therapy (PORT) in the modern era for N0-N1 margin-negative non-small cell lung cancer (NSCLC) following surgical resection and evaluate the association between PORT dose and overall-survival (OS). **Methods:** We performed a retrospective study of non-metastatic stage II and III N0-N1 margin-negative NSCLC surgically-treated patients within the National Cancer Data Base from 2003-2011. Cox proportional hazards regression was performed for multivariable analyses of OS and PORT dose. Radiation modalities included non-conformal beam radiation, 3D-conformal radiation (3D-CRT), and intensity-modulated radiation therapy (IMRT). **Results:** We identified 2,167 (6.7%) and 30,269 (93.3%) patients with surgically-resected stage II or III N0-N1 margin-negative NSCLC who were treated with and without PORT, respectively. The proportion of patients treated with PORT (dose range: 45-74 Gy) decreased from 8.9% in 2003-2006 to 4.1% in 2010-2011. Among patients receiving PORT, the use of high-dose (60-74 Gy) PORT rose throughout the study period, starting at 34.8% in 2003-2006 and rising to 49.3% in 2010-2011. Overall, patients who received PORT had worse survival (HR = 1.30; 95% CI 1.20-1.40) compared to those not receiving PORT. This association was unchanged when limited to patients receiving modern treatment with 3-CRT or IMRT (HR = 1.35; 95% CI: 1.10-1.65]. Examining the association between dose and overall survival revealed that patients treated at doses < 50 Gy or ≥ 54 Gy had worse OS compared to no PORT while a trend showing decreased survival was observed among those receiving 50-53.9 Gy (HR = 1.14; 95% CI: 0.99-1.30). Limiting the analysis to patients receiving 3D-CRT or IMRT showed worse survival for patients receiving ≥ 60 Gy (HR = 1.43; 95% CI: 1.04-1.95) and similar survival between no PORT and the remaining dose groups. **Conclusions:** The use of PORT for N0-N1 margin-negative NSCLC decreased from 2003-2011. We found no evidence of benefit from PORT for resected N0-N1 margin-negative NSCLC, regardless of dose or technique. PORT should be approached with caution in this group of patients, regardless of radiotherapy technique.

7539 Poster Session (Board #286), Mon, 8:00 AM-11:30 AM

Common and rare *EGFR* mutations (*EGFR*m) in the RADIANT trial: Final follow-up with 5 year data. *First Author: Frances A. Shepherd, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Data on *EGFR*m in early stage NSCLC are limited. RADIANT was a prospectively randomized Phase 3 trial of adjuvant erlotinib (E) v placebo (P) in 973 patients (pts) with completely resected Stage IB–IIIA NSCLC that was EGFR +ve by IHC or FISH (ASCO14 #7501; ESMO14 #1178PD). **Methods:** *EGFR*m in exons 18–21 was determined by WAVE HS and confirmed by Sanger sequencing. Two *EGFR*m groups were defined: Common refers to exon del19 or L858R irrespective of the presence of another *EGFR*m; Rare Only refers to *EGFR*m without del19 or L858R. Exploratory analysis of disease-free survival (DFS) was performed by subgroup (June 11, 2014 data cutoff). **Results:** 921 pts had *EGFR*m status determined; 198 pts (21.5%) had *EGFR*m (161 Common, 37 Rare Only). There was no sex difference between the groups, but pts with Rare Only *EGFR*m were less likely to be Asian (32.4% *v* 47.2%) or non-smokers (48.6% *v* 62.7%). With a median follow-up of 5 years, updated DFS by mutation type is shown below. The DFS HR was lower in the Common group (HR [E/P] 0.75, CI 0.48, 1.16) than in the Rare Only group (HR 1.19, CI 0.44, 3.22). **Conclusions:** The effect of E on DFS in *EGFR*m subgroups remains inconclusive. Clinical trial information: NCT00373425.

				DFS		
***EGFR*m (n) Subgroup**		**Arm**	**n**	**Events**	**Median (m)**	**HR (E/P), 95% CI**
Common* (161):	Del 19/L858R	**E**	**102**	**49**	**47.8**	0.75 (0.48–1.16)
		P	**59**	**34**	**28.5**	
	Del 19	E	56	29	46.4	0.82 (0.46–1.46)
		P	33	19	26.4	
	L858R	E	46	20	54.1	0.68 (0.35–1.34)
		P	26	15	29.3	
Rare Only (37):	All	**E**	**19**	**7**	**NR**	1.19 (0.44–3.22)
		P	**18**	**9**	**46.5**	
	Exon 20 (21)	E	11	4	NR	0.96 (0.27–3.43)
		P	10	6	40.7	

Rare Only (n)**		Detail	Arm	n	DFS Min, Max
Exon 18 G719X (8)		G719A, G719A+E709A, G719A+E709K	E	5	0.0+, 58.0+
	G719A		P	3	39.7+, 47.6+
Other Exon 18 (4)		L692, G719A+E709A, G719A+E709K	E	3	0.0+, 28.2
	V689L		P	1	59.7+
Exon 19 (2)		R748T	E	1	54.4+
	L747S		P	1	57.5+
Exon 20 Ins_dup (17)		A767_S768Ins, H773_V774ins, V774_C775ins, A767_V769dup, N771_H773dup, P772_H773dup	E	10	0.0+, 54.5+
	N771_H773dup, P772_H773ins, A767_V769dup, A763_Y764ins, H773dup		P	7	16.2, 59.7+
Exon 20 other (4)		S768I	E	1	58.0+
	R776H, S768I+V774M, R776H		P	3	39.7+, 64.0+
Exon 21 (8)		L861Q, E868K	E	2	1.9, 42.1+
	D830N, L861Q, L844P, V845E		P	6	1.8, 58.3+

NR = Not Reached. *Includes 12 pts with another EGFRm in addition to del19 or L858R. + Indicates censoring; **Pts may have > 1 rare *EGFR*m.

7540 Poster Session (Board #287), Mon, 8:00 AM-11:30 AM

Final follow-up (f/u) results from RADIANT: A randomized double blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection in patients (pts) with stage IB–IIIA *EGFR* positive (IHC/FISH) non-small cell lung cancer (NSCLC). *First Author: Mary E.R. O'Brien, Royal Marsden Hospital, London, United Kingdom*

Background: Adjuvant chemotherapy for NSCLC has reached a plateau. The use of the tyrosine kinase inhibitor (TKI), E, was explored in the adjuvant setting given success in advanced setting.We report final f/u from RADIANT. **Methods:** Completely resected IB–IIIA NSCLC pts were randomized 2:1 to receive E 150 mg daily or P for 2 years. The primary endpoint was disease free survival (DFS) in the full analysis set (FAS). Secondary endpoints included overall survival (OS) in the FAS and DFS and OS in *EGFR* mutation (M+) subset (del19/L858R). 973 pts were randomized and the planned final analysis was performed after 410 DFS events (April 2013 data cutoff, ASCO14 #7501). A subsequent exploratory analysis occurred after final f/u (June 2014 cutoff). **Results:** The median f/u is 59.6m (95% CI 56.7–61.2). There was no statistically significant difference in DFS or OS overall or in the *EGFR* M+ group. The OS data remain immature with 33.5% deaths in the E arm and 31.4% in the P arm. The most common site of relapse (>15% pts) overall and in *EGFR* M+ were lung and brain in E treated pts and lung, bone and brain in P pts. Among the 13 pts in the *EGFR*M+ subgroup with brain as site of relapse, 11 of these patients relapsed after E cessation. There were no new safety concerns. **Conclusions:** Overall adjuvant E did not prolong DFS; a trend for E benefit previously observed (ASCO14 #7513) in *EGFR* M+ subgroup is no longer apparent. EGFR mutation status was not a stratification factor in this trial and was not a prognostic factor (ESMO14 #1177PD). Further results from ongoing trials are awaited to determine the role of TKI in *EGFR* M+ early stage lung cancer. Clinical trial information: NCT00373425.

Full Analysis Set

				HR (95% CI)	P-Value
		E (N=623)	P (N=350)		
DFS	Median	55	56.2	0.94 (0.78–1.144)	0.5620
	# Events (%)	280 (44.9)	168 (48.0)		
OS	Median	NR	NR	1.12 (0.890–1.413)	0.3306
	# Events (%)	209 (33.5)	110 (31.4)		
***EGFR* M+ Subset**					
				HR (95% CI)	P-Value
		E (N=102)	P (N=59)		
DFS	Median	47.8	28.5	0.75 (0.482–1.158)	0.1906
	# Events (%)	49 (48.0)	34 (57.6)		
OS	Median	NR	NR	1.19 (0.609–2.310)	0.6142
	# Events (%)	26 (25.5)	13 (22.0)		

HR: Hazard Ratio; NR: Not Reached.

7541 Poster Session (Board #288), Mon, 8:00 AM-11:30 AM

A phase II study of concurrent chemoradiotherapy with cisplatin and oral S-1, followed by surgery for locally advanced non-small cell lung cancer. *First Author: Tomoshi Tsuchiya, Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*

Background: This study was designed to evaluate the feasibility of concurrent chemoradiotherapy followed by surgery in locally advanced non-small cell lung cancer (NSCLC). We defined locally advanced NSCLC as pathologically proven hilar and/or mediastinal lymph node metastases by endobronchial ultrasound-guided transbronchial needle aspiration (E-BUS/TBNA), or chest wall invasion. **Methods:** Twenty-three patients were enrolled in this study between May 2011 and April 2014. The patients received 40 mg/m2 S-1 twice orally per day on days 1 through 14 and 29 through 42, and cisplatin (60 mg/m2) was injected intravenously on days 8 and 36. The patients also underwent radiotherapy, receiving a total dose of 40 Gy in 20 fractions beginning on day 1. Surgical resection was performed 4 to 6 weeks after completing the induction treatment. **Results:** The 23 analyzed patients consisted of 5 stage IIB and 18 stage IIIA patients. Thirteen patients with histopathological lymph node metastases were diagnosed by E-BUS/TBNA. Twenty patients completed two courses of induction chemotherapy and radiotherapy, and achieved surgery (87.0%). Grade 3 adverse reactions included neutropenia (21.7%), leukocytopenia (8.7%), pneumonia (8.7%), increased serum total bilirubin (4.3%), nausea (4.3%), and diarrhea (4.3%). No grade 4 adverse reactions were identified. Radiologically, 7 (30.4%) of the 23 patients achieved partial response, and 14 patients (60.8%) achieved stable disease. Pathologic findings suggested that all operated patients were curatively resected. Comparing preoperative and postoperative histopathology, 6 (26.1%) complete responses were identified. Accordingly, 13 patients (56.5%) were histopathologically downstaged by CRT. **Conclusions:** Induction treatment using S-1 plus cisplatin and concurrent radiotherapy followed by surgical resection is a feasible and promising new treatment modality for potentially resectable NSCLC. In addition, there was a low incidence of adverse reactions. Evaluation of histopathological downstaging revealed sufficient anticancer effects for preoperative treatment. Clinical trial information: UMIN000008205.

7542 Poster Session (Board #289), Mon, 8:00 AM-11:30 AM

Retrospective analysis between PD-L1 expression and prognosis for stage III non-small cell lung cancer patients who received concurrent chemoradiotherapy. *First Author: Takaaki Tokito, Division of Respirology, Neurology and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan*

Background: Programmed cell death 1 (PD-1) receptor-ligand interaction is a major pathway often hijacked by tumors in order to suppress immune control. We investigated whether the expression of programmed death–ligand 1 (PD-L1) is related to clinicopathologic or prognostic factors in patients with locally advanced NSCLC who received concurrent chemoradiotherapy (CRT). **Methods:** We retrospectively reviewed consecutive stage III NSCLC patients who received CRT at Kurume University. The expression of PD-L1 was evaluated by immunohistochemical analysis in specimens of NSCLC. Survival analysis was obtained by Kaplan-Meier methods. **Results:** A total of 52 patients with a median age of 67 years were eligible for this study. Forty-three patients were men, and 46 patients were current or ever smokers. The most predominant histological type was adenocarcinoma (28 patients), followed by squamous cell carcinoma (21 patients). All of the patients received platinum-based doublets. Expression of PD-L1 in tumor cells was observed in 73%. NSCLC patients with PD-L1-negative tumors showed longer progression-free and overall survival than those with PD-L1-positive (median PFS, 17 versus 11 months; $p = 0.31$, median OS, 52 vs 25 months; $P = 0.38$; respectively), and higher progression-free rate at 2 years and overall survival rate (38% and 26%, 83% and 52%, respectively). **Conclusions:** There was a trend toward a poor survival in expression of PD-L1 in stage III NSCLC patients who received CRT.

7543 Poster Session (Board #290), Mon, 8:00 AM-11:30 AM

Correlation between high-resolution computed tomography findings and IASLC/ATS/ERS classification of small lung adenocarcinomas in Japanese patients. *First Author: Yujin Kudo, Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan*

Background: Small pulmonary nodule detection rates have increased owing to computed tomography (CT) screening of lung cancer, and new image guided-bronchoscopy techniques have been developed to improve diagnostic yield. Additionally, limited surgical resection for small peripheral lung adenocarcinomas has been reported. Recently, the IASLC/ATS/ERS classification emphasized the prognostic significance of histologic subtypes. We evaluated the correlation between high-resolution CT (HRCT) findings and this classification of small lung adenocarcinomas. **Methods:** We reviewed the data of 220 consecutive lung adenocarcinoma (≤ 3 cm) patients who received segmentectomy or more extended resection with lymph node dissection in our hospital. From the HRCT findings, the tumors were classified as pure solid, part-solid, or pure ground glass opacity (GGO) nodules. Pathologic tumor invasiveness (pTI) was evaluated by the degree of vascular invasion, lymphatic permeation, or visceral pleural invasion. **Results:** The tumors were classified as pure GGO nodules in 16 patients (7.2%), part-solid in 91 (41.3%), and pure solid in 113 (51.3%) from the HRCT findings. We pathologically diagnosed 44 noninvasive and 176 invasive adenocarcinomas (IAs) [lepidic (LPA), papillary, acinar, solid predominant adenocarcinoma, and invasive mucinous adenocarcinoma]. Lymph node metastasis was present in 31 patients (14.1%) and pTI in 101 (45.9%). All pure solid tumors were IAs with a high pTI frequency (75.2%) or lymph node metastasis (26.5%). All pure GGO nodules were non-IAs or LPA. Among the part-solid nodules, IA was detected in 67.0% of the patients and pTI in 16.5%. The consolidation/tumor (C/T) ratio and consolidation size were associated with IA (optimal cut-off values: 0.4 and 8 mm) or pTI (0.8 and 15 mm). **Conclusions:** The HRCT findings correlated with the IASLC/ATS/ERS classification and were useful for malignancy evaluation. Most pure solid tumors have malignant potential including pTI or lymph node metastasis. For part-solid tumors, the C/T ratio and consolidation size were important for predicting pTI or making a diagnosis of IA according to this classification.

7544 Poster Session (Board #291), Mon, 8:00 AM-11:30 AM

Comprehensive analysis of driver mutations in Chinese squamous cell lung carcinomas by targeted next-generation sequencing. *First Author: Sheng Yang, Department of Medical Oncology, Cancer Institute/Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College Beijing, China, Beijing, China*

Background: The aim of the study was to analyze the driver mutation profiles in a large cohort of Chinese SqCLCs to identify potential therapeutic targets. **Methods:** We detected approximately 2,800 COSMIC mutations from 50 oncogenes and tumor suppressor genes on 159 samples by using Ion Torrent semiconductor-based next-generation sequencing.We conducted FISH for fibroblast growth factor receptor 1 (*FGFR1*) and cyclin D1 (*CCND1*) amplification on 172 and 246 samples, respectively. In addtion, we analyzed PTEN expression by immunohistochemistry on 172 samples. **Results:** Somatic mutations were detected in 73.6% (117/159) of patients. The most commonly mutated gene detected in this study was *TP53* (89 cases, 56.0%), followed by *CDKN2A* (14 cases, 8.8%), *PI3KCA* (14 cases, 8.8%), *KRAS* (7 cases, 4.4%), and *EGFR* (5 cases, 3.1%). The incidences of *FGFR1* amplification, *CCND1* amplification and loss of PTEN expression in this cohort of patients were 16.9% (29/172), 11% (27/246) and 43.6% (75/172), respectively. The frequency of *EGFR* mutation was significantly higher in female and never smokers, while *TP53* mutations were significantly more common in men and smokers. The incidence of *FGFR1*amplification in current smokers was significantly higher than that in former smokers and never smokers (P_{trend}= 0.025). The incidence of *FGFR1* and *CCND1* amplification significantly increased with increment of total cigarette smoking dosage (P_{trend} < 0.001 and P_{trend} = 0.006, respectively). Loss of PTEN expression was more frequent in elders (*P*= 0.047), male gender (*P*= 0.033), patients with early stage (*P*= 0.042) and positive pleural invasion (*P*= 0.030). No significant association was observed between the molecular abnormalities and overall survival. **Conclusions:** Somatic mutations were detected in nearly three-fourth (73.6%) of Chinese SqCLC patients. *FGFR1* amplification, *CCND1* amplification and loss of PTEN expression are also frequent alterations in SqCLC. Comprehensive analysis of driver mutations in our study could facilitate the development of targetd therapies and optimize the therapeutic strategies for patients with SqCLC.

7545 Poster Session (Board #292), Mon, 8:00 AM-11:30 AM

Prognostic significance of a diagnosis of multiple lung cancers. *First Author: Jarushka Naidoo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The Martini-Melamed criteria (J Thor Card Surg, 1975) have been used since 1975 to clinically differentiate MLCs from lung metastases, which impacts upon treatment choices. The survival of patients (pts) with MLCs compared to those with one lung cancer (LC), and either local or distant recurrent LC, is unclear. Herein, we evaluated the Martini-Melamed criteria for its ability to appropriately identify patients with MLCs. **Methods:** After IRB approval, we conducted a retrospective review of all pts who underwent an R0 resection for stage IA-IIIA LC from 2008-2013 in our institution. Clinicopathologic data for all pts was collected. MLCs were defined using the Martini-Melamed criteria. We used the Kaplan-Meier method to assess overall survival (OS) of pts with one LC, recurrent LC, or an MLC, from the time of surgery/pathologic confirmation of their one LC, recurrent disease or MLC respectively. **Results:** 2,858 pts were identified: one LC (n=2403), recurrent LC (n=347), MLCs (n=108). Median OS for pts in these subgroups was: one LC (32.3mos, 95% CI: 30.8-34.6mos), MLC (not reached=NR), recurrent LC (10.5mos, 95% CI: 9.5-13.7mos). The 2-year OS for pts in these subgroups stratified by stage is depicted in the table. **Conclusions:** Pts with MLCs had a 2-yr OS that stage for stage, was similar to pts with one resected LC. Pts with recurrent LC had a poor 2-yr OS by original stage. Clearly, the Martini-Melamed criteria identify a clinically significant patient population with a different disease natural history. However, translational studies in MLCs are needed to investigate the tumor biology and patient features that underpin this distinct clinical entity.

Lung Cancers by Original Stage (n)		Two-year Overall Survival	Log-rank p value
One Lung Cancer (2403)	IA	0.77	<0.01
	IB	0.71	
	IIA	0.63	
	IIB	0.68	
	IIIA	0.57	
Multiple Lung Cancers (108)	IA	0.83	0.44
	IB	0.75	
	II/III	0.88	
Recurrent Lung Cancer (341)	IA	0.31	0.046
	IB	0.18	
	IIA	0.29	
	IIB	0.33	
	IIIA	0.08	

7546 Poster Session (Board #293), Mon, 8:00 AM-11:30 AM

Patterns and effectiveness of surveillance after curative intent surgery in stage I-IIIA non-small cell lung cancer. *First Author: Christine Agnes Ciunci, Hosp of the Univ of Pennsylvania, Philadelphia, PA*

Background: The optimal strategy for imaging surveillance of non-small cell lung cancer (NSCLC) patients after curative intent surgery is unknown. Current guidelines recommend computed tomography (CT) every 6-12 months for 2 years and then annually. There are no large population-based studies identifying how patients are managed, or comparing the effectiveness of chest radiography (CXR) and CT surveillance. **Methods:** We performed a retrospective cohort study using Surveillance, Epidemiology and End Results (SEER)-Medicare data to determine the primary surveillance modality following surgical resection in stage I-IIIA NSCLC between 1998 and 2009. Primary surveillance modality was defined as the imaging study used between 90-365 days after surgery. Comparative effectiveness of CT vs. CXR surveillance was explored in terms of overall survival (OS) using a stratified Cox model based on stage and adjusted for age, gender, race, CMI, Charlson comorbidity index, and adjuvant chemotherapy. **Results:** 5,968 (54%)patients were followed by CT, and 5,083 (46%) by CXR. Patients with earlier stage, older age, and lower census median income (CMI) were less likely to undergo CT surveillance (p<0.001). CT surveillance increased over the study period from 23% in 1998 to 68% in 2009 (p<0.001). In the analysis of surveillance modality and OS, a significant interaction was identified between imaging and diagnosis year (p<0.001). The effect of CT surveillance on OS steadily improved over time, and was significantly better than CXR in the most recent time periods of study (Table). **Conclusions:** OS was improved in patients with CT surveillance in the most recent time periods of analysis supporting surveillance guidelines. Further studies to determine how CT surveillance leads to improved outcomes, to evaluate the appropriate interval of CT imaging, and to elucidate why patients are not followed according to guidelines are warranted.

Multivariable Cox Regression for Overall Survival with CT surveillance as reference group.

Diagnosis year	Adjusted HR	95% Confidence Interval
1998-2000	1.09	0.96-1.25
2001-2003	0.97	0.88-1.08
2004-2006	0.82*	0.74-0.91
2007-2009	0.69*	0.61-0.78

*p<0.001

7547 Poster Session (Board #294), Mon, 8:00 AM-11:30 AM

Prognostic role of expression levels of FABP3 and AKR1B10 genes in adenocarcinoma stage I patients. *First Author: Vienna Ludovini, Medical Oncology, S. Maria della Misericordia Hospital, Perugia, Italy*

Background: In resected lung cancer, no reliable clinical or molecular predictors are currently available for identifying patients with high risk for recurrent disease. In a previous study, we selected 5 genes up-regulated and 4 genes down-regulated which were predictive for clustering adenocarcinoma (ADC) patients in early relapse (ER) and non relapse (NR) using Affimetrix human microarray HG-U133Plus 2.0. Here we validate our results using an independent cohort of patients with lung ADC stage I to identify novel genes involved in the risk of ER compared to NR disease. **Methods:** From tissue banking of 180 consecutive resected NSCLC patients, we selected frozen specimens of ADC with corresponding normal lung of stage I patients. Quantification of mRNA expression levels of 9 genes (5 up-regulated: CLCA2, FABP3, H19, TFPI2, AKR1B10 and 4 down-regulated: CYP3A5, ALDH3A1, SCGB3A2, SCGB1A1), were analyzed by real-time one-step RT-PCR using QuantiFast assay (Qiagen).The gene expression levels and their association with relapsed disease and molecular features were assessed by t-test and Fisher's exact test, respectively. The logistic regression model was used for multivariate analysis. **Results:** Seventy-nine patients were evaluable, 23% of which had an ER. The mean expression levels of CYP3A5 and SCGB3A2 was down-regulated in ER respect to NR (0.31 vs 1.12; 0.80 vs 2.07 respectively). P53 mutations were associated with smoking history (p = 0.01) and had a tendency to significance with FABP3 (p = 0.07). In the univariate analysis the mean expression levels of AKR1B10 and FABP3 were correlated with a worse disease free survival (DFS) (p = 0.024 and p = 0.017 respectively). In the multivariate analysis the mean expression levels of all genes showed a tendency to predict the ER in the overall population (p = 0.06). The multivariate analysis adjusted for age, smoking, stage high AKR1B10 and FABP3 expression levels maintain their prognostic effect for a poor DFS (p = 0.003). **Conclusions:** It is possible to define through gene expression, a characteristic gene profiling of ER patients. Such features may have important implications for future targeted therapies. This study was supported by Italian Association for Cancer Research (AIRC).

7548 Poster Session (Board #295), Mon, 8:00 AM-11:30 AM

Utility of ^{18}F-FDG PET and CT to assess response to neoadjuvant chemotherapy. *First Author: Jamie E. Chaft, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Perioperative chemotherapy improves survival in resected NSCLCs. Neoadjuvant administration allows for *in vivo* assessment of efficacy. Major pathologic response (MPR), defined as <10% viable tumor tissue in the surgical resection specimen, strongly correlates with clinical outcomes in lung cancers. (Hellmann, Lancet Oncol 2014) Unfortunately, it is a minority of tumors that demonstrate MPR after standard induction chemotherapy and adaptive strategies are needed. The understanding of the clinical utility of non-invasive mid-and post-treatment PET and CT scans is essential for adaptive trial design. **Methods:** This analysis is derived from a completed phase 2 trial of PET response-adaptive therapy that treated 40 pts with clinical stage IB-IIIA NSCLCs (primary >2 cm & SUVmax≥4.5). Pts received 2 cycles of cis- or carboplatin + gemcitabine (squamous) or pemetrexed (adenocarcinoma/other), followed by repeat PET + CT. Pts with suboptimal response (<35% decrease in SUV) were switched to vinorelbine + docetaxel q2 wks. This analysis utilizes non-parametric tests to assess the correlation of % change in SUV of the primary tumor (PERCIST) and the % change in size on CT (RECIST) with MPR after 2 cycles and at completion of induction therapy. **Results:** 40 pts were treated. 15 pts has <35% decrease in SUV, of whom 13 were switched to vinorelbine/docetaxel, and 2 to definitive radiotherapy only. 27 pts had R_0resections. 6 tumors demonstrated MPR. In all settings, PET response correlated with MPR and CT response did not (see Table). **Conclusions:** ^{18}F-FDG PET response, but not CT response, in the primary tumor after 2 and 4 cycles of chemotherapy correlates with major pathologic response, a surrogate for survival. The use of early PET response to offer alternative therapies to pts who are not benefiting should be considered. NCT01443078 was supported in part by Eli Lilly. Clinical trial information: NCT01443078.

	% decrease, median (range)		p-value
	MPR	no MPR	
All pts after 2 cycles			
PET	71 (23 – 87)	49 (+51 – 86)	0.016
CT	31 (0 – 43)	21 (+6 – 38)	0.19
Pts not assigned to switch after 2 cycles			
PET	75 (65 – 87)	54 (36 – 86)	0.007
CT	33 (0 – 43)	24 (2 – 38)	0.094
All pts after 4 cycles			
PET	76 (67 – 94)	64 (+24 – 87)	0.034
CT	44 (16 – 51)	38 (+6 – 64)	0.26

7549 Poster Session (Board #296), Mon, 8:00 AM-11:30 AM

Aneuploidy of anaplastic lymphoma kinase (ALK) gene and association with non squamous lung cancer patient characteristics and outcomes. *First Author: Taofeek Kunle Owonikoko, Emory Univ, Atlanta, GA*

Background: ALK gene translocation resulting in aberrant activation of ALK signaling is a genetic driver in subsets of NSCLC. Aneuploidy of the ALK gene is also frequently observed but its impact has not been well studied. **Methods:** We analyzed the results of molecular tests performed in a CLIA-certified lab for lung cancer patients treated at our institution. Patient demographics, treatment and outcome data were retrieved from the electronic records. Univariate and multivariable analysis was performed to test for association between ALK gene aneuploidy, percentage of aneuploid cells, minimum and maximum number of ALK gene copies per cell and the following covariates: ALK gene rearrangement, gender, stage, race, age, PFS and OS. Survival was estimated by the Kaplan-Meier method and compared between defined groups using a Cox proportional hazards model and log rank test. **Results:** We analyzed data from 259 patients, male (48%); Black (33%), Asian (4%), White (63%); median age 65yrs; stage: I (32%), II (12%), III (16%) and IV (40%). The median PFS and OS were 14.4 months (95% CI: 9.7 – 20.1) and 79.7 months (95% CI: 22.9 – NA), respectively. ALK FISH rearrangement was present in 3 (4.8%) of 63 patients tested by FISH. Aneuploidy of the ALK gene was present in 46 (73%) cases with 40% aneuploid cells per case. Minimum and maximum number of copies of ALK gene in aneuploid cells were 2.63 (± 0.61) and 4.02 (± 2.03), respectively. There was no association between ALK gene aneuploidy and patient characteristics but ALK gene aneuploidy, percentage aneuploid cells and high ALK polysomy were negatively correlated with presence of ALK FISH rearrangement. Absence of aneuploidy (HR: 0.29; 0.09-0.95; p,0.040) and higher stage at diagnosis were independently associated with a higher risk of progression on multivariable analysis. **Conclusions:** There is inverse association of ALK gene aneuploidy and ALK gene rearrangement. The association between ALK polysomy and higher risk of disease progression is worthy of further study to elucidate the underlying biology.

7550 Poster Session (Board #298), Mon, 8:00 AM-11:30 AM

Conditional survival estimates for lung cancer histologic subtypes in the U.S. (2004-2008). *First Author: Kailash Mosalpuria, University of Nebraska Medical Center, Omaha, NE*

Background: Conditional survival (CS) is a more accurate measure of survival probability among cancers associated with a poor prognosis. We calculated lung cancer-specific CS estimates to help clinicians and patients with informed decision making. **Methods:** Lung cancer patients with at least 3 years of follow-up were identified from the Surveillance Epidemiology and End Results registry (2004-2008). American Joint Commission on Cancer, sixth edition was used for staging non-small cell lung cancer (NSCLC). Stages 1 to 3 SCLC were classified as limited stage (LS), and stage 4 was classified was extensive stage (ES). Multivariate Cox regression models were built separately by stage to calculate the adjusted 1-6 year cancer-specific survival and overall survival. The multiplicative law of probability was then used to compute the X-year conditional survival where the (x+y) year survival is divided by y years of patients who have survived. The following were adjusted: age, sex, ethnicity, marital status, SEER region, year of diagnosis, radiation, and definitive surgery. **Results:** A total of 127,992 patients were included in the final cohort. Patients diagnosed with stage IA NSCLC had a 3-year survival probability of 73%. This increased to 76% in patients who were alive at 3 years following diagnosis. The three- year conditional overall survival (COS) estimates from diagnosis (time 0) to 3 years for the other stages were as follows: stage 1B: 54% to 68%, stage 2A: 54% to64%, stage 2B: 37% to 58%, stage 3A: 25% to 51%, stage 3B: 14% to 43%, and stage 4: 6% to 29%. For Stage 1A NSCLC 3-year conditional cancer-specific survival (CCSS) estimates improved from 82% to 87%, stage 1B: 63% to 80%, stage 2A: 62% to74%, stage 2B: 44% to 69%, stage 3A: 30% to 60%, stage 3B: 18% to 53%, and stage 4: 8% to 35%. For LS-SCLC, 3-year COS improved from 16% at diagnosis to 52% at 3 years; for ES-SCLC it increased from 3% to 47%. For LS- SCLC, 3-year CCSS improved from 19% at 0 years to 63% at 3 years whereas for ES-SCLC it improved from 4% to 53%. **Conclusions:** Three-year COS and CCSS estimates improve dramatically over time for survivors with advanced stages. These prognostic data are critical to patients for both treatment and non-treatment related life decisions.

7551 Poster Session (Board #299), Mon, 8:00 AM-11:30 AM

PD-L1, PD-1, and CTLA-4 as prognostic biomarkers in resected non-small cell lung cancer. *First Author: Taofeek Kunle Owonikoko, Emory Univ, Atlanta, GA*

Background: Reliable assessment of predictive or prognostic biomarker is critical for successful incorporation of immune checkpoint inhibitors into lung cancer management. We assessed the prognostic relevance of immune checkpoint mediators in resected NSCLC. **Methods:** We determined PD-L1 expression by immunohistochemistry using our instituional tumor bank samples. Mutations, expression and copy number variations (CNV) in genes encoding for PD1, PD-L1 and CTLA-4 were assessed using TCGA data. Survival estimates were performed by the Kaplan-Meier method. Differences in disease free and overall survival (DFS, OS) between patients with high or low PD-L1 protein expression were assessed by univariate and multivariate survival analyses using Cox proportional hazards model using different cutpoint definitions of staining intensity (0, 1, 2, 3), percent cell staining (0-100%) and immunoscore (0-300). Prognostic impact of genetic alterations was assessed in the overall population and in subsets of adenocarcinoma, squamous, smokers and non smokers. **Results:** We employed 208 institutional NSCLC samples (Caucasian 199, African American 9; Male/Female 101/107; squamous 63, non squamous 138) and 763 NSCLC cases from the TCGA database. PD-L1 protein expression was higher in smokers, non squamous cancers and females but not significantly different by race, tumor stage or grade. Low PD-L1 immunoscore in cancer cells (< 10 vs. ≥ 10, < 35 vs. ≥ 35, or < 33.33 vs. ≥ 33.33) and in adjacent normal tissue (0 vs. > 0, < 10 vs. ≥ 10, or < 2 vs ≥ 2) was significantly associated with a higher risk of recurrence and poor OS. High tumor to normal ratio for PD-L1 staining was also associated with higher risk of recurrence and poorer OS. Mutations in CTLA4, PD-1 and PD-L1 genes were very rare. No association of CTLA-4 or PD-L1 gene expression differences or CNV with survival in patients groups defined by histology or smoking status.. High ratio of PD-1 gene expression in tumor to normal was associated with higher median OS [3.8 (1.8, 6.6) vs. 1.6 (0.5, 5.4) years; $p = 0.022$]. **Conclusions:** PD-L1 protein expression is higher in females, non squamous cancers and smokers. PD-L1 protein but not PD-L1 gene expression may be a useful prognostic marker in resectable NSCLC.

7552 Poster Session (Board #300), Mon, 8:00 AM-11:30 AM

A phase II feasibility study of preoperative chemotherapy with bevacizumab for resectable stage II/IIIA non-squamous non-small cell lung cancer. *First Author: Yoshihiro Miyata, Hiroshima University, Hiroshima, Japan*

Background: Bevacizumab (Bev) has been demonstrated to improve response and survival rates in patients with advanced non-small cell lung cancer (NSCLC). This phase II trial assessed the feasibility of the addition of Bev to preoperative chemotherapy in resectable non-squamous NSCLC. **Methods:** Patients with clinical stage II/IIIA non-squamous NSCLC were recruited from 6 institutions. Three cycles of cisplatin (Cis) (75 mg/m^2), pemetrexed (Pem) (500 mg/m^2), and Bev (15 mg/kg) were administered on day 1 and every 21 days thereafter, followed by surgical resection. The primary endpoint was the complete resection rate (CRR) after completion of 3 cycles of chemotherapy. The sample size was set at 30 patients. The treatment was considered feasible if the CRR was ≥ 80%. **Results:** Thirty patients were eligible. Grade 3 toxicities included neutropenia (7%), nausea (7%), hypertension (23%), and pulmonary embolism (3%). There were no grade 4 events, and 27 (90%) patients completed 3 cycles with full doses of chemotherapy. Twenty-nine patients (97%) exhibited radiologic tumor reduction. The objective responses to chemotherapy were as follows: complete response, 0%; partial response, 37%; stable disease, 50%; and progressive disease, 10%. Five patients dropped out from the study before surgery due to the patient's decision in one patient, adverse events in three and disease progression in one. Disease control and surgical eligibility was confirmed in 25 (83%) patients after completion of 3 cycles of induction chemotherapy. These patients underwent surgery, and all achieved complete resection (CRR after completing three cycles of induction chemotherapy, 83%). Neither grade 3/4 morbidity within 28 days after surgery nor treatment-related mortality within 84 days after surgery was observed. **Conclusions:** Preoperative chemotherapy with combined Cis, Pem, and Bev for clinical stage II/IIIA non-squamous NSCLC is considered feasible. These data provide further evidence that Bev may be used as a promising candidate for future randomized trial arm for patients with locally advanced NSCLC. Clinical trial information: UMIN000004278.

7553 Poster Session (Board #301), Mon, 8:00 AM-11:30 AM

Phase I study of vorinostat with concurrent chemoradiotherapy (CRT) for locally advanced non-squamous non-small cell lung cancer (NSCLC). *First Author: Ranee Mehra, Fox Chase Cancer Center, Philadelphia, PA*

Background: Vorinostat (V) is a potent class I & II (HDAC 6) inhibitor of histone deacetylases. In A549 and A375 cell lines (CL's), V intensified RT induced decrease in clonogenic survival via impaired DNA repair. In CL's V downregulated thymidylate synthase (TS), a target of pemetrexed (P). **Methods:** This is a phase I trial of V plus C (cisplatin) or CP (carboplatin), P and RT for ECOG PS 0-1 pts with stage IIIA/B non-squamous NSCLC. V was dose-escalated in a 3+3 design (V at dose levels (DL1-3) 100, 200 and 300mg) with CRT: C (75 mg/m2) and P (500mg/m2) Q21 days x 4 with folic acid, B12, steroids), and RT (60 Gy). DL1b included CP AUC 5, P, RT and V 100mg. V was dosed for 3 consecutive days before cycle 1, and was then taken orally once a day 3 times/week during CRT. Surgical resection after CRT was allowed. The primary endpoint was to determine the MTD. Correlative analyses include TS and HDAC expression. This study was approved & funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by Merck & Co., Inc. **Results:** Eighteen pts (51 - 80 years) enrolled from May 2010 to September 2014. Three evaluable (Ev) pts were treated on DL 1 (V 100), with no DLT. 3 Ev pts, and 2 Non-Ev pts (1 not eligible, 1 discontinued due to P-associated rash) were treated on DL 2 (V 200). At DL2, 2 pts had a DLT of grade (G) 4 hyponatremia (HNa). Accrual resumed with 3 pts on DL1, with 2 DLTs at DL1 (HNa and heart failure). Six pts were treated on DL1b with no DLTs. G 1 & 2 toxicities: nausea, anorexia, dysphagia, dehydration, esophagitis, fatigue, pain. G 3 toxicities: nausea, hyperglycemia, anemia, leukopenia. Fourteen pts completed 4 cycles of CRT and V. Two pts stopped V due to myelosuppression. One pt developed CLL 18 months after therapy. Among all pts the best response to date is CR:2, PR:4, SD: 8 pts. Three pts underwent resection, with no viable tumor in 2 specimens. With a median follow up of 15.4 months, the median PFS/OS have not been reached. **Conclusions:** With the exception of G4 HNa, no unexpected toxicities were noted with V and CRT. Esophagitis was mild. Assessment of PFS/OS and correlatives are ongoing. The recommended Phase 2 dose is CP AUC 5, P 500mg/m2 and V100mg 3x/week with RT. Clinical trial information: NCT01059552.

7554 Poster Session (Board #302), Mon, 8:00 AM-11:30 AM

Clinicopathological characteristics of squamous cell carcinoma of the lung with programmed cell death ligand 1 (PD-L1) protein expression. *First Author: Tiffany Huynh, Massachusetts General Hostpital, Boston, MA*

Background: PD-L1 expression by immunohistochemistry (IHC) reportedly predicts patient response to anti-PD-1/PD-L1 therapies in early phase clinical trials for solid tumors. However, there is limited data on the patient/tumor characteristics associated with PD-L1 expression in squamous cell carcinoma of the lung (SqCC). **Methods:** PD-L1 (E1L3N, 1:200, Cell Signaling Technology), PTEN, and CD8 IHC were performed on tissue microarrays of resected SqCCs (n = 162). Subsets of patients underwent clinical molecular (SNaPshot) and FISH testing. Cases with 10% or more tumor cells exhibiting negative or reduced PTEN expression were considered to have PTEN loss. PD-L1 expression in tumor cells and CD8 expression in tumor infiltrating lymphocytes (TILs) were semiquantitatively evaluated. PD-L1 expression, defined as 5% or more of the tumor cells exhibiting membranous staining, was correlated with clinicopathological and molecular features as well as patient outcomes. **Results:** The study cohort consisted of 96 Stage I, 41 Stage II, 22 Stage III, and 3 Stage IV cases. Of those, 43 (27%) exhibited PD-L1 expression, which was associated with large tumor size ($p = 0.001$), advanced pathologic stage (Stage II or higher vs. Stage I, $p = 0.041$), nodal metastasis ($p = 0.014$), increased CD8+ TILs (grade 2-3 vs. 0-1, $p < 0.001$), and PTEN loss ($p = 0.019$) by univariate analysis. In multivariate analysis, large tumor size ($p = 0.048$) and increased CD8+ TILs ($p < 0.001$) remained significant. A Cox proportional-hazards model revealed a borderline significance of PD-L1 expression with shorter progression free survival (PFS) ($p = 0.063$), while advanced pathologic stage was associated with shorter PFS ($p = 0.02$) and increased CD8+ TILs with longer PFS ($p = 0.01$). **Conclusions:** As reported in other tumors, PD-L1 expression is significantly associated with CD8+ TILs in SqCC, and it may predict unfavorable patient outcomes. Interestingly, it is also associated with PTEN loss. There are currently limited targeted therapy options for SqCC, but blockade of the PD-1/PD-L1 pathway may offer promising treatment options for SqCC patients with PD-L1 expression.

7555 Poster Session (Board #303), Mon, 8:00 AM-11:30 AM

Clinicopathological and molecular parameters of lung adenocarcinomas (ADC) associated with programmed cell death ligand 1 (PD-L1) protein expression. *First Author: Tiffany Huynh, Massachusetts General Hostpital, Boston, MA*

Background: Recent efforts in targeting the PD-1/PD-L1 pathway in solid tumors have resulted in durable responses in early phase clinical trials. Additionally, it has been reported that PD-L1 overexpression by immunohistochemistry (IHC) could serve as a predictor of patient response to anti-PD-1/PD-L1 therapies. However, the association of clinicopathological and molecular features with PD-L1 expression in ADC is not well-defined. **Methods:** PD-L1 (E1L3N, Cell Signaling Technology) and CD8 IHC were performed on tissue microarrays of 242 resected ADC that underwent detailed histological analysis. Clinical molecular testing had been performed in a subset (n = 128). Membranous expression of PD-L1 (any intensity) in 5% or more tumor cells was defined as positive. CD8+ tumor infiltrating lymphocytes (TILs) were evaluated using a 4-tier grading system (0-3). PD-L1 expression was correlated with clinicopathological and molecular features as well as prognosis. **Results:** Pathologic stage was 0 in 1, I in 188, II in 37, III in 9, and IV in 7. Of the 242 cases, 38 (15.7%) exhibited PD-L1 expression which was significantly associated with smoking history ($p = 0.008$), large tumor size ($p = 0.007$), solid or acinar predominant pattern ($p < 0.001$), high nuclear grade (grade 3, $p < 0.001$), vascular invasion ($p = 0.012$), increased CD8+ TILs (grade 2-3, $p < 0.001$), and *KRAS* mutations ($p = 0.001$). By multivariate analysis high nuclear grade ($p = 0.011$), *KRAS*mutations ($p = 0.004$), and increased CD8+ TILs ($p = 0.005$) remained significant. In addition, advanced stage (II or higher vs. I, $p = 0.056$) had a borderline significance of PD-L1 expression. There was no difference in 5 year progression-free survival (PFS) for PD-L1 positive (65%) and negative (69%) patients, while advanced stage correlated with shorter PFS ($p = 0.039$) in a cox proportional-hazards regression model. **Conclusions:** PD-L1 overexpression is significantly associated with increased CD8+ TILs and *KRAS* mutations in resected ADC. The latter suggests that targeting the PD-1/PD-L1 pathway may be a viable treatment option for patients with *KRAS* mutated ADC in which there are currently no effective targeted therapies available.

7556 Poster Session (Board #304), Mon, 8:00 AM-11:30 AM

Isolated Thoracic Perfusion with Chemofiltration (ITP-F) for progressive and pre-treated malignant pleural mesothelioma. *First Author: Karl R. Aigner, Medias Klinikum, Burghausen, Germany*

Background: Treatment of patients (pts.) with progressive malignant pleural mesothelioma (MPM) after multimodal therapy remains a therapeutic challenge. Survival of the pts. is low and the treatment options are sparse. We report on a phase II study on isolated thoracic perfusion with subsequent chemofiltration as a locoregional therapeutic strategy in this situation. **Methods:** 21 pts. (19 male, 2 female, mean age 65.5 yrs.) with epitheliolid mesothelioma were included in this study after informed consent. 10 pts. had prior surgical resection, all pts. had adjuvant/additive therapy, general including cisplatin and pemetrexed. Following multimodal therapy all pts. demonstrated progress in CT scan. No pt. had abdominal, cerebral or bone metastases. After insertion of a venous and arterial 21 ch. stop flow catheter via a femoral access, the inferior caval vein was blocked distal the right atrium, the arterial catheter was blocked in the aorta at the diaphragm. Chemotherapy consisted of 60 mg/m^2 cisplatinum and 15 mg/m^2 mitoxantron q 3 weeks till progress. The agents were administered via the arterial access, followed by 15 min of thoracic perfusion followed by chemofiltration for 45 min. The procedure was done under general anesthesia. Endpoint of the study was overall survival. Median follow-up was 48 month. **Results:** A total of 107 cycles (mean 5) were administered. Toxicity was low with leucopenia and thrombocytopenia CTC grad I in 9 pts. and mucositis grad II in 6 pts.. Surgical complications CTC grad I occurred in 40 % of the pat. (lymphatic fistula). There was no gastrointestinal or neuro- toxicity. One year survival was 50% (Kaplan-Meier), 2 year survival was 37.5% and 3 year survival was 37.5%. Median survival was 12 months. **Conclusions:** Intraarterial, isolated thoracic perfusion with subsequent chemofiltration (ITP-F) for pretreated patients with MPM, which are progressive after multimodal therapy, is a valuable additional treatment option with low side effects. It offers in a palliative situation a reasonable survival with good quality of life.

7557 Poster Session (Board #305), Mon, 8:00 AM-11:30 AM

Treatment-free interval (TFI) after first-line therapy as a prognostic and predictive factor in malignant pleural mesothelioma (MPM): Findings from the NGR015 phase III trial with NGR-hTNF plus best investigator choice (BIC) versus placebo plus BIC. *First Author: Vanesa Gregorc, Department of Oncology, San Raffaele Scientific Institute, Milan, Italy*

Background: Historically, the TFI (time from end of first-line to start of second-line therapy) has been reported as a prognostic factor and predictive marker of benefit of next treatment line across various tumors. Prognostic and predictive TFI values were assessed on MPM patients failing a front-line pemetrexed-based regimen and randomly assigned to receive NGR-hTNF 0.8 μg/m^2 (n = 200) or placebo (n = 200) both given with BIC (gemcitabine, vinorelbine, doxorubicin or supportive care). **Methods:** The prognostic value of TFI, treated as continuous variable or split at sample median (4.8 months; 95% CI 4.2-5.1), was tested exclusively in the NGR015 placebo arm. Multivariate Cox models for OS and PFS were adjusted for age, sex, PS, histology, EORTC score, prior disease control and neutrophil to lymphocyte ratio. To assess whether TFI was predictive of benefit with NGR-hTNF, treatment-by-covariate interaction tests were applied on the whole dataset. **Results:** Continuous TFI data were independently related to OS (p = .005). Compared with patients with long TFI ($\geq$ median, n = 201), those with short TFI ($<$ median, n = 198) had a significantly worse OS (median, 6.3 vs 11.7 months; HR = 1.81; p $<$ .0001). Poor prognostic effects of short TFI were confirmed in multivariate models (HR = 1.98; p $<$ .0001) and persisted after stratifying for chemotherapy agent (HR = 1.96; p $<$ .0001). Similar results were shown for PFS. A significant interaction test was reported only between treatment group and TFI for OS (p = .008) and, consistently, for PFS (p = .009). In patients with short TFI, NGR-hTNF plus BIC vs placebo plus BIC significantly improved OS (median, 9.0 vs 6.3 months; HR = 0.69; p = .02) and PFS (6-month rate, 25% vs 12%; HR = 0.71; p = .03). In sensitivity analyses, similar differences in outcome were detected by moving the TFI cutpoint from the median to a more practical 6-month threshold (OS HR = 0.74; p = .04). **Conclusions:** A short TFI is an independent poor prognostic factor and predictive clinical marker of benefit with NGR-hTNF in MPM patients with rapidly progressing disease after first-line therapy. Clinical trial information: NCT01098266.

7558 Poster Session (Board #306), Mon, 8:00 AM-11:30 AM

Prognostic and predictive value of neutrophil-to-lymphocyte ratio (NLR) in previously treated patients with malignant pleural mesothelioma (MPM) enrolled in the NGR015 phase 3 trial. *First Author: Alessandra Bulotta, Department of Oncology, San Raffaele Scientific Institute, Milan, Italy*

Background: NGR-hTNF, a tumor-targeted antivascular agent, promotes a vessel normalization that improves intratumor T-cell infiltration and chemotherapy uptake. The prognostic role of baseline blood NLR, an index of host immune response to tumor, has inconsistently been reported in retrospective MPM series. We assessed NLR in a homogenous population receiving systemic therapy after failure of first-line pemetrexed-based regimen. **Methods:** We used NLR data from patients randomly assigned in the NGR015 trial to receive NGR-hTNF (n = 200) or placebo (n = 200) both given with best investigator choice (BIC: gemcitabine, vinorelbine, doxorubicin or supportive care). The prognostic effects of NLR splitted at sample median (4; 95% CI, 4 to 4) were tested exclusively in the NGR015 placebo arm through Cox models adjusted for age, sex, PS, histology, EORTC score, prior disease control and treatment-free interval (TFI). In patients with short TFI ($<$ median of 4.8 months), the addition of NGR-hTNF to BIC was associated with increased OS (p = 0.02) and PFS (p = 0.02) compared with placebo plus BIC. **Results:** NLR was univariately related to survival, along with TFI, histology, EORTC score and prior disease control. In multivariate models, high NLR (HR = 1.95; p $<$ 0.0001), short TFI (HR = 1.98; p $<$ 0.0001), nonepithelial histology (HR = 1.63; p = 0.02) and poor EORTC score (HR = 1.73; p = 0.02) remained independently associated with worse OS. Median OS in low and high NLR subsets was 9.5 and 6.3 months, respectively. Patients with low NLR resulted more sensitive to NGR-hTNF effects as measured by PFS (HR = 0.74) than those with high NLR (HR = 1.19; interaction p-value = 0.03). In patients with low NLR (n = 174), NGR-hTNF plus BIC vs placebo plus BIC tended to improve PFS (5.5 vs 2.8 months; p = 0.06). In patients with low NLR and short TFI (n = 88), NGR-hTNF plus BIC vs placebo plus BIC significantly increased PFS (5.5 vs 2.3 months; p = 0.04) and OS (17.2 vs 8.4 months; p = 0.007). **Conclusions:** NLR is an independent prognostic factor in pretreated MPM. A low NLR predicts benefit with NGR-hTNF in patients with short TFI who had a rapidly progressing disease after first-line therapy. Clinical trial information: NCT01098266.

7559 Poster Session (Board #307), Mon, 8:00 AM-11:30 AM

Phase I study of intra-pleural administration of GL-ONC1, an oncolytic vaccinia virus, in patients with malignant pleural effusion. *First Author: Lee M. Krug, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: GL-ONC1 is an attenuated vaccinia virus genetically engineered with the insertion of RUC (luciferase)-GFP, LacZ (beta-galactosidase), and gusA (beta-glucuronidase) genes. We investigated the feasibility, safety, and recommended dose of GL-ONC1 when administered intrapleurally. **Methods:** Pts with pleural effusion from malignant pleural mesothelioma (MPM), NSCLC, breast cancer, or other solid tumor, and a free pleural space were eligible. Single doses of 1x10^7, 1x10^8, 1x10^9, or 3x10^9 plaque forming units were administered, and escalation used a 3+3 design. Virus was infused with 500cc Ringer's Lactate over 1hr through a pleural catheter. Fluorescent-imaging guided, thoracoscopic pleural biopsies were performed 2-9 days later. Blood, sputum, urine, and pleural fluid were analyzed for viral shedding by viral plaque assays (VPA). No chemotherapy or radiation was administered during the course of the study (-14 days to 60 days). **Results:** 14 pts have been treated: MPM (11), NSCLC (2), breast (1). Among 13 evaluable pts (1pt with NSCLC was not evaluable due to the rapid development of brain metastases) no dose limiting toxicities occurred. The most common toxicities were fever (7 pts), chills (6), and flu-like symptoms (5), all grade 1/2 occurring mostly in the 24hr after infusion. One patient at dose level 4 had transient grade 3 AST/ALT elevation. 1/28 urine and 5/28 pleural fluid post-treatment samples had +VPA. Positive GL-ONC1 infection of tumor specimens was identified in 6 of 8 pts with epithelioid MPM based on VPA, IHC and GFP imaging. 5 of the 9 pts with epithelioid MPM had time to progression $\geq$ 9 mo (18 mo in one pt). Pts with NSCLC and breast cancer progressed quickly at metastatic sites. **Conclusions:** Single dose, intrapleural administration of GL-ONC1 is safe, but is best suited for patients with MPM whose disease is limited to the pleura. We are now exploring multi-day treatment, and also treatment in conjunction with pleurectomy for pts with MPM. Supported by Genelux Corporation (NCT01766739). Clinical trial information: NCT01766739.

7560 Poster Session (Board #308), Mon, 8:00 AM-11:30 AM

The association of T cells with survival in mesothelioma. *First Author: Serena J Chee, Mesothelioma Applied Research Foundation, Alexandria, VA*

Background: Mesothelioma is a rare, aggressive cancer associated with asbestos inhalation. Treatment results are poor regardless of the modality used, with median survival of 4-18 months. Immunotherapy is now established as an important therapeutic option in many solid tumours including mesothelioma, but predictive markers for benefit are absent. Previous studies suggest that CD8 infiltration in mesothelioma may confer survival benefit. TIL density may therefore identify patients with ongoing immune attack, accessible for boosting by immune activation. **Methods:** Tissue Microarrays (TMA) were constructed with triplicate 1mm cores from a consecutive series of 213 formalin-fixed paraffin-embedded samples from mesothelioma patients. TMA slides were stained for T-cell populations - CD3, CD4, CD8 and CD45RO. Positive cells in 3 high-powered fields (X40) per core were manually scored. The mean score was used to account for tumour heterogeneity. Medians were used as cut point between high and low counts and correlated with clinical data. **Results:** In contrast to previous smaller studies (Yamada et al, 2010; Ankuru et al, 2008), density of tumour infiltrating CD3, CD4 and CD8 cells was not associated with survival outcomes ($p = 0.224$, $p = 0.205$, $p = 0.243$ respectively). However, a high CD4:CD8 ratio (> 0.61) was associated with better survival ($p = 0.007$) with significant ROC curve analysis (AUC = 0.764, $p = 0.001$). Furthermore, a low CD45RO level was also associated with better survival ($p = 0.002$) in this cohort. **Conclusions:** In this unselected mesothelioma cohort, better survival is associated with a high CD4:CD8 ratio and low density of CD45RO memory T cells. Comparison with data from other cancer types suggest that, disease specific immune regulation controls outcome, which is reflected in the particulars of the immune infiltrate in each cancer. For example, a high CD4:CD8 ratio is similarly associated with better survival in cervical cancer (Shah et al., 2011) but not in colorectal cancer (Diederischsen et al., 2003). A better understanding of these immunological drivers and comparative immunometry with other solid tumours types is needed to tailor disease-specific choices for immunotherapy in mesothelioma.

7561 Poster Session (Board #309), Mon, 8:00 AM-11:30 AM

Activity and safety of trabectedin in patients with sarcomatoid / biphasic malignant pleural mesothelioma (MPM). *First Author: Diego Luigi Cortinovis, Az Ospedale S. Gerardo, Monza, Italy*

Background: The efficacy of available MPM therapies is poor in patients (pts) with sarcomatoid/biphasic histotypes , and their prognosis remains dismal. The use of Trabectedin (T) in MPM is justified by its peculiar mechanism of action, involving modulation of the tumor's inflammatory microenvironment, and the demonstrated activity against a range of tumours, including sarcomas. We aimed to study the activity and safety of T in pts with both epithelioid and biphasic/sarcomatoid MPM. **Methods:** *ATREUS,* an Italian multicenter single arm phase II trial, evaluates T as second line therapy in pts with epithelioid histotype and as first/second line in biphasic/sarcomatoid pts. In the latter cohort, the study needed to enroll 17 evaluable pts to reject with a 10% one sided alpha error the null hypothesis that 12-week progression free survival (12w PFS) is $\leq 15\%$ and an 85% power to show 12w PFS in $\geq 40\%$ of pts. Overall survival and safety were secondary endpoints. Pts were treated with T, 1.3 mg/m^2, over 3 hours every 21 days, until progression or unacceptable toxicity. **Results:** The cohort of sarcomatoid/biphasic pts is now complete and results are reported below. Twenty three pts were enrolled and 17 were evaluable (14 M and 3 F, median age 67.9 years). Ten, six and one pts had stage IV, III and II disease, respectively. Seven (41.2%) were treatment naïve. At 12 weeks 7/17 pts (41.2%, 95% CI: 18.4-67.1) were alive and free of progression. Five patients (29.4%) had sustained response with PFS ≥ 18 weeks. By the time of analysis all pts interrupted treatment. Interruption reasons were disease progression in 12 pts, death (4 pts) and consent withdrawal in one pt. The most frequent grade ≥ 3 treatment related toxicities were non febrile neutropenia (11.8%), nausea (17.6%), vomiting, mucositis and fever/infection (each observed in one patient, 5.9%). Two serious adverse events , classified as possibly related to T, occurred. One was fatal. **Conclusions:** T demonstrated its activity in terms of PFS and was well tolerated in this population of patients with advanced sarcomatoid/biphasic MPM. These optimistic results merit to be further investigated in a larger sample. Clinical trial information: NCT02194231.

7562 Poster Session (Board #310), Mon, 8:00 AM-11:30 AM

MicroRNA prognostic signature in malignant pleural mesothelioma. *First Author: Francesco Grossi, Lung Cancer Unit, IRCCS AOU San Martino - IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*

Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor mainly associated with asbestos exposure and characterized by a poor outcome (median overall survival (mOS) $<$ 1 year), therefore requiring novel therapeutic approaches. MicroRNA (miR) play a role in tumorigenesis and progression in MPM. This study aimed to identify miR associated with poor prognosis. **Methods:** We identified 26 unresected MPM patients (11 long survivors (LS), OS $>$ 3 years and 15 short survivors (SS), OS $<$ 1 year). Total RNA, from formalin-fixed paraffin-embedded biopsy and 3 normal pleura (NP) samples, were miR profiled using the Agilent Human miR Microarray including 2006 miR. Expression data were normalized by GeneSpring software (*v.*12.6). Class-comparison analysis between MPM/NP and SS/LS was performed using a t-test adjusted for multiple comparisons using Benjamini-Hochberg.OS curves were estimated using the Kaplan-Meier method and compared with the log-rank test. *In silico*validation was performed using miRseq data from TCGA portal based upon 16 patients (LS: 8; SS: 8). Candidate miR were assessed by univariate analysis using Kaplan-Meier method and median as cutoff. **Results:** Patients' characteristics: median age 67 years (53-77); 81% males, 19% females; 73% epithelioid histotype, 12% sarcomatoid, 12% biphasic, 3% not otherwise specified. No differences in age, gender and histotype observed among LS and SS. Class-comparison analysis reported 30 miR significantly up-regulated and 11 down-regulated in MPM *vs* NP; univariate analysis reported 14 miR significantly associated with OS and differentially expressed in MPM. A miR signature, based on the top prognostic miR (miR-99a, miR-125b, let-7b, let-7c, let-7i, miR-1224), classified patients into low or high-risk. The latter had a significantly shorter mOS (4.1 months, 95% CI 2.2-5.9) compared to low-risk patients (mOS not reached, Log-rank $p < 0.001$). *In silico*validation confirmed low expression of miR-99a, miR-125b and let-7c associated with shorter OS. PI3K/AKT, WNT were associated with these top miR by pathway analysis. **Conclusions:** A prognostic miR signature was identified by profiling a cohort of unresected MPM, underlying the clinical potential of miR as predictors of survival.

7563 Poster Session (Board #311), Mon, 8:00 AM-11:30 AM

High throughput therapeutic screening of malignant pleural mesothelioma (MPM) to identify correlation of sensitivity to FGFR inhibitors with BAP1 inactivation. *First Author: Constantine Alifrangis, Imperial College London, London, United Kingdom*

Background: Small molecule inhibitors have failed to find a role in the treatment of MPM patients. We utilised a high throughput therapeutic screen to identify novel compounds with efficacy in MPM, and performed comprehensive molecular characterisation to identify clinically relevant subgroups within a panel of MPM cell lines. **Methods:** 26 MPM cell lines including immortalised and primary early passage lines underwent Illumina whole exome sequencing, copy number analysis and Affymetrix array transcriptome profiling. In parallel a high throughput drug screen was performed utilising a panel of targeted therapeutic agents. **Results:** From a drug screen of 896 cancer cell lines across all tumour types, MPM lines featured amongst the most sensitive 5% to FGFR inhibitors. We validated this sensitivity in a panel of early passage MPM cultures and with multiple FGFR inhibitors and also siRNA silencing of FGFR family members. We did not detect FGFR mutations or amplifications in the MPM. However we identified *BAP1* loss, either through truncating mutations or promoter methylation-induced silencing, in those MPM lines with enhanced responses to FGFR inhibition. This association was further confirmed using *BAP1* overexpression constructs and *BAP1* shRNA knockdown, which modulated response to FGFR inhibition in mesothelioma cell lines. Baseline gene expression pathway analysis shows significant activation of MAPK pathway signalling in *BAP1* mutant compared to wild type MPM. Furthermore, we observe significantly increased levels of both FGFR1 and FGFR3 receptor transcripts and of FGF9 and FGF18 in *BAP1*mutant versus wild type MPM cell lines. We validated this observation in a panel of 54 human MPM tumours. **Conclusions:** We show that a subgroup of mesotheliomas demonstrate exquisite sensitivity to FGFR inhibition when compared to other tumour types. We identify *BAP1* loss as a potential biomarker for FGFR inhibitor efficacy to define this subgroup and furthermore describe activation of FGFR signalling in *BAP1* inactivated MPM. This data would suggest a clinically relevant MPM subgroup against which FGFR inhibition could be directed in future clinical studies.

7564 Poster Session (Board #312), Mon, 8:00 AM-11:30 AM

Confirmation of high prevalence of BAP1 inactivation in mesothelioma. *First Author: Andrea Cercek, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Efforts to elucidate tumorigenic mutations in mesothelioma are essential to advance therapy. Prior efforts to characterize the molecular heterogeneity of this disease have been limited by sample condition and testing platforms. Herein, we describe efforts to prospectively test patients using next-generation sequencing with matched patient germline controls. **Methods:** Sequential mesothelioma patients were approached for consent to our IRB protocol NCT01775072 to perform MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), a comprehensive molecular profiling platform based on solution-phase exon capture and next generation sequencing to detect somatic genetic alterations in FFPE tumor specimens. MSK-IMPACT involves hybridization capture and deep sequencing of all protein-coding exons of 341 key cancer-associated genes, including all genes that are druggable by approved therapies or are targets of experimental therapies being investigated in clinical trials at MSKCC. **Results:** 40 patients with mesothelioma underwent MSK-IMPACT testing (see Table 1). 6 samples had low tumor content and in 3 of those no alterations were identified. In 2 samples with sufficient tumor content, no alterations were identified. Among 37 samples with results, *BAP1* was the most common alteration (57%). **Conclusions:** Using MSK-IMPACT, *BAP1* inactivation is the most common alteration. Other aberrations previously reported at high frequency were identified but albeit at lower frequencies (*NF2* and p16, previously reported as 40% and 75% respectively). For multiple samples with deep coverage, no alterations were identified. The high incidence of BAP1 mutations in this systematic testing makes this pathway ideal for developing and testing targeted therapies.

7565 Poster Session (Board #313), Mon, 8:00 AM-11:30 AM

Mesothelin-targeted immunotherapy CRS-207 in combination with standard of care chemotherapy as treatment for malignant pleural mesothelioma (MPM). *First Author: Raffit Hassan, Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: MPM is an aggressive disease with poor prognosis and is relatively refractory to currently available therapies. CRS-207 is live-attenuated *Listeria monocytogenes* engineered to express the tumor-associated antigen mesothelin. Stimulation of potent innate and adaptive immunity by CRS-207 may act synergistically in combination with chemotherapy that alters the tumor environment to be more susceptible to immune-mediated killing. **Methods:** Eligible patients were chemotherapy-naïve with unresectable MPM, good performance status (ECOG 0 or 1) and adequate organ function. Patients received 2 prime vaccinations with CRS-207 (1×10^9 CFU) 2 weeks apart, followed by 6 cycles of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) 3 weeks apart and 2 CRS-207 boost vaccinations 3 weeks apart. Subjects were followed every 8 weeks until disease progression. Clinically stable patients received CRS-207 maintenance vaccinations every 8 weeks. Objectives of the study include safety, immunogenicity, objective tumor responses and tumor marker kinetics. **Results:** Twenty-six subjects (88% male; median age: 69) have been enrolled as of Jan 15 2015. As of Jan 2015, 10/26 were on treatment. Median time on treatment was 7.1 months (range: 1.0-22.5). No treatment-related unexpected toxicities have been observed. The most common adverse events related to CRS-207 were Grades 1/2 infusion-related fever, chills/rigors, hypotension and nausea/vomiting. Of 24 subjects evaluable, 63% (15/24) had confirmed partial response (PR) post CRS-207 and chemotherapy and 29% (7/24) had stable disease (SD). Median duration of response was 4.8 months (range: 3.6-7.2) and PFS was 7.5 months (range: 7.1-8.6) for the first 16 subjects enrolled. Treatment, follow-up, median overall survival and immune response evaluations are ongoing and will be presented at the meeting. **Conclusions:** CRS-207 can be safely combined with chemotherapy and showed encouraging anti-tumor activity with 63% of subjects having objective tumor responses and 92% disease control. These results are considerably better than those expected with chemotherapy alone and warrant further evaluation. Clinical trial information: NCT01675765.

7566 Poster Session (Board #314), Mon, 8:00 AM-11:30 AM

Immune escape correlates with an inflamed phenotype in malignant mesothelioma. *First Author: Arun Khattri, The University of Chicago, Chicago, IL*

Background: Malignant mesothelioma (MM) is commonly associated with an inflammatory reaction, although the specific patterns of immune escape remain incompletely understood. We used emerging, high-fidelity gene expression data from the TCGA Mesothelioma cohort to interrogate subgroups based on expression of immune related genes, and determined associated immune escape mechanisms. **Methods:** RNA-seq data from 76 MM from *TCGA* were analyzed using genes representative of 1. T-cells, 2. NK-cells, 3. neutrophils, 4. dendritic cells/macrophages, as well as genes associated with immune escape (immune checkpoints and cellular immune escape). Using this gene set, unsupervised, hierarchical clustering was performed to identify intrinsic immune subgroups. Groups were correlated with T-cell inflammation (Kindler ASCO 2014), based on the 12-gene inflammation signature (Harlin/Gajewski Cancer Res 2009). **Results:** MM tumors readily clustered into two large groups with 35% of tumors showing high levels of inflammation (group 1), presence of all four immune cell components, and 80% of tumors showing a TCIP-high phenotype. Non-inflamed tumors (group 2) showed low immune cell related gene expression and were 85% non-T-cell inflamed. Prominent immune escape was present in all group 1 tumors, including expression of PD-1/PD-L1, CTLA4, LAG3, and FOXP3 (however not B7H3). Inflammation strongly correlated with presence of immune escape (functional immune response) in group 1, while group 2 tumors exhibited neither infiltration with immune cells, nor immune escape (immunological ignorance). **Conclusions:** MM can be classified into inflamed/group 1 and non-inflamed/group 2 tumors. Group 1 tumors show simultaneous infiltration with multiple immune cell components, and prominent immune escape. Inflamed and non-inflamed MM may require differential treatment strategies for immunotherapy.

7567 Poster Session (Board #315), Mon, 8:00 AM-11:30 AM

Evaluation of CXCR4 expression on tumor and circulating tumor cells (CTCs) as predictive response marker for CXCR4 antagonist LY2510924 in combination with carboplatin-etoposide in extensive-disease small cell lung cancer (ED-SCLC). *First Author: Ravi Salgia, The University of Chicago, Chicago, IL*

Background: Small cell lung cancer (SCLC) can express CXCR4 chemokine receptor, and inhibition potentially synergizes with cytotoxic and targeted therapeutics in vitro in SCLC. Baseline CXCR4 expression on tumor tissue or CTCs may help predict response to treatment with CXCR4 antagonist LY2510924 (LY). **Methods:** In an open-label, randomized phase 2 study (NCT01439568), patients (pts) with ED-SCLC received up to six 21-day cycles (C) of carboplatin (Day [D] 1) and etoposide (D1-3) (SOC) alone or in combination with 20 mg qd sc LY (D1-7) (LY+SOC). Exploratory analyses evaluated CXCR4 expression on available baseline tumor tissue (IHC H-score) and on CTCs collected at baseline, C1D7, and C2D1 (CellSearch). Receiver operating characteristic (ROC) curves and their AUCs (95% CIs) were generated to determine optimal cutoff values for CXCR4 expression on tissue and CTCs and number of CTCs as predictors of 6-month progression-free survival (PFS). Hazard ratios (HRs) through 4 months (end of treatment), using the optimal cutoffs at baseline, were generated. **Results:** 90 pts were randomized to SOC (N = 43) or LY+SOC (N = 47). Optimal ROC cutoffs were $\geq$ 210 (H-score) for CXCR4+ tissue ($\geq$ 210: N = 31, $<$ 210: N = 38; AUC = 0.631 [0.496, 0.765]); $\geq$ 7% CXCR4+ on CTCs ($\geq$ 7%: N = 44, $<$ 7%: N = 26; AUC = 0.702 [0.577, 0.828]); and $\geq$ 6 CTCs/7.5 mL blood ($\geq$ 6: N = 60, $<$ 6: N = 18; AUC = 0.607 [0.471, 0.742]). In evaluating pts with a baseline value above each optimal cutoff, the HR (95% CI) was 0.787 (0.211, 2.933) for CXCR4+ tissue (LY+SOC: N = 16, SOC: N = 15); 0.476 (0.147, 1.548) for % CXCR4+ on CTCs (LY+SOC: N = 20, SOC: N = 24); and 0.403 (0.151, 1.076) for CTCs (LY+SOC: N = 31, SOC: N = 29). For pts considered high risk (ie, $\geq$ 6 CTCs and $\geq$ 7% CXCR4+ CTCs), the HR was 0.489 (0.150, 1.589) (LY+SOC: N = 18, SOC: N = 23). **Conclusions:** Selected ED-SCLC pts with high levels of CTCs and/or CXCR4 expression on CTCs and/or tumor tissue at baseline may benefit by the addition of LY to SOC. Further investigation of LY in a preselected pt population is warranted. Clinical trial information: NCT01439568.

7568 Poster Session (Board #316), Mon, 8:00 AM-11:30 AM

Prophylactic cranial irradiation (PCI) and consolidation thoracic radiotherapy (TRT) for extensive stage small cell lung cancer (ES-SCLC): A systematic review and meta-analysis. *First Author: Yu Yang Soon, National University Cancer Institute, Singapore, Singapore*

Background: The role of PCI and TRT in ES-SCLC is controversial. We performed a systematic review of all comparative studies to investigate the benefits and harms of PCI and TRT in ES-SCLC. **Methods:** We searched MEDLINE, CENTRAL from date of inception and various conference proceedings from 2009 to November 2014 for eligible studies. The primary outcome is overall survival (OS). Secondary outcomes include progression-free survival (PFS), freedom from brain metastasis and toxicity. The Cochrane risk of bias instrument was used to assess the risk of methodological bias and the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach was used to assess the quality of evidence. Hazard ratios (HR), confidence intervals (CI), p values (p) was estimated with random effects models using Revman 5.3. **Results:** We found 2 randomized controlled trials (RCTs) and 3 non-RCTs, including 2192 patients comparing PCI versus no PCI; 4 RCTs and 1 non-RCT including 782 patients comparing TRT versus no TRT. The risk of methodological bias was low for 2 RCTs evaluating PCI and 2 RCTs evaluating TRT. Meta-analysis of these low risk bias RCTs showed that PCI decreased the risk of brain metastasis development (HR 0.43, 95% CI 0.30 to 0.60, $p < 0.001$, high quality evidence) but did not improve OS (HR 0.95, 95% CI 0.48 to 1.91, $p = 0.89$) or PFS (HR 0.91, 95% CI 0.63 to 1.32, $p = 0.62$) (moderate quality of evidence). There was high quality evidence that TRT improved OS (HR 0.82, 95%CI 0.69 to 0.97, $p = 0.02$) and PFS (HR 0.76, 95%CI 0.64 to 0.89, $p < 0.001$). The incidence of grade 3-4 toxicities of PCI and TRT ranged from 1 to 20%. **Conclusions:** There was high quality evidence that PCI reduced the risk of brain metastasis development and TRT improved survival in ES- SCLC. Toxicity rates were variable and are probably related to dose and treated volume effects.

7569 Poster Session (Board #317), Mon, 8:00 AM-11:30 AM

Loss of somatostatin receptor 2 expression and lung cancer growth. *First Author: Jonathan Lehman, Vanderbilt Univ School of Medcn, Nashville, TN*

Background: Small cell lung cancer (SCLC) is a neuroendocrine cancer of the lung responsible for up to 25% of lung cancer deaths. Targeted therapies for SCLC are sorely needed. Somatostatin receptors (SSTR) are G protein-coupled receptors with effects on cell cycling, angiogenesis, and apoptosis which signal by inhibition of adenylate cyclase, Ca influx, and act through multiple kinases. SSTR2 is highly expressed in SCLCs and we hypothesize that its signaling supports cancer growth. **Methods:** Tumor microarrays containing 98 SCLCs were scored based on SSTR2 staining intensity and % tumor staining. Tumors were categorized as SSTR2 expressing (score > 0) which comprised 48% of the samples, or non expressing, and analyzed by Cox proportional hazard model including: age, smoking hx, stage, and SSTR2 expression. These results led to evaluation of SSTR2 expression and immunoblotting of multiple cell lines and tumors. We established SSTR2 shRNA knockdown lines including bronchial carcinoid, squamous cell carcinoma (SCC), and SCLC lines. We evaluated these lines with proliferation, flow cytometry, clonogenic assays, and a SCC cell line *in vivo* with mouse xenografts. **Results:** Non SSTR2 expressing SCLCs had a median survival by Kaplan Meier in limited stage (LS) disease of 36 compared to 12 months in SSTR2 expressing SCLCs suggesting SSTR2 expression has clinical relevance ($p = 0.001$). The 95% confidence interval for the hazard ratio was 0.23-0.87 for LS disease. There was no significant difference in survival in extensive stage disease. Most SCLC and a subset of SCC lines expressed SSTR2. Knockdown led to up to 3 fold decreases in cell viability *in vitro* in multiple lines and constructs. Xenograft experiments showed dramatically reduced ki67 staining and reduced tumor weight and growth curves in an SSTR2 shRNA H520 line. Phosphoprotein array and immunoblots suggest dysregulation of pAKT and AMPK signaling with SSTR2 knockdown. **Conclusions:** SSTR2 expression in SCLC is associated with worse outcomes suggesting a role in cancer progression. Our data support this hypothesis and suggest downstream changes in pAKT and AMPK contribute to this phenotype. Overall, this suggests SSTR2 antagonism or downstream mediators may be future targets in lung carcinoma.

7570 Poster Session (Board #318), Mon, 8:00 AM-11:30 AM

New ARCHITECT plasma pro-gastrin-releasing peptide assay and lung cancer: Implications for diagnosis, follow-up, and prognosis. *First Author: Benjamin Nisman, Hadassah Hebrew University Medical Center, Jerusalem, Israel*

Background: Pro-gastrin-releasing peptide (proGRP) is a precursor of the neuropeptide hormone produced by small cell lung cancer (SCLC) and considered as a potential serum marker for this disease. However, proGRP was shown to be more stable in plasma compared to serum. In this prospective study we evaluated the new proGRP assay in plasma format. **Methods:** Plasma proGRP was determined using the ARCHITECT i System (Abbott Diagnostics, Wiesbaden, Germany) in four cohorts: healthy individuals ($n = 100$) and patients with benign lung diseases (BLD, $n = 102$), non-small cell lung carcinoma (NSCLC, $n = 241$), and SCLC ($n = 90$). **Results:** The median (95 percentile) concentrations of plasma proGRP in healthy, BLD, NSCLC and SCLC were: 38 (64), 39 (64), 40 (121) and 680 (17695) pg/ml, respectively. There was no association with age, gender or smoking. The proGRP assay proved to be effective in distinguishing SCLC from NSCLC with area under the curve 0.941, 95%CI 0.906-0.975, 84.4% sensitivity, 95% specificity, at a cut-off 121 pg/ml. False-negative results in SCLC were associated with lack of thyroid transcription factor-1 (Fisher's Exact Test, $P = 0.0006$). False-positive results in NSCLC were associated with large cell neuroendocrine carcinoma (LCNEC) (Fisher's Exact Test, $P < 0.0001$). The elevated proGRP was found in 44.5% (5 of 11) patients with LCNEC. Fifty patients with SCLC were followed by plasma proGRP during chemotherapy. The decline of proGRP during chemotherapy below a cut-off (121 pg/ml) was associated with objective image based response (Fisher's Exact Test, $P = 0.0003$). In multivariate Cox regression analysis the proGRP response adjusted for imaging response and ECOG performance status independently affected progression free survival (PFS, hazard ratio [HR] = 0.38, 95%CI 0.20-0.74, $P = 0.009$) and overall survival (OS, HR = 0.32, 95%CI 0.16-0.63, $P = 0.003$). **Conclusions:** Plasma proGRP is a highly specific and sensitive marker supporting diagnosis of high grade neuroendocrine lung tumors, mainly SCLC. Elevation of proGRP in NSCLC is associated with LCNEC. The changes in the plasma proGRP during SCLC chemotherapy showed a significant association with imaging assessments of response, PFS and OS.

7571 Poster Session (Board #319), Mon, 8:00 AM-11:30 AM

Survival impact of switching to different topoisomerase I or II inhibitors-based regimens (topo-I or topo-II) in extensive-disease small cell lung cancer (ED-SCLC): supplemental analysis from JCOG0509. *First Author: Shogo Nomura, Center for Research Administration and Support, National Cancer Center, Kashiwa, Japan*

Background: The J0509 (phase III study for chemotherapy-naive ED-SCLC) demonstrated amrubicin plus cisplatin (AP) was inferior to irinotecan plus cisplatin (IP). However, median overall survival (OS) of both AP and IP (15 and 17 mo) was more favorable than those of previous trials (9-12 mo), probably because switching to different topo-I or topo-II in the second-line therapy, especially the use of topo-II in IP arm, was frequent. This analysis aimed to investigate whether observed survival benefit of IP arm can be explained by the treatment switching, and how post-protocol chemotherapy affected the result of J0509. **Methods:** Two analysis sets from J0509 were used: all randomized 283 pts and 250 pts who received post-protocol chemotherapy. One pt without initiation date of second-line therapy was excluded. A rank-preserving structural failure time (RPSFT) model was used to estimate "causal survival benefit" that would have been observed if all pts had been followed with the same type of regimen as randomized throughout the follow-up period. Additionally, to assess the survival impact of second-line use of topo-II, OS after initiating second-line therapy (OS2) was analyzed by multivariate Cox models. **Results:** %treatment switching in IP arm and AP arm was 65.2% (92/141) and 43.7% (62/142). By RPSFT model, estimated OS excluding the effect of the treatment switching was 2.7-fold longer in IP (topo-I) arm than AP (topo-II) arm. This causal survival benefit was stronger than the original report of J0509 (nearly 1.4-fold extension by Cox model), indicating that re-challenging topo-I in IP arm appeared beneficial. The multivariate Cox analysis for OS2 ($n = 250$) revealed second-line use of topo-II was detrimental (hazard ratio, 1.5; 95%CI, 1.1-2.1). Among sensitive relapsed pts in IP arm, OS2 was favorable in the following order: irinotecan-based regimen $>$ the other topo-I $>$ topo-II. **Conclusions:** IP remains the standard therapy. Re-challenging topo-I, especially irinotecan-based topo-I, seemed beneficial for IP-sensitive pts. This result should be confirmed in further investigations with large sample size. Clinical trial information: 000000720.

7572 Poster Session (Board #320), Mon, 8:00 AM-11:30 AM

Phase II study of topotecan and cisplatin with sequential radiotherapy in elderly small cell lung cancer patients (Okayama Lung Cancer Study Group; OLCSG 0102). *First Author: Toshio Kubo, Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan*

Background: The standard treatment for elderly patients with localized small cell lung cancer (LD-SCLC) has not been established. The Okayama Lung Cancer Study Group previously performed a phase I trial using low-dose split cisplatin and topotecan (TP) therapy for elderly SCLC patients and determined the recommended dose. Here, we performed a phase II trial using low-dose split TP therapy with sequential thoracic radiotherapy (TRT) for elderly LD-SCLC patients. **Methods:** Patients aged ≥76 years with untreated LD-SCLC and a performance status of 0–2 were enrolled. Topotecan (1.0 mg/m^2, days 1–3) and cisplatin (20 mg/m^2, days 1–3) were administered for a maximum of four courses, and sequential TRT (1.8 Gy/day for a total of 45 Gy) was added. The primary endpoint was the overall response rate (ORR). We assumed that an ORR of 0.90 in eligible patients would indicate potential usefulness, whereas an ORR of 0.70 was the lower limit of interest, with $\alpha = 0.05$ and $1-\beta = 0.80$. **Results:** A total of 22 cases were registered between 2004 and 2014. Of these, 19 individuals were male, the median age was 79 years, and the median Charlson Comorbidity Index value was 3. The median number of chemotherapy courses was 3, the proportion of patients who could initiate TRT was 63.6%, and the proportion of patients who could complete whole planned treatment was 45.5%. The ORR was 0.68 (15/22 cases; 95% confidence interval, 0.47–0.89), which was below the threshold. The median progression-free survival and overall survival were 9.1 months and 22.2 months, respectively. The observed grade 3–4 toxicities included neutropenia in 95.5% of patients, thrombocytopenia in 50.0%, anemia in 36.0%, and febrile neutropenia in 32.0%. **Conclusions:** Although low-dose split TP and sequential TRT exerted positive effects on survival, the primary endpoint was not met and severe bone marrow suppression was observed. Therefore, further consideration of the regimen including the timing of TRT is required. Clinical trial information: C000000134.

7573 Poster Session (Board #321), Mon, 8:00 AM-11:30 AM

Detection of circulating tumor cells in the peripheral blood of patients with small cell lung cancer (SCLC) using both the CellSearch platform and immunofluorescence: Correlation with clinicopathological features. *First Author: Ippokratis Messaritakis, Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, Greece*

Background: The diagnosis of SCLC is based on morphology and immunocytochemistry using cytokeratins and neuroendocrine markers. We aimed to evaluate the clinical significance of the detection of Circulating Tumor Cells (CTCs) in patients with SCLC using the CellSearch system (CS) and immunofluorescence (IF). **Methods:** Peripheral blood was obtained from 101 patients with SCLC before treatment, 68 patients after one cycle of 1st line chemotherapy (etoposide/platinum) and 52 patients at the time of disease progression. CTCs were detected by double immunofluorescent staining of one million PBMC's on cytospins using anti-TTF1 and anti-CD56 antibodies, and by the CS using anti-CK antibody. **Results:** Prior to the initiation of 1st line treatment, 61% of patients had detectable CTCs by IF and 78% with the CS (range: 1-169 and 2-10000 CTCs, respectively). After 1 cycle of chemotherapy, the positivity of CTC detection decreased to 44% (range: 1-56 CTCs) and 45% (range: 1-4882 CTCs) using IF and CS, respectively; at the time of disease progression (PD) the detection of CTCs almost reached the baseline levels (60% and 74%; range: 2-186 and 1-11143 CTCs for IF and CS, respectively). The detection of CTCs at baseline, after 1 cycle of chemotherapy and on PD was significantly associated with decreased PFS (7.0 vs 8.5 months, p = 0.021; 5.6 vs 8.1 months, p = 0.018; 5.7 vs 7.6 months, p = 0.014, respectively) and OS (11.0 vs 26.0 months, p = 0.021; 8.9 vs 17.0 months, p = 0.009; 10.0 vs 17.0 months, p = 0.021, respectively) compared to the patients with undetectable CTCs. Multivariate analysis revealed that performance status, disease stage and the detection of CTCs after 1 cycle of chemotherapy and at the time of progression emerged as independent factors associated with reduced PFS and OS. **Conclusions:** Detection of CTCs using either immunofluorescence or the CellSearch is an adverse prognostic factor correlated with poor clinical outcome in patients with SCLC receiving 1st line chemotherapy.

7574 Poster Session (Board #322), Mon, 8:00 AM-11:30 AM

Distribution and clinical significance of CTLA4, PD-1 and PD-L1 in peripheral blood of patients with small-cell lung cancer. *First Author: Ying Cheng, Jilin Provincial Cancer Hospital (JPCH), Changchun, China*

Background: Cytotoxic T lymphocyte associated antigen 4 (CTLA4), programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) are key components of immune checkpoints and the most attractive targets in immunotherapy for cancer. These antigens are abundant in tumor samples, however their distribution and clinical value in liquid biopsy (such as blood) of small-cell lung cancer (SCLC) patients remains unclear. **Methods:** 60 healthy and 230 chemotherapy-naïve patients with SCLC were recruited. Venous blood samples were collected prior to chemotherapy (baseline) and after the second cycle of chemotherapy (2nd cycle), and flow cytometry was used to analyze the level of CTLA4, PD-1 or PD-L1 with or without CD3, CD4, CD8 or CD25. Immunohistochemistry was used to detect PD-L1 expression in SCLC cell line H446. **Results:** Cells of CTLA4$^+$, CD3$^+$CTLA4$^+$ and CD4$^+$CTLA4$^+$ in SCLC were (1.06±1.51)%, (4.12±5.30)% and (3.95±2.80)%, respectively and PD-1$^+$, CD3$^+$PD-1$^+$, and CD4$^+$PD-1$^+$ were (7.96±3.38)%, (25.86±8.49) % and (20.92±8.31) %, which were not different from those in control. However, level of CD4$^+$CD25$^+$CTLA4$^+$cells were higher in SCLC than that in control, (6.77±4.71)% vs (1.91±1.27)%, $P<$ 0.001 and CD8$^+$ PD1$^+$cells were less in SCLC than that in control, (11.49±5.23) % vs (22.56±4.21)%, $P<$ 0.001, neither of which were associated with age, sex, smoke or disease stage. Level of CD4$^+$CD25$^+$CTLA4$^+$cells was dropped to (5.77±3.77)% after 2nd cycle compare to that at baseline ($P=$ 0.04), but level of CD8$^+$PD1$^+$cells was not altered. Interim analysis showed neither the level of CD4$^+$CD25$^+$CTLA4$^+$ nor CD8$^+$PD1$^+$cells before or after treatment was related to progression–free survival or overall survival of patients. Although PD-L1 was highly expressed in H446, it was rarely found in peripheral blood. **Conclusions:** We for the first time showed that CTLA4 was highly expressed in regulatory T cells and PD-1 decreased in CD8 in peripheral blood of SCLC patients, suggesting their unique mechanisms involved in immune regulation. CD4$^+$CD25$^+$CTLA4$^+$level changed after treatment implies its potential role in predicting treatment efficacy.

7575 Poster Session (Board #323), Mon, 8:00 AM-11:30 AM

Clinical correlation of genomic mutations in small cell lung cancer. *First Author: Afshin Dowlati, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: Genomic studies in small cell lung cancer (SCLC) lag far behind those performed in non-small cell lung cancer (NSCLC). Unlike NSCLC, where specific mutations such as ALK and EGFR are associated with distinct clinical behavior, no such data exists for SCLC. We have established a clinical- pathologic database on all SCLC patients treated at our medical center and recently added genomic analysis. **Methods:** Targeted exome sequencing data of 324 genes was obtained on a total of 36 patients. Genes were organized for analysis into two groups: (I) genes with mutations validated to be oncogenic, and (II) genes harboring any detectable mutation, validated or not. The specific type of mutation was not considered, only its presence/absence, except for TP53, which were additionally characterized as either disruptive (D) or non-disruptive (ND). Principal clinical correlates were OS, PFS, and chemo-response. Survivor distribution was estimated using Kaplan-Meier methods and difference of OS, PFS between/among groups was examined by log-rank test. The effect of continuous measurements including age, and number of genes alternated on survival (OS, PFS) was estimated using Cox model. **Results:** The cohort was typical for SCLC, containing a majority of extensive disease (78%), chemo-sensitive (66%) male (56%) patients. The median OS for all patients was 11.4 mo (95% CI: 7.9-55.5 mo). While no Group I genes significantly correlated with OS, PFS was significantly worse for patients with no TP53 mutation (NEG) compared to its presence (p = 0.023); as well as when comparing NEG, D and ND mutations (p = .047). There was a trend for PTEN loss to negatively impact OS (p = .101) and PFS (p = .171). When Group II genes were considered, two: GPR124 (p = .035) and IL7R (p = .094) were predictive of OS; and 3 genes: TP53 (p = .028), CREBBP (p = .057) and GPR124 (p = .056) were predictive of PFS. The total number of mutated genes had no significant clinical correlation. No gene mutation significantly correlated with chemo-response. **Conclusions:** This study is the first to describe gene mutations, including TP53 and several novel genes, with significant clinical correlation to OS and PFS. We can expect that as our cohort grows, a full landscape of genes important to SCLC will emerge.

7576 Poster Session (Board #324), Mon, 8:00 AM-11:30 AM

Identification of *RICTOR* amplification as a recurrent and potentially actionable alteration in small cell lung cancer patients. *First Author: Snehal Dabir, Case Western Reserve University, Cleveland, OH*

Background: Genomic analysis of SCLC is in its infancy relative to NSCLC and no known correlations to clinical outcomes have been reported for any SCLC mutation. Thus, we tested SCLC cancer diagnostic biopsies for genomic mutations by targeted exome sequencing of a panel of cancer-related genes using FFPE tissue. We identified recurrent *RICTOR* amplification in 5 of 36 total patient tumors examined. Here we report the clinical importance of *RICTOR* amplification in our SCLC cohort and its potential to represent a new actionable subgroup in this disease. **Methods:** Survivor distribution was estimated using Kaplan-Meier methods and the difference of OS, PFS between/among groups was examined by log-rank test. All tests are two-sided and p-value ≤ 0.05 were considered statistically significant. SCLC cell lines were assayed for growth inhibition in the IncuCyte ZOOM using drugs that target the PI3K/AKT/mTORC1/2 pathways. **Results:** *RICTOR* amplification was found in 4 men and 1 women, with a median age of 63 years. RICTOR typically co-amplified with the nearby genes *IL7R* and *FGF10*; suggesting a focal amplification of these genes on chromosome 5p13. *RICTOR* was the most frequent amplified gene identified in our SCLC cohort; greater than *FGFR1* and *MYC*. The OS of patients with RICTOR amplification was significantly decreased ($p = 0.036$) while PFS approached significance ($p = 0.062$). Cell growth inhibition studies with SCLC cell lines demonstrated sensitivity towards mTORC1/2 inhibitors (INK128 and AZD2014) by cells with higher CNV for *RICTOR*. Ongoing experiments will expand the number of cell lines studied to determine the correlation between *RICTOR* CNV, protein and growth inhibition. **Conclusions:** Amplification of *RICTO*R may represent a clinically significant mutation in SCLC and may represent a predictive marker for targeted therapy with mTORC1/2 inhibitors in small cell lung cancer patients.

7577 Poster Session (Board #325), Mon, 8:00 AM-11:30 AM

Conditional survival estimates for small cell lung cancer receiving prophylactic cranial irradiation in the U.S. (1988-1997). *First Author: Yan Xing, Mt Auburn Hosp, Belmont, MA*

Background: Conditional survival (CS) has emerged as a clinically useful measure of prognosis for cancer patients with poor prognosis. We examined the efficacy of prophylactic cranial irradiation (PCI) on cancer-specific CS estimates for small cell lung cancer (SCLC) patients. **Methods:** SCLC patients on whom PCI data was available were identified from the Surveillance Epidemiology and End Results registry (SEER) from 1988-1997. PCI data were not available after 1997. Multivariate Cox regression models were built separately by each stage to calculate the adjusted 1-6 year cancer-specific survival and overall survival. The multiplicative law of probability was then used to compute the X-year conditional survival where the (x+y) year survival is divided by y years of patients who have survived. Variables adjusted for included age, sex, ethnicity, marital status, SEER region, year of diagnosis, and radiation. **Results:** Data on 9,134 patients was included. Utilization of PCI in limited stage (LS)-SCLC increased from 18% in 1988 to 23% in 1997 ($P < 0.001$). Patients with LS-SCLC from Midwest were less likely to receive PCI (36% vs. 40%, $p < 0.001$) compared to other SEER regions and those aged 50-79 years with LS-SCLC were less likely to receive PCI (59% vs. 16%, $p < 0.001$). The 3- year conditional overall survival (COS) from diagnosis (time 0) to 3 years for LS-SCLC receiving PCI improved from 23% (all patients at diagnosis) to 54% (patients alive at 3 years from diagnosis) whereas similar estimates for those not receiving PCI were 17% and 48%. For extended stage (ES) SCLC receiving PCI, the 3-year COS improved from 4% to 49% whereas the 3-year COS for those not receiving PCI improved from 5% to 50%. Three-year conditional cancer-specific survival (CCSS) for LS-SCLC receiving PCI improved from 28% to 65% and for those not receiving PCI improved from 20% to 59%. For ES-SCLC receiving PCI, the 3-year CCSS improved from 5% to 60% whereas in those not receiving PCI, it improved from 6% to 62%. **Conclusions:** Three-year COS and CCCS estimates improve dramatically over time for SCLC survivors. These prognostic data provide more accurate prognosis helping clinicians and patients with informed decision making.

7578 Poster Session (Board #326), Mon, 8:00 AM-11:30 AM

Small cell lung cancer: Why has it become an orphan disease? *First Author: Shakun M. Malik, Clinical Investigations Branch CTEP/DCTD, Rockville, MD*

Background: Lung cancer remains the leading cause of death in US and worldwide. Substantial progress has recently been made in non-small cell lung cancer (NSCLC) with the discovery of molecular targets leading to the targeted drug development. Positive trials have led to the approval of a number of targeted therapies in NSCLC. However, therapies for small cell lung cancer (SCLC) have lagged behind with the current standard treatment reflecting the prevailing state-of-the-art from the early 1980s. We wanted to identify the reasons for the lack of progress in the treatment of SCLC. **Methods:** We searched all the randomized clinical trials of SCLC through a search of the National Cancer Institute Cancer Therapy Evaluation Program database (through June 31, 2014). We also conducted a search of Medline with the MeSH terms "Small Cell Lung Carcinoma", "phase III", and "phase II", for peer-reviewed randomized clinical trials. **Results:** Trials for limited-stage SCLC have decreased over time with 9/44 trials being positive. Of these 9 positive trials, 8 studied radiation dose/sequencing. In extensive-stage SCLC, there were 14 positive trials, with a number of these being either non-inferiority trials or studying chemotherapy intensification rather than a new drug. In relapsed/refractory disease, 7/13 trials were positive and the majority tested topotecan. **Conclusions:** The discovery of molecular drivers in SCLC that are targetable lag far behind NSCLC. The number of randomized trials studying new drugs in SCLC trials is limited. Since the approval of topotecan in 1996 the US FDA has approved no new drugs for the treatment of small cell lung cancer patients.

Randomized comparative trials in SCLC.

Stage and publication year	No. of trials	Total sample size on all trials	Median trial sample size
Limited stage	44	11149	262
1960-1985	10	1954	199
1986-1995	16	3809	237
1996-2005	13	3753	314
2006-2014	5	1633	281
Extensive stage	51	13964	226
1960-1985	4	1577	373
1986-1995	15	3133	154
1996-2005	11	2741	227
2006-2014	21	6513	216
Relapsed/Refractory	13	2569	141
1960-1985	0	0	-
1986-1995	1	130	130
1996-2005	3	382	106
2006-2014	9	2057	180

7579 Poster Session (Board #327), Mon, 8:00 AM-11:30 AM

Impact of accurate staging with ^{18}F-FDG-PET and brain MRI on clinical benefit of prophylactic cranial irradiation (PCI) in patients with limited stage (LS) small cell lung cancer (SCLC). *First Author: Mihong Choi, National Cancer Center, Goyang, South Korea*

Background: The latest randomized study using brain MRI as initial brain assessment has suggested PCI had a negative survival effect in extensive stage SCLC (Abstr 7503, ASCO, 2014), which is contrary to the results of earlier studies that had not necessarily included brain MRI and PET as initial evaluation. Furthermore, as the survival of LS-SCLC pts improves, there has been a great need to critically address the benefit-risk issue of PCI (*Lee J* et al, J Clin Oncol, 2006). Thus, we sought to evaluate the effect of initial brain MRI and PET evaluation on the clinical outcome and benefit of PCI in LS-SCLC pts. **Methods:** We retrospectively collected data from 264 pts with histologically-proven LS-SCLC who had complete or partial response after concurrent chemoradiotherapy including platinum-based regimen from April 2001 to April 2013 at National Cancer Center Hospital (Goyang, Korea). Among them, 130 pts who had both brain MRI and whole body ^{18}F-FDG-PET as initial staging work-up are included in this analysis. **Results:** In the 130 pts, the 5-year cumulative brain metastasis (BM) rate was 39.6% and the 5-year overall survival rate was 53.2%. Among them, 46 received PCI (25 or 30Gy in total) and 84 did not. There was no difference in clinical characteristics such as age (60 v 63 years; $p = 0.140$) and TNM stage (I-II/IIIA/IIIB) (22/28/45% v 24/43/33%; $p = 0.147$). Between the two groups (PCI vs No PCI), there was no significant difference in the 5-year cumulative BM rate (36.7 vs 41.8%, $p = 0.231$) and the 5-year overall survival rate (56.9 vs 51.5%, $p = 0.985$). Subgroup analysis showed PCI tended to decrease the 5-year cumulative BM rate in patients with stage I-IIIA SCLC ($n = 79$) (29.5 vs 41.7%, $p = 0.104$) but not in patients with stage IIIB SCLC ($n = 51$) (46.5 vs 41.3%, $p = 0.876$). **Conclusions:** LS-SCLC pts accurately staged with brain MRI and PET exhibited excellent overall survival with the 5-year survival rates after achieving objective response after CCRT, exceeding 50% regardless of PCI. Considering the risk of neurotoxicity, the role of PCI should be more critically readdressed in this group of LS-SCLC pts with greater potential for long-term survival and even cure.

7580 Poster Session (Board #328), Mon, 8:00 AM-11:30 AM

Phase II trial of single agent amrubicin (A) in patients (pts) with previously treated advanced thymic malignancies (TM). *First Author: Heather A. Wakelee, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA*

Background: There are limited treatment options for pts with TM and chemotherapy efficacy is often restricted by cumulative toxicity such as neuropathy (taxanes) and cardiomyopathy (anthracyclines). This trial investigated single agent amrubicin (A), a third generation anthracycline and topoisomerase II inhibitor with minimal cardiac toxicity, in TM pts. **Methods:** This was an open-label investigator-initiated single drug trial at 2 institutions with overall response rate (RR) as the primary endpoint. Eligible pts had TM (thymoma (T) or thymic carcinoma (TC)) with progressive disease (PD) or relapse after $\geq$ 1 prior chemotherapy regimen, and adequate organ function including left ventricular ejection fraction (LVEF) of $>$ 50%. The initial treatment plan consisted of A at 40 mg/m^2 IV days 1-3 repeated in 21-day cycles with growth factor support. **Results:** 33 pts (14T/19TC) enrolled from 7/2011 to 4/2014: 14 women/19 men; age 30-81 yo; 9 Asian, 1 African-American, 23 White. A high rate of febrile neutropenia (FN) led to an amended starting dose of 35 mg/m^2 days 1-3 of 21-day cycles. In total, 7 pts experienced FN with 1 related death. Other grade 3/4 possibly related events included thrombocytopenia (n = 3), neutropenia (without fever, n = 3), anemia (n = 7), lethargy/fatigue (n = 7), perirectal abscess (n = 2), palmar-plantar erythrodysesthesia (n = 3), syncope (n = 2), venous embolism (n = 2), and 1 pt each with sepsis, oral abscess, pneumonia, UTI, mucositis, chest pain, and epigastric pain. Other toxicities were mild and A was generally well tolerated. No significant changes in LVEF were noted on serial echocardiograms. RR was 18% (n = 6, all partial): 29% (n = 4) in T and 11% (n = 2) in TC. Disease control rate (DCR) at first evaluation was 88% overall (n = 29): 100% (n = 14) in T and 78% (n = 15) in TC. 4 pts had PD or died before first assessment. All but 5 pts received at least 4 cycles, and 17 received 10 or more cycles, with 34 cycles as the highest number to date. 5 pts remain on therapy. **Conclusions:** Amrubicin, at 35 mg/m^2 IV days 1-3 on a 21-day cycle, shows promise as a single agent in pre-treated pts with T and TC with an 18% RR and no unexpected toxicity. Further exploration as a single drug or in combination is warranted. Clinical trial information: NCT01364727.

7581 Poster Session (Board #329), Mon, 8:00 AM-11:30 AM

Somatostatin analogs as mainteinance therapy in heavily pretreated thymic epithelial tumors. *First Author: Giovannella Palmieri, Department of Clinical Medicine and Surgery and Rare Tumors Reference Centre Campania Region, University, Napoli, Italy*

Background: Thymic epithelial tumors are rare neoplasms with a particular biological behavior, treated with a combination of therapeutic strategies such as surgery, chemotherapy, radiotherapy and target agents. No continuation maintenance therapy exists for these rare tumors. An high uptake of indium-labeled octreotide (111In-DTPA-D-Phe1-octreotide) and curative application of somatostatin analogs in thymic tumors have been widely demonstrated. **Methods:** Eighteen patients (nine women and nine men, median age 54.5 years; range 32-78) with advanced thymic tumors (seven patients with stage III; seven with IVa; Four with IVb according to the Masaoka-Koga staging system), histotype sec WHO revised by central review (three AB, two B1, three B2, five B3, three B2/B3, two thymic carcinoma) with a partial response or stable disease to conventional chemotherapeutic regimens platinum or not platinum-based, after performed OctreoScan, were enrolled in this monocentric referral center study. The schedule includes administration of long-acting analog octreotide (30 mg/every 28 days intramuscularly), until progression of disease was documented. Median time to progression and toxicity were evaluated. **Results:** Median follow-up was of 43 months with a median time to progression of 14,5 months (range 77-2). Treatment was generally well tolerated with acceptable toxicity: Grade 1 diarrhea (5 patients), Grade 2 hyperglycemia (4 patients). No patients interrupted treatment because of toxicity. **Conclusions:** The current study indicates that single-agent somatostatin analogs maintenance therapy is a potential treatment strategy for advanced TETs OctreoScan positive which responde to previous conventional chemotherapy. In particular, somatostatin analogs may provide an effective maintenance treatment duration regardless of histotype and stage of disease with an acceptable toxicity and an improved patients'compliance.

7582 Poster Session (Board #330), Mon, 8:00 AM-11:30 AM

Effectiveness of somatostatin analogs plus prednisone in aggressive histotype and advanced stage of thymic epithelial tumors. *First Author: Margaret Ottaviano, Department of Clinical Medicine and Surgery and Rare Tumors Reference Centre Campania Region, University, Naples, Italy*

Background: Thymic epithelial tumors (TETs) are rare neoplasms characterized by histological variability. Efficacy of octreotide/lanreotide with or without prednisone in TETs OctreoScan positive has been widely demonstrated in thymoma, but no clearly in thymic carcinoma. **Methods:** Twelve patients (five men, seven women; median age 47 years; range 27-70) with advanced stage disease according to the Masaoka-Koga staging system (seven with IVa stage; five with IVb stage), and aggressive histotype according to WHO classification, revised by central review (two B2/B3; five B3; one B3/thymic carcinoma; four thymic carcinoma) were enrolled in this monocentric referral study. All the patients showed a progressive disease according to RECIST 1.1 criteria to previous conventional chemotherapeutic regimens platinum or not platinum-based. All the patients performed OctreoScan. The schedule includes administration of long-acting analog octreotide (30 mg/every 28 days intramuscularly) plus prednisone 0.2 mg/kg/day until progression of disease was documented. Median time to progression, overall response rate and toxicity were evaluated. **Results:** The median time to progression was 6 months (range 3-24), the overall response rate was 74.9%, particularly three patients (25%) obtained stable disease; four patients (33.3%) partial response; two patients (16.6%) complete response; three patients (25%) progression disease. One patient with Good Syndrome interrupted treatment after 6 months for infection disease. One patient has been lost to follow-up after 24 months of treatment. One patient died after progression disease for PRCA. Treatment was generally well tolerated with acceptable toxicity: no symptomatic cholelithiasis (1 patient), Grade 1 diarrhea (two patients) hyperglycemia (1 patient). One patient with thymic carcinoma and IV b stage had PS improvement from 2 to 1 sec ECOG, and one patient had complete remission of pericardial and pleural effusion after six months treatment with symptomatic relief. **Conclusions:** Somatostatin analogs plus prednisone is an effective treatment in aggressive histotype and advanced stage disease of TETs.

TPS7583 Poster Session (Board #331a), Mon, 8:00 AM-11:30 AM

ALCHEMIST: a clinical trial platform to bring genomic discovery and molecularly targeted therapies to early-stage lung cancer. *First Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Molecularly targeted therapies, specifically those directed toward epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangement have improved outcomes in a subset of patients with advanced non-small cell lung cancer (NSCLC). However, the role of molecular testing and targeted therapies for earlier stage disease remains unclear. Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is a National Cancer Institute (NCI) sponsored National Clinical Trials Network (NCTN) initiative to address these unanswered questions. **Methods:** ALCHEMIST is a clinical trial platform that currently consists of three integrated protocols: ALCHEMIST Screening (A151216; NCT02194738), ALCHEMIST-EGFR (A081105; NCT02193282), and ALCHEMIST-ALK (E4512; NCT02201992). In ALCHEMIST-Screening, up to 8,000 patients with pathologically confirmed stage IB ($\geq$ 4 cm)-IIIA non-squamous NSCLC will be enrolled either before or after surgical resection. Tumors will be centrally genotyped for *EGFR* mutations and *ALK* rearrangements. Blood and tumor samples will also be collected for advanced genomic analysis at the NCI. Patients with *EGFR* mutations or *ALK* rearrangements will be referred to ALCHEMIST-EGFR or-ALK treatment trials, respectively. All other patients will be followed for relapse and survival. Available biopsies at recurrence will be collected to characterize clonal evolution. In the treatment trials, patients will be randomized to placebo vs. erlotinib or crizotinib after completion of standard adjuvant therapy. Treatment will continue for two years. Both trials are double blind studies with a primary endpoint of overall survival (OS). ALCHEMIST-EGFR will enroll 410 patients, which provides 85% power with one-sided type I error rate of 0.05 to demonstrate an OS hazard ratio (HR) of 0.67 favoring erlotinib. ALCHEMIST-ALK will enroll 378 patients to provide 80% power and one-sided type I error of 0.05 to demonstrate an OS HR of 0.67 favoring crizotinib. ALCHEMIST is currently enrolling patients at over 500 centers nationwide. Additional treatment trials for specific molecular subsets may be added in the future. Clinical trial information: NCT02194738.

TPS7584 Poster Session (Board #331b), Mon, 8:00 AM-11:30 AM

Neoadjuvant erlotinib in stage III NSCLC patients (pts) with activating EGFR mutations (EVENT trial). *First Author: Cengiz Inal, Albert Einstein Coll of Medcn, Bronx, NY*

Background: Results with standard chemoradiotherapy for stage III NSCLC pts have plateaued and systemic relapse remains the biggest challenge. Genomic driven strategies are desperately needed as there is yet to be an approved targeted agent for locally advanced disease. Erlotinib improved objective response rate (ORR) and prolonged progression free survival (PFS) compared with chemotherapy in pts with EGFR-mutated advanced NSCLC. Mediastinal nodal clearance (pN0) after neoadjuvant therapy is a consistent surrogate marker for long term survival.We aim to evaluate rates of pN0 following neoadjuvant erlotinib in stage III NSCLC pts with activating EGFR mutation. **Methods:** 3 out of 55 planned pts have been enrolled in this single arm, open label phase II study. Based on historical data, pN0 rate of $\geq$ 30% will justify further study and the rate of $\leq$ 15% will be considered ineffective. With optimal two-stage design, if $\geq$ 3 out of initial 19 pts have pN0, additional 36 pts will be accrued in the second stage. Neoadjuvant erlotinib will be considered for further studies if pN0 is observed in $\geq$ 12 among total 55 pts. With 80% power and type I error of 0.05, the probability of early stopping at the first stage is 68.4% if the true response rate (TR) is 15% and 13.3% if TR is 30%. Total of 55 pts will ensure that the 95% CI for the estimated TR will be within +/- 15.7% by the end of this study. Stage IIIA/B NSCLC patients with N2 disease, activating EGFR mutations, ECOG PS 0-2, preserved organ function and no prior chemotherapy or radiation are eligible. Pts are treated with neoadjuvant erlotinib 150 mg PO daily for two months and then restaged. Pts with significant clinical down staging and deemed medically fit for surgery will have surgical resection. Pts with non-progressive disease who do not undergo surgery will have mediastinal restaging. Therapy after surgery or mediastinal restaging is at the discretion of the treating physician. The primary objective is to estimate the rate of pN0 after neoadjuvant erlotinib. Secondary objectives include PFS, OS, ORR from neoadjuvant erlotinib, and surgical resection rate. The translational studies in pre and post erlotinib tumor biopsy are also planned. Clinical trial information: NCT01857271. Clinical trial information: NCT01857271.

TPS7585 Poster Session (Board #332a), Mon, 8:00 AM-11:30 AM

NCI 9448: Phase I study of trametinib in combination with chemoradiation for KRAS-mutant non-small cell lung cancer. *First Author: Steven H. Lin, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Concurrent chemoradiotherapy is the standard management approach for unresectable, non-metastatic locally advanced non-small cell lung cancer (NSCLC). However, progress has been slow in making substantial improvements in the outcomes of these patients. Preclinical data suggests that adding molecular targeted drugs affecting specific pathways could enhance radiation effects, and Kras mutated NSCLC may be particularly susceptible for MEK1/2 inhibition for radiation sensitization. This trial tests the safety of combining trametinib (GSK1120212), a potent MEK1/2 inhibitor, with standard carboplatin and paclitaxel chemoradiotherapy, for the treatment of locally advanced NSCLC. **Methods:** This is a multi-center, NCI UM1-sponsored, phase I clinical trial. Patients with unresectable stage II-III NSCLC with Kras mutation who can receive concurrent carboplatin (AUC 2.0) and paclitaxel (50 mg/m2) with once-daily trametinib and 60 Gy radiotherapy delivered in 30 fractions are eligible. Two additional cycles of consolidation chemotherapy (carboplatin AUC 6.0 and paclitaxel 200 mg/m2) are given after completing concurrent chemoradiotherapy. Trametinib is delivered at the starting dose level of 1.0 mg, and Time-to-Event-Continuous Reassessment Method (TiTE-CRM) is used for dose escalation at 4 levels (0.5, 1.0, 1.5, and 2.0 mg). CTCAE v4.0 is used to determine dose-limiting toxicity (DLT), with the Pr(tox) within 70 days at 0.6 for general DLTs, and 0.3 for severe DLTs. Primary objective of the trial is to determine the maximum tolerated dose (MTD) and safety of trametinib as measured by rate of grade 3 or worse non-hematologic toxicities attributed to chemoradiation within 70 days of start of therapy, as well as pharmacokinetic studies. Secondary objectives include response rate, overall survival, patterns of recurrence, dose delay and percentage of dose delivered, and biomarker exploratory endpoints. The maximum number of patients is 30. **Conduct to Date:** The trial was activated October 28, 2013 at MD Anderson, and recently at Ohio State University. So far 7 patients have enrolled on study. Clinical trial information NCT01912625. Clinical trial information: NCT01912625.

TPS7586 Poster Session (Board #332b), Mon, 8:00 AM-11:30 AM

Phase I/II study of tumor-infiltrating lymphocyte (TIL) infusion and low-dose interleukin-2 (IL-2) in patients with advanced malignant pleural mesothelioma (MPM). *First Author: Mark Doherty, Department of Medical Oncology, University College Hospital Galway, Galway, Ireland*

Background: MPM is a disease with poor outcomes, and only modest benefits from existing systemic therapies. Preclinical studies have shown that MPM often contains populations of TILs, and that these can be expanded ex vivo. Therapy using autologous TIL infusions and IL-2 following lymphodepleting chemotherapy has been successfully used in advanced melanoma. The therapeutic potential for TILs in MPM has not yet been explored. **Methods:** This is a single arm, phase I/II study to evaluate the feasibility, safety, and efficacy of TIL therapy for advanced MPM at the Princess Margaret Cancer Centre. Eligibility criteria include: advanced MPM, suitable surgical candidate for TIL harvesting from tumor, ECOG performance status 0-1, adequate organ function, and successful expansion of TILs. TILs are harvested from fresh tumor tissue, evaluated for suitability, and expanded ex-vivo. Patients are treated with a lymphodepleting chemotherapy regimen containing cyclophosphamide (60mg/m^2 x 2 days) and fludarabine (25mg/m^2 x 5 days), followed by infusion of expanded TILs. This is followed by low-dose IL-2 therapy (125000 IU/kg/day subcutaneously) for 2 weeks. The treatment protocol is adapted from that used in melanoma TIL studies, and no dose exploration is planned. The primary objective is determining the feasibility and safety of the regimen. Efficacy as measured by objective response rate (modified RECIST) is a secondary objective. The planned sample size is 10 patients. An informal interim analysis will be performed after 6 patients have been treated to review treatment toxicities and feasibility, given the lack of previous experience with this treatment in MPM. Correlative studies include analysis of peripheral blood mononuclear cells and assessment of persistence of infused TILs. Patients are currently being screened for TIL expansion at the Princess Margaret Cancer Centre.

8000 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

AZD9291, a mutant-selective EGFR inhibitor, as first-line treatment for *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC): Results from a phase 1 expansion cohort. *First Author: Suresh S. Ramalingam, The Winship Cancer Institute of Emory University, Atlanta, GA*

Background: AZD9291 is an orally administered EGFR TK inhibitor with activity against the sensitizing *EGFR* mutations (EGFRm) and the T790M resistance mutation. It has demonstrated anticancer activity in patients with EGFR-TKI pre-treated EGFRm T790M positive advanced NSCLC. **Methods:** Treatment-naïve patients with EGFRm advanced NSCLC received AZD9291 at doses of 80 mg/day or 160 mg/day (sequential cohorts) in the first-in-human phase I study (AURA, NCT01802632). EGFRm status was tested locally at the treating site and/or confirmed by central testing (cobas EGFR mutation test). Salient eligibility included presence of measurable disease, WHO performance status of 0 or 1, and acceptable organ function. Stable brain metastases were permitted. The objective of these cohorts was to investigate safety, tolerability, and anticancer activity of AZD9291 in the first-line EGFRm treatment setting. **Results:** Sixty patients were enrolled (30 each in 80 mg and 160 mg dose cohorts). Patient baseline characteristics: median age 63.5; male 25%; WHO performance status 0.57%, 1.43%; Asian 72%, and white 23%; central mutation test result exon 19 del 37%, L858R 40%, other *EGFR* sensitizing mutations 3%, T790M 8%. At the data-cutoff of 2 December 2014, 52 out of 60 patients remain on study treatment with a median treatment exposure of 260 days and 171 days for 80 mg and 160 mg cohorts, respectively. The objective response rate was 70% (95% CI 57, 81): 80 mg, 60%; 160 mg, 80% and the median progression-free survival (PFS) has not been reached. The disease control rate was 97% (95% CI 89, 100): 80 mg, 93%; 160 mg, 100%. Overall, the 3- and 6-month PFS rates were 93% and 87%, respectively (7/60 events, 12% mature). Grade ≥ 3 AEs were reported by 33% of patients. The incidences of grade 3 skin rash and diarrhea for the two dose cohorts combined were 1/60 and 2/60, respectively. **Conclusions:** AZD9291 has a manageable tolerability profile and is associated with promising anticancer activity as first-line treatment of EGFRm advanced NSCLC. A Phase III study to compare AZD9291 to erlotinib or gefitinib has been initiated (NCT02296125). Clinical trial information: NCT01802632.

8001 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts). *First Author: Lecia V. Sequist, Massachusetts General Hospital, Boston, MA*

Background: Rociletinib is an oral inhibitor of mutant EGFR, including the T790M resistance mutation. We reported robust activity in T790M positive pts identified by tumor genotyping treated at 500mg-1000mg BID (active doses) [NCT01526928]. We now present data from the pt subset with T790M detected by plasma genotyping. **Methods:** For the overall phase 1/2 study, pts had EGFR-mutant NSCLC and treatment with ≥ 1 EGFR inhibitor, ECOG PS 0-1. Brain metastases were allowed. In phase 2, T790M pos by central tumor genotyping was required. Plasma EGFR status was assessed by BEAMing (Sysmex), a quantitative assay using emulsion PCR then flow cytometry. **Results:** 345 pts were enrolled at active doses, median age 62 yrs, 66% female, 69% ECOG 1, 87% from US sites, median prior therapies 3 (45% ≥ 2 prior TKIs). Response data are available for 219 with tissue genotyping and 113 with plasma genotyping. The RECIST objective response rate (ORR) was ~48% in T790M pos pts, regardless of genotyping method. ORR was 33-36% among T790M neg pts, (see Table). There were 17 pts T790M pos in plasma but with neg (9) or failed (8) tissue genotyping, and 5/17 responded. There were 16 pts T790M pos in tissue but with neg plasma genotyping and 6/16 responded. 3/8 who were neg by both methods responded. The majority of T790M negative responders were on an EGFR TKI immediately before rociletinib (10/12 tissue and 10/10 plasma). Serial plasma data typically showed a decrease in the levels of T790M over time. Related all grade AEs in ≥ 15% patients were: hyperglycemia (40%), diarrhea (28%), nausea (23%), fatigue (21%), decreased appetite (17%). **Conclusions:** Rociletinib is associated with durable response and is well tolerated in pts with EGFR mutant T790Mpos NSCLC. One-third of T790M neg pts also respond, which cannot be explained by retreatment effect. Serial plasma data shows T790M decrease in most pts, including non-responders, suggesting T790M is not always the dominant growth driver. Plasma genotyping by BEAMing may be a complementary method to select patients. Clinical trial information: NCT01526928.

Table: Outcome by genotype/ biopsy type		T790M +	T790M -
Tissue genotype	ORR (%)	ORR: 91/186 (49)	12/33 (36)
	DoR (days)	1-394+	1-283+
Plasma genotype	ORR	40/83 (48)	10/30 (33)
	DoR	1-394+	74-329

8002 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following platinum-based chemotherapy: Overall survival (OS) analysis from the global phase III trial LUX-Lung 8 (LL8). *First Author: Jean-Charles Soria, Gustave Roussy Cancer Campus and University Paris-Sud, Paris, France*

Background: Treatment options for pts with advanced SCC of the lung progressing after platinum-based chemotherapy are limited. Overexpression of EGFR, ErbB receptors and the dysregulation of their downstream pathways are implicated in SCC pathobiology. Primary analysis of LL8 (2nd line A, an irreversible ErbB family blocker vs E, a reversible EGFR tyrosine kinase inhibitor [TKI; only TKI approved in this setting], in pts with SCC of the lung) showed significantly better progression-free survival (PFS) with A. OS and updated PFS are reported here. **Methods:** Pts with stage IIIB/IV disease were randomized 1:1 to receive A (40 mg/day) or E (150 mg/day) until disease progression. Primary endpoint: PFS; key secondary endpoint: OS. Other endpoints: objective response (ORR), disease control (DCR), patient reported outcomes and safety. 632 events and a sample size of 800 pts was needed to detect a HR of 0.8 with 80% power for OS. **Results:** OS was significantly better with A (n = 398) vs E (n = 397), with a 19% reduced risk of death (median 7.9 vs 6.8 mos; HR [95% CI] 0.81 [0.69–0.95]; p = 0.008). Significant differences in OS were seen at 6 (63.6 vs 54.6%; p = 0.010), 12 (36.4 vs 28.2%; p = 0.016) and 18 (22.0 vs 14.4%; p = 0.013) mos. PFS (median 2.6 vs 1.9 mos; HR [95% CI] 0.81 [0.69–0.96]; p = 0.010), ORR (5.5 vs 2.8%; p = 0.055) and DCR (50.5 vs 39.5%; p = 0.002) were all better for A vs E. More pts had improved global health status/quality of life (35.7 vs 28.3%; p = 0.041), cough (43.4 vs 35.2%; p = 0.029) and dyspnea (51.3 vs 44.1%; p = 0.061) with A vs E. Adverse event (AE) profiles were comparable (G ≥ 3 AEs: 57.1 and 57.5% for A vs E) with a higher incidence of drug-related G3/4 diarrhea (9.9/0.5 vs 2.3/0.3%), G3 stomatitis (4.1 vs 0%) with A and a higher incidence of G3 rash/acne with E (5.9 vs 10.4%). Preliminary data from FoundationOne analysis of tumor blocks will be shown. **Conclusions:** A significantly improved OS vs E in pts with SCC of the lung in a 2nd line setting. PFS and DCR were also significantly better. With a manageable AE profile, added QoL benefit, and symptom control seen in LL8, A should be preferred over E for these pts. Clinical trial information: NCT01523587.

8003 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Cabozantinib (C), erlotinib (E) or the combination (E+C) as second- or third-line therapy in patients with EGFR wild-type (wt) non-small cell lung cancer (NSCLC): A randomized phase 2 trial of the ECOG-ACRIN Cancer Research Group (E1512). *First Author: Joel W. Neal, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA*

Background: Cabozantinib (C) is a small molecule inhibitor of multiple receptor tyrosine kinases, including MET, VEGFR2 & RET. MET is involved in tumor differentiation & VEGFR2 is a mediator of angiogenesis. Erlotinib (E) is FDA approved for the treatment of NSCLC. **Methods:** The primary objective of this randomized phase II study was to compare progression-free survival (PFS) of patients (pts) treated with E vs. C, & E vs E+C; each comparison had 91% power to detect a PFS hazard ratio (HR) of 0.5 with a 1-sided 0.10-level test stratified on prior number of therapies & ECOG PS. Secondary objectives included overall survival (OS), RECIST 1.1 response & CTCAE v4 toxicity. Pts were selected with previously treated (1-2 regimens) metastatic non-squamous EGFR wt NSCLC. Submission of archival tissue for central MET IHC testing was required. Oral daily dosing was: E-150 mg; C-60 mg; E+C-150 mg E, 40 mg C. Imaging was performed every 8 weeks. Pts optionally crossed over to E+C following progression on E or C. **Results:** One hundred and twenty-five pts were enrolled, of which 115 were eligible and treated (E, n = 39; C, n = 39; E+C, n = 37). Pt characteristics were balanced between arms except for lower rate of brain mets history on E (p = 0.02). Median follow up is 8.5 m. Compared with E (median 1.9 m), PFS was significantly improved on C (3.9 m, HR 0.33, p = 0.0002, 80% CI 0.22-0.49) and E+C (4.1 m, HR 0.31, p = 0.0002, 80% CI 0.21-0.46). Similarly, compared with E (median 4.0 m), OS was significantly improved on C (HR 0.52, p = 0.02) and E+C arm HR 0.50, p = 0.02). Grade 3-4 treatment-related hypertension & mucositis were higher on C and grade 3-4 diarrhea was higher on E+C. Overall worst grade toxicities were also significantly higher on C and E+C. MET IHC results were available on 88 patients from the primary analysis & 85% were positive (1-3+ membrane or cytoplasm staining with MET4 antibody). There was no correlation between MET status and PFS. **Conclusions:** C & C+E significantly improved PFS over E alone in pts with EGFR wt NSCLC. Cabozantinib-based regimens are promising for further investigation in this patient population. Funded by ECOG-ACRIN and NCI Contract No. HHSN261200800001E. Clinical trial information: NCT01708954.

8004 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Randomized phase III study of nedaplatin (N) plus docetaxel (D) versus cisplatin (C) plus D for advanced or relapsed squamous cell carcinoma of the lung (SqLC): WJOG5208L. *First Author: Takehito Shukuya, Department of Respiratory Medicine, Juntendo University, Tokyo, Japan*

Background: N is a second-generation platinum compound with lower nausea/vomiting and nephrotoxicity than C. N plus D (ND) showed a promising efficacy with acceptable toxicity for advanced SqLC in the previous phase II study. **Methods:** Eligible patients (pts) were those with pathologically proven SqLC with stage IIIB/IV or postoperative recurrence, aged 20-74 and ECOG PS 0-1. Pts were randomized 1:1 to ND (N 100 mg/m^2 and D 60mg/m^2 intravenous, q3w, up to 6 cycles) or C plus D (CD) (C 80 mg/m^2 and D 60mg/m^2 intravenous, q3w, up to 6 cycles) according to stage, gender and institution. The primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS), response rate (RR) and adverse events (AEs). Target sample size of 350 provided 90% statistical power to detect a hazard ratio of 0.71 with *one-sided* type I error of 0.05. **Results:** Between July 2009 and July 2012, 355 pts were randomized. Of 349 for efficacy analysis (ND 177; CD 172), baseline characteristics were well-balanced between two arms. ND had a significantly longer OS ($p = 0.037$, *one-sided stratified log-rank test*). The OS HR was 0.81 (90%CI, 0.67-0.98) with a median OS of 13.6 months [m] for ND and 11.4 for CD. ND had a longer PFS ($p = 0.050$) with a HR of 0.83 (0.69-1.00) and a median PFS of 4.9 m in ND and 4.5 in CD. RR was 54.5% in ND vs 52.9% in CD ($p = 0.829$). Grade 3 or higher AEs of nausea (4.0% vs 14.3%), fatigue (3.4% vs 10.9%), hyponatremia (13.6% vs 30.3%) and hypokalemia (2.3% vs 8.6%) are more frequent in CD. Grade 3 or higher AEs of neutrophils (82.5% vs 70.3%) and platelets (9.0% vs 0.0%) are more frequent in ND, but there was no difference in grade 3 or higher febrile neutropenia (13.6% vs 15.4%). Treatment related deaths occurred in 4 and 3 pts in ND and CD, respectively. **Conclusions:** ND showed a significantly longer OS as compared to CD with different toxicity profile. ND will be considered as a new standard treatment for advanced or relapsed SqLC. Clinical trial information: UMIN000002015.

8005 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Whole brain radiotherapy for brain metastases from non-small lung cancer: Quality of life (QoL) and overall survival (OS) results from the UK Medical Research Council QUARTZ randomised clinical trial (ISRCTN 3826061). *First Author: Paula Mary Mulvenna, Department of Clinical Oncology, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom*

Background: Brain metastases affect up to 40% of patients with non-small cell lung cancer (NSCLC), and for inoperable cases whole brain radiotherapy (WBRT) and dexamethasone is standard treatment. However there are no randomised clinical trials to show whether WBRT improves either QoL or survival. **Methods:** A phase III randomised non-inferiority trial with a primary outcome measure of quality adjusted life years (QALYs). Patients with brain metastases from NSCLC (not suitable for resection or stereotactic radiotherapy) were randomly allocated to either optimal supportive care, including dexamethasone, plus WBRT 20 Gy/5f (OSC+WBRT) or OSC alone. QALYs were generated from OS and patients' weekly completion of the EQ-5D questionnaire. OSC alone was considered non-inferior to OSC+WBRT if not greater than 7 QALY days worse (80% power and a 1-sided 5% significance level required 534 patients.) Secondary outcome measures include sub-group analyses to identify/validate predictive classifications. **Results:** From 2007-2014 538 patients were recruited from 69 UK and 3 Australian centres. Baseline characteristics were balanced between arms and reflect everyday clinical practice: male 58%, median age 66 years (range 38 – 85), Karnofsky performance status < 70 38%, 54% had extracranial metastases, 30% had a solitary brain metastasis and 59% diagnosed with brain metastases within 28 days of randomisation. By January 2015 522/538 patients had died. There was no significant difference in OS from randomisation (hazard ratio 1.05 (95% CI 0.89 – 1.26) median survival OSC+WBRT v OSC (65 v 57 days)), overall QoL or steroid use between the 2 groups. The difference between the mean QALYs was -1.9 days (OSC+WBRT 43.3 v OSC 41.4 QALY days), two-sided 90% confidence interval for difference -9.1 to +6.6 QALY days. **Conclusions:** This is the only large randomised trial evaluating the utility of WBRT in this disease. Although the results include the pre-specified non-inferiority margin, the estimate of the difference in QALYs suggests WBRT provides no additional clinically significant benefit for this group of patients. Clinical trial information: 3826061.

8006 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Interim results of a phase II study of the BRAF inhibitor (BRAFi) dabrafenib (D) in combination with the MEK inhibitor trametinib (T) in patients (pts) with *BRAF* V600E mutated (mut) metastatic non-small cell lung cancer (NSCLC). *First Author: David Planchard, Gustave Roussy, Villejuif, France*

Background: In 78 *BRAF* V600E mut NSCLC pts, single agent D induced an overall response rate (ORR) of 32%. The combination of D and T (DT) has demonstrated significant improvements in efficacy compared with BRAFi monotherapy in *BRAF*V600 mut metastatic melanoma. Here, we report interim safety (33 pts) and efficacy (24 pts) data for NSCLC pts enrolled in this phase II DT study. **Methods:** This single-arm, 2-stage, phase II study was in advanced *BRAF*V600E mut NSCLC pts who failed at least 1 line of chemotherapy. D was dosed at 150 mg orally twice daily and T at 2 mg once daily. The primary endpoint was investigator-assessed ORR per RECIST 1.1 criteria. A minimum response rate (≥ 6 out of first 20 pts) was required to continue into the second stage. **Results:** Median age of 33 pts was 66 yrs (range 49–88 yrs). Most pts were female (64%), White (82%), former smokers (73%), and had adenocarcinoma (88%). Twenty-seven pts (82%) remain on therapy, and 6 have stopped (4 with disease progression, 2 due to adverse events [AEs]). Twenty-four pts were evaluable for efficacy (confirmed response). ORR was 63% ($n = 15$, partial responses; 95%CI 40.6%–81.2%), with responses being observed by the first scan (6 weeks) and disease control rate (DCR) for > 12 weeks was 88% (95% CI 67.6%–97.3%). Independent review response rates were consistent with investigator-assessed response. Most common ($> 20\%$) AEs were pyrexia, diarrhea, nausea, vomiting, decreased appetite, asthenia, cough, peripheral edema, and rash, mostly grade 1 or 2. Grade 3 AEs occurred in 39% of pts; most frequent were hyponatremia (6%), neutropenia (6%), and dehydration (6%). One pt (3%) had a grade 4 AE (hyponatremia) and 1 pt (3%) had a fatal serious AE of pleural effusion. AEs leading to a dose reduction were reported in 9 pts (27%). Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 2 pts (6%). **Conclusions:** DT in *BRAF* V600E mut advanced NSCLC pts shows early antitumor activity with an ORR of 63% and a manageable safety profile. The study met the criteria for progression to the second stage. Clinical trial information: NCT01336634.

8007 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase II study of cabozantinib for patients with advanced *RET*-rearranged lung cancers. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: RET rearrangements are found in 1-2% of non-small cell lung cancers and are drivers of growth in vitro and in vivo. Cabozantinib is a multi-tyrosine kinase inhibitor with activity against RET. **Methods:** This is a single-institution, open-label, phase II trial. Eligible patients (pts) had stage IV *RET*-rearranged lung cancer, KPS $> 70\%$, and measurable disease (RECIST v1.1). Cabozantinib was administered at 60 mg daily until progression or unacceptable toxicity. Study endpoints included response at 12 weeks, objective response, progression-free survival (PFS), overall survival (OS), and toxicity. Simon two-stage minimax design: H_0 10% vs H_A 30% overall response rate (ORR). Five responses of a maximum of 25 patients were required to meet the primary endpoint. **Results:** Twenty pts were treated. The median age was 56 (range 38-80 years). All pts had adenocarcinoma and 60% (12/20) were female. The median number of prior chemotherapy lines was 1 (range 0-5). There were no complete responses. The rate of any partial response (PR) at 12 weeks was 33% (5/15, 95% CI 12-62%). ORR was 28% (5/18, 95% CI 10-53%) with 5 confirmed PRs. Stable disease rate was 72% (13/18, 95% CI 51-93%) including 2 unconfirmed PRs. Median PFS was 7 mo (95% CI 3 mo-not reached). Median OS was not reached. Toxicities were mostly grade 1 or 2 and included fatigue, diarrhea, palmar-plantar erythrodysesthesia, transaminitis, and thrombocytopenia. At least 1 dose reduction was required in 60% (12/20) of pts. Eight patients remain on treatment between 1 and 23 mo. **Conclusions:** Cabozantinib is active in patients with *RET*-rearranged lung cancers and responses can be durable. This study has met its primary endpoint. A larger, confirmatory, multi-center trial is now warranted. Clinical trial information: NCT01639508.

8008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Efficacy and safety of the ALK inhibitor alectinib in *ALK*+ non-small-cell lung cancer (NSCLC) patients who have failed prior crizotinib: An open-label, single-arm, global phase 2 study (NP28673). *First Author: Sai-Hong Ignatius Ou, Chao Family Comp Cancer Ctr UC Irvine Medcl Ctr, Orange, CA*

Background: The ALK inhibitor crizotinib is approved for patients (pts) with *ALK*-rearranged (*ALK*+) NSCLC, but most pts progress within a year and CNS progression is common. The NP28673 study (NCT01801111) investigated the efficacy and safety of alectinib, a highly selective, CNS-active ALK inhibitor, in *ALK*+ NSCLC pts who had progressed on crizotinib. **Methods:** Eligible pts (≥ 18 yrs; locally advanced or metastatic *ALK*+ NSCLC [by FDA-approved FISH test]; failed on/intolerant to crizotinib) received alectinib 600mg p.o. BID until progression, death or withdrawal. Crizotinib was the only prior ALK inhibitor permitted. Primary endpoint was objective response rate (ORR) by independent review committee (IRC) using RECIST v1.1. Secondary endpoints included ORR by investigator; duration of response (DOR); CNS ORR and DOR; progression-free survival (PFS); disease control rate (DCR), CNS progression rate, overall survival, and safety. **Results:** 138 pts from 16 countries were enrolled by the 18 Aug 2014 cut-off. Median age 52 yrs; 80% had prior chemo; 60% had baseline CNS mets (60/83 treated). Median follow-up was 30 wks. In the response-evaluable population assessed by IRC (122 pts with measurable disease at baseline), ORR was 49.2% (95% CI 40.0–58.4; all PRs); DCR was 79.5% (95% CI 71.3–86.3). For patients with prior chemo and crizotinib (n = 96), ORR was 43.8% (95% CI 33.6–54.3); DCR was 78.1% (95% CI 68.5–85.9). For patients with baseline measurable CNS disease (n = 34), IRC-assessed CNS ORR was 55.9% (95% CI 37.9–72.8), including five CRs. Updated ORR, DOR and PFS data will be presented. Overall, 27.5% of pts had grade 3–5 adverse events (AEs), most commonly dyspnea (3.6%) and pulmonary embolism (2.2%); low rates of dose interruptions (19.6%), reductions (8.7%), and withdrawals (8.0%) due to AEs were seen. **Conclusions:** Alectinib was well tolerated and achieved a robust treatment response, including excellent intracranial activity, in *ALK*+ NSCLC pts who had progressed on crizotinib; most had also failed prior chemo and had CNS mets. A phase 3 trial of first-line alectinib vs crizotinib and an expanded access program are ongoing. Clinical trial information: NCT01801111.

8009 Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC). *First Author: David R. Spigel, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: Treatment options are limited for patients (pts) with advanced SQ NSCLC who fail platinum-based doublet chemotherapy (PT-DC). We report results of a randomized, open-label, global phase III study of NIVO, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, vs DOC in pts with SQ NSCLC and with disease progression (PD) during/after one prior PT-DC regimen. **Methods:** Pts (N = 272) were randomized 1:1 to receive NIVO 3 mg/kg (n = 135) Q2W or DOC 75 mg/m^2(n = 137) Q3W until PD, discontinuation due to toxicity, or other reasons. The primary objective was overall survival (OS). Secondary objectives included investigator-assessed objective response rate (ORR; RECIST v1.1), progression-free survival (PFS), efficacy by PD-L1 expression (PD-L1 testing not required for enrollment), quality of life, and safety. **Results:** Superior OS was observed with NIVO vs DOC (HR = 0.59; 95% CI: 0.44, 0.79; p = 0.00025). NIVO improved PFS vs DOC (HR = 0.62; 95% CI: 0.47, 0.81; p = 0.0004). ORR was 20% (27/135) for NIVO and 9% (12/137) for DOC (p = 0.0083). OS HRs favored NIVO regardless of PD-L1 expression (**Table**). Grade 3–4 drug-related AEs occurred in 7% (9/131) of NIVO and 55% (71/129) of DOC pts. No deaths were related to NIVO vs 3 DOC-related deaths. **Conclusions:** CheckMate 017 met its primary objective, demonstrating superior OS of NIVO vs DOC in pts with advanced, previously treated SQ NSCLC and demonstrated PFS and ORR superiority. Tumor PD-L1 status was neither prognostic nor predictive for efficacy endpoints. The safety profile of NIVO 3 mg/kg Q2W is acceptable and favorable vs DOC. NIVO represents a significant improvement in second-line therapy for SQ NSCLC. Clinical trial information: NCT01642004.

	NIVO (n = 135)	DOC (n = 137)
mOS, mo (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
1-yr OS, % (95% CI)	42 (34, 50)	24 (17, 31)
Median duration of response, mo (range)	Not Reached (2.9–20.5+)	8.4 (1.4+–15.2+)
mPFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)
1-yr PFS, % (95% CI)	21 (14, 28)	6 (3, 12)

PD-1 expression	NIVO (n)	DOC (n)	OS HR (95% CI)
≥ 1%	63	56	0.69 (0.45, 1.05)
< 1%	54	52	0.58 (0.37, 0.92)
≥ 5%	42	39	0.53 (0.31, 0.89)
< 5%	75	69	0.70 (0.47, 1.02)
≥ 10%	36	33	0.50 (0.28, 0.89)
< 10%	81	75	0.70 (0.48, 1.01)

8010 Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR). *First Author: Alexander I. Spira, Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax, VA*

Background: MPDL3280A (anti-PDL1) has demonstrated promising response rates in NSCLC that correlated with PD-L1 expression on tumor-infiltrating immune cells (IC) and/or tumor cells (TC) (Horn et al, ASCO 2015). **Methods:** Previously treatedNSCLC patients (pts) were stratified by PD-L1 IC status, histology and prior lines of therapy and randomized to 1200 mg IV q3w MPDL3280A (M) or 75 mg/m^2 IV q3w docetaxel (D). PD-L1 expression was centrally evaluated by IHC using the SP142 antibody assay. Pts were scored as TC0, 1, 2 or 3 and IC0, 1, 2 or 3. The primary endpoint was OS (data cutoff, January 30, 2015; median follow-up, 12 mo). **Results:** 287 pts were randomized. In this interim analysis, improved efficacy was observed with increasing PD-L1 expression (e.g., OS HR, 0.47; PFS HR, 0.56 and ORR, 38% vs 13% in TC3 or IC3 pts), while pts with the lowest PD-L1 levels (TC0 and IC0) did not appear to benefit from M (OS HR, 1.22; see table). ITT OS HR was 0.78. Safety was evaluable for 277 pts. Despite a longer median treatment duration for M (3.6 vs 2.1 mo for D), fewer pts receiving M (43%) vs D (56%) experienced Gr ≥ 3 AEs. There were no unexpected toxicities. **Conclusions:** This is the first randomized study in non-squamous and squamous NSCLC to demonstrate that inhibition of the PD-L1/PD-1 pathway may lead to improved survival. Furthermore, these data showed that PD-L1 biomarker selection, using a highly sensitive and specific IHC assay measuring PD-L1 on both TC and IC, can identify both pts most likely to derive improved OS, PFS and ORR and pts unlikely to benefit vs standard of care (NCT01903993). A second randomized study in this pt population is ongoing. Clinical trial information: NCT01903993.

Efficacy.

	TC3 or IC3		TC2/3 or IC2/3		TC1/2/3 or IC1/2/3		TC0 and IC0		ITT	
	M	D	M	D	M	D	M	D	M	D
n =	24	23	50	55	93	102	51	41	144	143
OS										
Median, mo	NR	11.1	13	7.4	NR	9.1	9.7	9.7	11.4	9.5
HR[a] 95% CI	0.47 0.20-1.11		0.56 0.33-0.95		0.63 0.42-0.95		1.22 0.69-2.14		0.78 0.59-1.03	
PFS										
Median, mo	9.7	3.9	4.0	2.8	3.3	3.0	1.9	4.1	2.8	3.4
HR 95% CI	0.56 0.28-1.11		0.70 0.45-1.08		0.87 0.63-1.20		1.15 0.72-1.82		0.96 0.76-1.20	
ORR, % (confirmed)	38	13	22	15	18	18	8	10	15	15

NR, not reached. [a]Stratified HR for ITT and unstratified HR for subgroups.

8011 Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Phase 1 study of pembrolizumab (pembro; MK-3475) plus ipilimumab (IPI) as second-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohort D. *First Author: Amita Patnaik, START, San Antonio, TX*

Background: Pembro is a potent anti–PD-1 monoclonal antibody. IPI, an anti–CTLA-4 antibody, has shown activity in advanced NSCLC. In melanoma, combined anti–PD-1 and anti–CTLA-4 treatment has shown robust efficacy and manageable toxicity. We report interim results from a phase 1 study evaluating pembro + IPI in patients (pts) with recurrent NSCLC. **Methods:** Pts with stage IIIB/IV NSCLC that recurred after ≤ 2 prior regimens received pembro + IPI every 3 wk for 4 cycles followed by maintenance pembro. Based on emerging data from the nivolumab + IPI advanced NSCLC study, doses were reduced from 10 mg/kg to 2 mg/kg for pembro and from 3 mg/kg to 1 mg/kg for IPI). Primary end point was safety and incidence of dose-limiting toxicities (DLTs) in the first 3 wk of dosing. Response was assessed every 6 wk per RECIST 1.1 by investigator review. **Results:** As of Dec 2014,17 pts were enrolled: 3 at pembro 10 mg/kg + IPI 3 mg/kg, 3 at pembro 10 mg/kg + IPI 1 mg/kg, and 11 at pembro 2 mg/kg + IPI 1 mg/kg. No DLTs or dose modifications were reported for the 15 pts treated at the time of analysis. 10 pts experienced drug-related AEs (DRAEs); none led to discontinuation or death. There were 2 gr 3 DRAEs, both rash. Gr 2 DRAEs were diarrhea and vomiting (n = 2 each) and chills, cough, decreased appetite, decreased weight, dehydration, depression, dysphonia, fatigue, myalgia, pruritus, and pyrexia (n = 1 each). Responses were seen in all dose groups among the 11 pts on treatment for ≥ 6 wk at the time of analysis, including 1 CR (9%) and 5 PRs (45%) (Table); all pts achieved disease control. 12 pts remain on treatment (range, 6 + to 26 + wk); 3 pts discontinued for PD. **Conclusions:** Preliminary data from KEYNOTE-021 cohort D demonstrate an acceptable toxicity profile and robust antitumor activity for pembro + IPI in pts with recurrent NSCLC.The use of lower pembro and IPI doses did not appear to negatively impact efficacy. Clinical trial information: NCT02039674.

	Pembro 10 + IPI 3 n = 3	Pembro 10 + IPI 1 n = 3	Pembro 2 + IPI 1 n = 5	Total n = 11
CR[a]	1 (33%)	0	0	1 (9%)
PR[a]	0	2 (67%)	3 (60%)	5 (45%)
SD ≥6 wk	2 (67%)	1 (33%)	2 (40%)	5 (45%)
ORR (CR+PR)[a]	1 (33%)	2 (67%)	3 (60%)	6 (55%)
Disease control rate (CR+PR+SD ≥6 wk)[a]	3 (100%)	3 (100%)	5 (100%)	11 (100%)

[a]RECIST v1.1 confirmed + unconfirmed.

8012 Clinical Science Symposium, Sun, 4:30 PM-6:00 PM

Clinical correlation and frequency of programmed death ligand-1 (PD-L1) expression in EGFR-mutant and ALK-rearranged non-small cell lung cancer (NSCLC). *First Author: Justin F. Gainor, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: PD-L1 expression has recently been associated with response to PD-1 blockade. Given recent clinical interest in combining PD-1/PD-L1 inhibitors with EGFR and ALK tyrosine kinase inhibitors (TKIs), we evaluated PD-L1 expression patterns and clinical outcomes in EGFR-mutant and ALK-positive patients (pts). **Methods:** PD-L1 (Clone E1L3N, Cell Signaling Technologies) and CD8 immunohistochemistry were performed on biopsy and resection specimens from pts with metastatic NSCLC. Membranous expression of PD-L1 in > 5% tumor cells was defined as positive. CD8+ tumor infiltrating lymphocytes (TILs) were evaluated using a 4-tier grading system (0-3). **Results:** We evaluated PD-L1 expression and CD8+ TILs in pts with metastatic, EGFR-mutant (N = 68) and ALK-positive (N = 28) NSCLC (Table). Median progression-free survival (mPFS) on EGFR TKIs was similar between PD-L1(+) and PD-L1(-) pts at baseline (6.7 vs. 13.2 months; $P = 0.08$), as was overall survival (mOS; 31.8 vs. 35.63 months; $P = 0.307$). mPFS on ALK TKIs was similar in PD-L1(+) and PD-L1(-) pts at baseline (5.6 vs. 11.1 months; $P = 0.28$), but mOS was shorter among PD-L1(+) pts (26.5 vs. 51.6 months; $P = 0.045$). To evaluate whether targeted therapy affects PD-L1 expression, we also compared pre- and post-TKI biopsies in each cohort. Among individual EGFR-mutant pts with paired, pre- and post-TKI biopsies (N = 58), PD-L1 expression levels varied between biopsies in 13 (22%) pts. Among individual ALK-positive pts with pre- and post-TKI biopsies (N = 8), PD-L1 expression levels varied between biopsies in 2 (25%) pts. **Conclusions:** EGFR-mutant and ALK-positive lung cancers may express PD-L1 and demonstrate CD8+ TILs. Expression is dynamic in a subset of pts with changes in PD-L1 expression and immune infiltrates observed over time and/or following treatment.

	EGFR Mutant			ALK+		
	Pre-TKI (%)	Post-TKI (%)	p	Pre-TKI (%)	Post-TKI (%)	p
PD-L1(+)	9/62 (15)	16/64 (25)	0.181	11/21 (52)	3/14 (21)	0.089
CD8+ TILS (2-3+)	12/62 (19)	13/65 (20)	1.000	6/18 (33)	0/14 (0)	0.024
PD-L1(+) and CD8+ TILs (2-3+)	3/61(5)	8/64 (13)	0.207	3/18 (17)	0/14 (0)	0.238

8013 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

First-in-human phase I study of EGF816, a third generation, mutant-selective EGFR tyrosine kinase inhibitor, in advanced non-small cell lung cancer (NSCLC) harboring T790M. *First Author: Daniel Shao-Weng Tan, National Cancer Centre Singapore, Singapore, Singapore*

Background: The emergence of T790M resistance mutations (mt) occurs in up to 50% of patients (pt) with NSCLC harboring a sensitizing EGFR mt treated with erlotinib or gefitinib. EGF816 is a covalent, irreversible, EGFR TKI that has nanomolar inhibitory potency against activating mt (L858R, ex19del) and T790M mt, with up to 60-fold selectivity over wild type (wt) EGFR in vitro. **Methods:** This multicenter, dose escalation study to determine the safety, tolerability and antitumor activity of EGF816, enrolled NSCLC pts with locally or centrally confirmed T790M status. Oral EGF816 was administered on a continuous 28-day schedule. Dose escalation started from 75 mg QD and was guided by an adaptive Bayesian logistic regression model to determine the maximum tolerated dose. Paired tumor biopsies were performed to evaluate pharmacodynamics. NCT02108964. **Results:** As of 26 Jan 2015, 57 pts have been treated (51 capsules, CAP; 6 tablets, TAB) across 6 cohorts (75, 150, 225, 300, and 350 mg for CAP; 225 mg for TAB). At the 4 Dec 2014 cutoff, 40 pts were evaluable for safety, median age 58.5y (range 34–76), 48% male and 80% East Asian. 2/6 pts experienced DLT at 350 mg (rash, n = 2; acute renal injury, n = 1). The most common adverse events (AE) regardless of study drug relationship were diarrhea (25%), stomatitis (22.5%), rash (17.5%) and pruritus (15%). The most common Grade 3/4 drug-related AE was rash (5%). RECIST responses and reduced pEGFR were observed at all dose levels. Amongst 22 evaluable pts, including 1 with *de novo* T790M mt, ORR (including unconfirmed responses) and disease control rate was 54.5% and 86.4% respectively. Only 1 pt experienced progressive disease at first evaluation – repeat testing revealed the tumor to be EGFR wt. PK shows rapid absorption with a median T_{max} of 3h and dose-proportional increases in C_{max} and $AUC_{(0\text{-}tau)}$ observed after single and multiple dosing. **Conclusions:** EGF816 is well tolerated with a manageable safety profile and antitumor activity against T790M mt NSCLC across all dose levels examined. Further study is ongoing to establish the optimal dose range to maximize therapeutic potential and facilitate future combinations. Clinical trial information: NCT02108964.

8014 Poster Discussion Session; Displayed in Poster Session (Board #336), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

ASP8273, a mutant-selective irreversible EGFR inhibitor in patients (pts) with NSCLC harboring EGFR activating mutations: Preliminary results of first-in-human phase I study in Japan. *First Author: Yasushi Goto, National Cancer Center Hospital, Tokyo, Japan*

Background: ASP8273 is a small molecule, irreversible tyrosine kinase inhibitor (TKI) that inhibits the kinase activity of EGFR activating mutations and T790M resistance mutation, with higher potency than wild type EGFR. **Methods:** NSCLC pts previously treated with at least an EGFR-TKI were enrolled into this open-label Phase I/II study which consists of a dose escalation and response expansion cohorts followed by the P2 at the RP2D. ASP8273 was administered orally once daily. All pts were assessed for AEs, PK and anti-tumor activity. In each dose-escalation cohort at least 3 pts were enrolled regardless of T790M status and in response expansion cohorts only pts with T790M were enrolled (NCT02192697). **Results:** As of 14 Nov. 2014, 30 Japanese pts were enrolled across 7 dose levels (25 - 600 mg) in the dose-escalation cohorts and 15 pts were enrolled in the response expansion cohorts at 4 dose levels (100 - 400 mg). Demographics of the pts were median age 65 yrs, 73% female, 62% ECOG PS1 and 51% received immediate prior EGFR-TKI. T790M status was 49% positive, 13% negative and 38% unknown, respectively. Most common AEs were diarrhea (56%), nausea (31%), vomiting (31%) and platelet count decreased (31%). A few events of rash (9%), QTc prolongation (7%), ILD-like events (2%) and no hyperglycemia have been reported. 9 DLTs were reported at doses of 400 – 600 mg (3 diarrhea, 2 colitis, 1 biliary tract infection, 2 nausea and 1 hyponatremia). Based on these safety findings, MTD was determined to be 400 mg. Median AUC and C_{max} after single- and multiple-dose of ASP8273 were increased with dose, respectively. RECIST responses were observed in pts enrolled in ≥ 100 mg. 50% (18/36) of all evaluable pts and 80% (12/15) pts with T790M have achieved PRs (includes confirmed and unconfirmed PRs). 300 mg once daily was chosen as RP2D based on the available safety, PK and anti-tumor activity data. **Conclusions:** ASP8273 under MTD has demonstrated anti-tumor activity in NSCLC pts with tumors harboring both EGFR activating mutations and T790M resistance mutation. The phase 2 part of this study will further investigate the clinical activity of ASP8273 at the RP2D in pts with T790M. Clinical trial information: NCT02192697.

8015 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Activity of AUY922 in NSCLC patients with EGFR exon 20 insertions. *First Author: Zofia Piotrowska, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: EGFR exon 20 insertions (ins20) represent a rare subtype (4%) of EGFR mutations and are refractory to EGFR-specific tyrosine kinase inhibitors (TKIs). No effective targeted therapies exist for patients (pts) with ins20; median PFS on the irreversible EGFR TKI Afatinib is 2.8 months (mos). A pt with EGFR ins20 achieved a durable RECIST partial response (PR) to AUY922, a Heat Shock Protein 90 (Hsp90) inhibitor, in a previous study (NCT01124864), so we designed this phase II investigator-initiated trial to assess the activity of AUY922 in NSCLC pts with EGFR ins20. **Methods:** This was a single-arm, multi-center, open-label study of AUY922 in advanced NSCLC pts with EGFR ins20 mutations. A Simon two-stage design was used, with a plan to enroll 10 pts in the 1st stage and an additional 19 pts in the 2nd stage if >1 PR or stable disease (SD) lasting > 3 mos was observed in the 1st stage. All pts were treated with AUY922 at 70mg/m2 IV weekly. The primary aim was to evaluate objective response rate (ORR) to AUY922. Here we report the complete results of the 1st stage. **Results:** Ten pts, including 7 females and 3 males, average age 55 (range 44-69), were enrolled. Median number of prior therapies = 1 (range 1-6.) 3 had received a prior EGFR TKI; none responded to TKI monotherapy. The most common toxicities were grade 1-2 visual changes (9 pts), diarrhea (9) and fatigue (8.) The only treatment-related grade 3 toxicity was hypertension (2).Among the 10 pts, we observed one PR and three SD lasting > 3 mos, thus triggering full enrollment to the 2nd stage of the study (Table). Median PFS estimate is 6.1 mos (95% CI, 1.2 to NR). Updated results and correlation with specific ins20 mutations will be presented. **Conclusions:** AUY922 may be an effective therapy for pts with EGFR ins20 mutations with med PFS 6.1 mo and is generally well-tolerated, though reversible low-grade ocular toxicity is common. To our knowledge, this is the first trial designed specifically for pts with this rare genotype. Further study of AUY922 in this population is warranted. **Clinical trial information:** NCT01854034 Clinical trial information: NCT01854034.

Patient	Duration of Treatment (Months)	Best RECIST Response
1	8.4	-35%
2	2.6	-25%
3	6.1	-11%
4	2.9	-4%
5	10.7+	-3%
6	1.4	0%
7	2.9	12%
8	4.6+	-29%
9	1.2	15%
10	2.5+	0%

+ Treatment is ongoing

8016 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

AZD3759, an EGFR inhibitor with blood brain barrier (BBB) penetration for the treatment of non-small cell lung cancer (NSCLC) with brain metastasis (BM): Preclinical evidence and clinical cases. *First Author: Dong-Wan Kim, Seoul National University Hospital, Seoul, South Korea*

Background: Increasing numbers of EGFRm+ NSCLC patients with BM have been reported, while effective treatment is lacking due to limited BBB penetration of currently available EGFR TKIs. Here we report preliminary data on AZD3759, an EGFR TKI with BBB penetration, for the treatment of BM. **Methods:** Preclinically, AZD3759 was assessed in both *in vitro* and *in vivo* assays, including MDCKII/Pgp and BCRP assays and CNS penetration in rats, mice and monkeys. PC-9 cells (Exon19Del) were transfected with luciferase and implanted through intra-carotid artery injection to establish a BM model in mice. Tumor growth was monitored weekly by a Xenogen Imaging System and the animal survival time was recorded. Blood and brain tissues were collected for pharmacokinetics, histopathology and pEGFR expression analyses. An ongoing, open label, dose escalation phase I study (NCT02228369; sponsor AstraZeneca) is investigating safety and tolerability of AZD3759 in patients with EGFRm+ advanced NSCLC. **Results:** AZD3759 has high passive permeability ($29.5x10^{-6}$ cm/sec) and is not a substrate of the efflux transporters Pgp or BCRP at the BBB. In vivo, AZD3759 reached distribution equilibrium in rats, mice and monkey ($K_{puu,brain}$ and $K_{puu,CSF} > 0.5$), suggesting BBB penetration. In the BM model, AZD3759 induced profound tumor regression and significantly improved animal survival. A correlation between free brain exposure and pEGFR modulation was also detected in tumor tissues on AZD3759 treatment. To date, 4 patients with measurable BM have been enrolled into 50mg bid and 100mg bid cohorts (3 patients and 1 patient, respectively). In the 2 evaluable patients with BM, one unconfirmed PR and one SD in the brain have been observed. C_{trough} CSF concentrations of these patients were 7.7 and 6nM, respectively, close to the pEGFR IC_{50} of AZD3759. No DLTs were reported to date and two cases of grade I skin rash were observed. **Conclusions:** Preclinical and initial clinical evidence indicate that AZD3759 is an EGFR TKI with BBB penetration with potential to treat EGFRm+ NSCLC patients with BM. Updated clinical data will be shared at the meeting. Clinical trial information: NCT02228369.

8017 Poster Discussion Session; Displayed in Poster Session (Board #339), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase I study of twice weekly pulse dose and daily low dose erlotinib as initial treatment for patients (pts) with EGFR-mutant lung cancers. *First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pts with EGFR-mutant lung cancers treated with EGFR tyrosine kinase inhibitors (TKI) develop clinical resistance, most frequently due to acquisition of EGFR T790M. Modeling suggests that a twice weekly pulse dose, and daily low dose erlotinib schedule may delay the emergence of EGFR T790M. Pulse dose erlotinib may have superior central nervous system (CNS) penetration. **Methods:** We evaluated toxicity, pharmacokinetics, and efficacy of twice weekly pulse-dose and daily low dose erlotinib in pts with EGFR-mutant lung cancers (NCT01967095). Using a 3+3 dose escalation, we assessed escalating pulse doses of erlotinib on days 1 -2 (D1-2), and 50mg low-dose erlotinib on days 3-7 (D3-7) weekly. Six pulse dose levels of erlotinib were tested: 600, 750, 900, 1050, 1200, and 1350 mg. Response was evaluated by RECIST 1.1. After the maximum tolerated dose (MTD) was determined, we treated an additional 10 pts at the MTD. **Results:** From Nov 2013 to January 2015, 34 pts were enrolled. Median age: 60; Women: 20 (59%); never-smoker: 23 (68%); EGFR L858R: 11 (24%) and Ex19del: 22 (65%). Three DLTs were seen: transaminitis (1050mg), mucositis (1350mg) and rash (1350mg) during the dose-escalation period. The MTD was determined to be erlotinib 1200mg D1, D2 and 50mg D3-7 weekly. In total, 16 pts were treated at the MTD. Treatment-related AEs were all grade 1-3. The most frequent treatment-emergent AEs (any grade) were rash (85%), diarrhea (79%), elevated AST (50%) and nausea (41%). Of the 16 pts treated at the MTD, 3 (19%) required a dose reduction of the pulse dose. Of 27 evaluable patients, 22 partial responses were seen (81%). Median-progression free survival is 11 months. 17 pts remain on study. 8 (24%) pts came off for progression, 7 (21%) for toxicity and 2 (6%) for non-adherence. Of those who progressed, 5/8 (62%) had EGFR T790M identified upon rebiopsy (none at MTD). Twelve pts (35%) had CNS disease at diagnosis; no pts came off study due to progressive or new CNS metastases. **Conclusions:** This kinetics-based EGFR TKI dosing schedule of pulse-continuous erlotinib was well-tolerated. TKI dose optimization may enhance efficacy. Further studies are planned in pts with brain metastases. Clinical trial information: NCT01967095.

8018 Poster Discussion Session; Displayed in Poster Session (Board #340), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Clinical activity and safety of PF-06463922 from a dose escalation study in patients with advanced ALK+ or ROS1+ NSCLC. *First Author: Alice Tsang Shaw, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) fusions define 2 molecular subsets of patients (pts) with non-small cell lung cancer (NSCLC). PF-06463922 is a selective, brain-penetrant ALK/ROS1 tyrosine kinase inhibitor (TKI) with potent activity against de novo fusions as well as resistance mutations, including *ALK G1202R*, that arise during treatment with other TKIs. **Methods:** In an ongoing phase I portion of a phase I/II study, pts had ALK+ or ROS1+ NSCLC, with or without central nervous system (CNS) metastases, and were TKI-naïve or had disease progression after prior treatment with 1–2 TKIs. Tumor tissue (archival sample or de novo biopsy) was required for enrollment. A continual reassessment method was used to estimate the maximum tolerated dose (MTD) and identify the recommended phase II dose (RP2D). PF-06463922 was administered on day –7 and then once daily (QD) starting day 1. Primary objective was to estimate the MTD and identify a RP2D. Other objectives included efficacy, safety, pharmacokinetics (PK), effect on cognitive function, effect on cytochrome P450 (CYP) 3A4 activity, biomarkers of drug response/resistance, and intracranial antitumor activity. **Results:** 18 ALK+ and 4 ROS1+ pts (CNS metastases, n = 17; prior ALK TKIs, n = 19) were enrolled across 7 dose levels (10–200 mg QD). Of 15 patients evaluated for efficacy, 6 (40%) had either confirmed or unconfirmed partial responses, 5 of whom previously received 1–2 TKIs and had progression following crizotinib +/- ceritinib; intracranial responses were observed in 5 pts. Common treatment-related adverse events (AE) were hypercholesterolemia and peripheral neuropathy (23% each). The most common grade ≥ 3 treatment-related AE was hypercholesterolemia (14%). One dose-limiting toxicity occurred in a pt who received < 16 of 21 planned 200 mg QD doses due to grade 1/2 CNS effects. PK analysis showed a dose-proportional increase in exposure with a half-life of 20–28 h and moderate CYP3A4 induction. 20 pts remain on treatment. **Conclusions:** PF-06463922 was well tolerated and had clinical activity in pts with ALK+/ROS1+ NSCLC, most of whom had CNS metastases and received ≥ 1 prior TKI. Identification of MTD and RP2D is ongoing. Clinical trial information: NCT01970865.

8019 Poster Discussion Session; Displayed in Poster Session (Board #341), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase II, open-label, multicenter study of the ALK inhibitor alectinib in an *ALK*+ non-small-cell lung cancer (NSCLC) U.S./Canadian population who had progressed on crizotinib (NP28761). *First Author: Leena Gandhi, Dana-Farber Cancer Institute, Boston, MA*

Background: Crizotinib is an approved treatment for patients (pts) with *ALK*-rearranged (*ALK*+) NSCLC. However, progression on crizotinib, particularly in the CNS, frequently occurs within a year. Alectinib is a highly selective ALK inhibitor; preclinical data show high CNS exposure and limited efflux. The NP28761 study (NCT01871805) investigated the efficacy/safety of alectinib in *ALK*+ NSCLC pts in the US and Canada who had progressed on crizotinib. **Methods:** Pts ≥ 18 yrs with locally advanced/metastatic *ALK*+ NSCLC (by FDA-approved FISH test) who progressed on crizotinib, with or without prior chemo, were enrolled; alectinib 600mg BID was given until progression, death or withdrawal. The primary endpoint was objective response rate (ORR) by an independent review committee (IRC) based on RECIST v1.1. Secondary endpoints included disease control rate (DCR = ORR plus stable disease); ORR and DCR in the CNS; progression-free survival; CNS progression rate; duration of response; overall survival; safety and quality of life. **Results:** By 24 Oct 2014, 87 pts were enrolled. Median age 54 yrs; 74% had prior chemo; 55% had baseline CNS mets (21/48 treated). Median follow-up was 21 wks. In the response-evaluable population assessed by IRC (69 pts with baseline measurable disease) ORR was 47.8% (95% CI 35.6–60.2); DCR was 79.7%. In pts with baseline measurable CNS disease (n = 16), IRC CNS ORR was 68.8% (95% CI 41.3–89.0), including 2 CRs; CNS DCR was 100%. When pts with baseline measurable and non-measurable CNS disease were both included (n = 48), CNS DCR was 87.5%, with 9 CNS CRs. 31% of pts had gr3–5 adverse events (AEs), most commonly increased blood CPK (8%), increased ALT (6%) and increased AST (5%); one gr5 AE (hemorrhage) occurred. Low rates of dose interruptions (29%), reductions (14%), and withdrawals (2%) due to AEs were noted. **Conclusions:** Alectinib was well tolerated and achieved a strong treatment response in *ALK*+ NSCLC pts who had progressed on crizotinib, with notable CNS activity, a common site of first progression on crizotinib. A global ph3 head-to-head trial of first-line alectinib vs crizotinib and an expanded access program are ongoing. Clinical trial information: NCT01871805.

8020 Poster Discussion Session; Displayed in Poster Session (Board #342), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Detection of frequent MET Exon 14 skipping events in pulmonary sarcomatoid carcinoma and response to targeted inhibition. *First Author: Xuewen Liu, Columbia University Medical Center; Sun Yat-sen University Cancer Center in China, New York, NY*

Background: Pulmonary sarcomatoid carcinoma (PSC) represents a category of highly aggressive carcinomas associated with a poor prognosis. New therapeutic strategies based on better knowledge of the molecular pathogenesis of PSC are needed. We recently identified a high frequency of a unique type of MET alterations leading to exon 14 skipping (exon 14Δ) in PSC. **Methods:** Whole-exome sequencing in a discovery set and targeted MET mutation screening in an independent validation set of PSC were performed. RT-PCR and Western blotting were performed to validate MET exon 14Δ. A lung adenosquamous cell line H596 (MET exon 14Δ and PIK3CA mutated) and a gastric adenocarcinoma cell line Hs746T (MET exon 14 Δ) were used for functional studies. Ablation of MET signaling by siRNA or pharmacological inhibitor (Crizotinib) was conducted, and subsequent MTS assays and Western blotting were then performed. Simultaneous MET signaling blockade and PIK3CA signaling inhibition using PIK3CA inhibitor (GDC0941) were performed to assess synergistic effects in H596 cells. **Results:** Alterations affecting MET exon 14 splice sites, including deletions at the 5' splice site (n = 3) and point mutations at the 3' splice site (n = 5) were found in 22% (8/36) of PSC. One PSC harbored MET exon 14Δ and a concurrent PIK3CA mutation. RT-PCR and Western blotting confirmed the presence of MET exon 14Δ in tumor and in H596 and Hs746T cells. Both MET siRNA silencing and crizotinib decreased cell proliferation and inhibited downstream AKT and MAPK activation in Hs746T cells, whereas effects were modest in H596 cells and negligible in control Calu-3 and HCC827 cells. Concomitant MET and PI3K blockade had synergistic effects in H596 cells. Migration/invasion assays in H596 and Hs746T cells, as well as further functional studies utilizing specific MET exon 14 expression constructs are ongoing. **Conclusions:** Our study finds that MET exon 14Δ alterations are a frequent and potentially targetable event in PSC. Our studies also suggest that concurrent PIK3CA mutations require combined treatment. Clinical studies assessing biomarker-driven MET/PI3K inhibition should be explored in PSC as well as other malignancies harboring MET exon 14Δ events.

8021 Poster Discussion Session; Displayed in Poster Session (Board #343), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Response to crizotinib and cabozantinib in stage IV lung adenocarcinoma patients with mutations that cause *MET* exon 14 skipping. *First Author: Paul K. Paik, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Mutations in the *MET* exon 14 RNA splice acceptor and donor sites, which lead to exon skipping, deletion of the juxtamembrane domain, and loss of Cbl E3-ligase binding to the resultant aberrant MET protein, were previously reported to be oncogenic in preclinical models (Kong-Beltran, *Cancer Res* 2006). These mutations occur in 4% of lung adenocarcinomas but have not been clinically assessed (TCGA 2014). We now report responses to the MET inhibitors crizotinib and cabozantinib in patients with stage IV lung adenocarcinomas harboring mutations leading to *MET* exon 14 skipping. **Methods:** Patients with stage IV lung adenocarcinomas harboring *MET* exon 14 splice site mutations (N=6) or a mutation deleting Y1003 in exon 14 (N=1) were identified through a clinical assay based on hybrid capture/next-generation sequencing of 341 oncogenes and tumor suppressors (MSK-IMPACT). MET IHC was performed on archival FFPE tissue. RNA skipping was confirmed by NanoString. Radiographic response to MET inhibition was assessed using RECIST 1.1 and PERCIST criteria. **Results:** Clinicopathologic data for those treated are in the table below. To date, 3 patients have been treated with off-label crizotinib and 1 with cabozantinib (NCT01639508). 3 of 4 patients (75%) developed a PR to treatment. The remaining patient had SD by RECIST, with PET imaging demonstrating a complete PERCIST response. **Conclusions:** *MET* exon 14 skipping is a novel oncogenic target that predicts for response to MET inhibitors. This appears to be a substantially better predictor of response than either protein expression or gene amplification. Patients with these splice site mutations should be treated on a clinical trial of a MET inhibitor. For those without access to a trial, use of off-label crizotinib should be considered.

ID	Age	Sex	Smoking status (pack years)	*MET* exon 14 variant	MET therapy	Response	MET IHC (H-score)
1	65	M	C (20)	MET p.V1001_F1007del (c.3001_3021delGTAGACTACCGAGCTACTTTT)	crizotinib (3rd line)	PR (-31%)	NA
2	80	M	F (20)	MET c.3024_3028delAGAAGGTATATT	crizotinib (3rd line)	PR (-30%)	300
3	90	F	N	MET c.3028G>C	crizotinib (3rd line)	PR (-47%)	NA
4	80	F	N	MET c.3028G>C	cabozantinib (3rd line)	SD (0%), CR (PERCIST)	300

8022 Poster Discussion Session; Displayed in Poster Session (Board #344), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Clinical and molecular characteristics of *NF1* mutant lung cancer. *First Author: Amanda J. Redig, Dana-Farber Cancer Inst, Boston, MA*

Background: *NF1* is a tumor suppressor that negatively regulates Ras, thus *NF1* mutant tumors may also be sensitive to inhibitors of MAP kinase signaling. *NF1* variants occur in lung cancer, but their clinical significance is unknown. We evaluated clinical and molecular characteristics of *NF1* mutant lung cancers, with comparison to *KRAS* mutant tumors. **Methods:** From 07/13-10/14, 591 lung tumors at our institution underwent targeted next generation sequencing (NGS) for mutations and copy number alterations in a 275 gene panel. *NF1* and *KRAS* cohorts were identified, with clinical and genomic analysis. Fisher's exact test was used to compare frequency of gene mutations between cohorts. **Results:** Among 591 pts, 60 had *NF1* mutations (10%) and 143 (24%) had *KRAS* mutations (Stage IV: *NF1* 26, 43%; *KRAS* 58, 41%). 15 *NF1* mutations (25%) occurred with other driver mutations (BRAF (2); ERBB2 (2); KRAS (9); XRAS (2)). There were 73 unique *NF1* variants: single copy deletion (1), splice site (12), loss of function/predicted damaging (49), predicted benign (11). 10 tumors had > 1 mutation. Tumor pathology was diverse: adenocarcinoma (38, 63%); squamous cell carcinoma (11, 18%); large cell neuroendocrine (2, 3%); mixed small cell carcinoma (2, 3%); other (7, 11%). In contrast, *KRAS* mutations (G12C:51, G12D:22, G12V:27, Q61H:8, other:35) occurred in adenocarcinomas (138, 97%) and seldom with other driver mutations (2, 1%). Both mutations were common in former (> 10 pack years) or current smokers (*NF1* 49, 82%; *KRAS* 120, 84%). Among pts without co-mutation, *TP53* mutations/2-copy deletions occurred more often with *NF1* mutation (33, 65%) than *KRAS* mutation (47, 35%) ($p < .001$). Similarly, *LKB1* mutations occurred in 8 (16%) *NF1* mutant tumors and 33 (25%) *KRAS*mutant tumors ($p = .24$). **Conclusions:** *NF1* mutations define a unique population of 10% of non-small cell lung carcinoma (NSCLC). *NF1* and *KRAS* mutations present in similar pt populations. *NF1* mutations occur more often with other driver mutations and with coexisting *TP53* mutations than *KRAS* mutations. Therapeutic strategies targeting *KRAS* activation, such as MEK inhibitors, may warrant investigation in *NF1* mutant tumors. Tumor suppressor inactivation patterns in these tumors may help further define novel treatment strategies.

8023 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Assessing the performance of Watson for oncology, a decision support system, using actual contemporary clinical cases. *First Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: IBM Watson for Oncology (WFO), trained by Memorial Sloan Kettering (MSK), is a cognitive computing system designed to assist medical oncologists making treatment decisions for individual patients. Recommendations are consistent with established guidelines and published evidence, as reflected in MSK's practice and historical cases. Treatment options are classified as Recommended (WFO-REC), For Consideration (WFO-FC), or Not Recommended (WFO-Not REC). Published evidence, medical logic, and drug information are presented for each treatment option. We sought to assess the current performance of WFO to benchmark accuracy and identify areas for development. **Methods:** 20 de-identified cases were selected from the practices of two MSK thoracic medical oncologists. Patients presented for initial consultation regarding first-line systemic therapy during 2014 and all necessary information to make a treatment decision was available at the time of initial consultation or within two weeks, including molecular pathology. Cases were entered into WFO using structured attributes. WFO recommendations were compared to those of the MSK thoracic medical oncologist (MSKMD-REC). **Results:** WFO-REC and MSKMD-REC matched 50% of the time. 25% of the MSKMD-RECs appeared in the WFO-FC category and 25% in WFO-Not REC. In the 16 cases with metastatic lung cancers, 88% of administered regimens were returned as WFO-REC or WFO-FC. All choices were within established guidelines. Cases where the MSKMD-REC appeared as WFO-Not REC involved elderly patients with co-morbidities not yet included in WFO. **Conclusions:** While WFO's choices today fall within evidence-based standards, WFO has the capacity to provide greater precision through iterative training and development. Elderly patients for whom care choices are heterogeneous based on co-morbid illnesses represent a challenge. Benchmarking against actual cases has helped us to prioritize development work to increase the number of attributes to include more co-morbid conditions and to incorporate patient preferences to improve precision.

8024 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Electronic medical record as a research tool: Virtual clinical trial comparing pemetrexed and gemcitabine, both given with cisplatin, in patients with lung adenocarcinomas. *First Author: Alexander Grigorenko, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The electronic medical record (EMR) is a tremendous research resource, but its use for exploring hypotheses has been limited by an inability to reliably and efficiently identify patient cohorts. We have created a system that uses advanced computational techniques and Memorial Sloan Kettering's (MSK) EMR data to overcome these challenges. To validate our system, we sought to replicate a phase III clinical trial comparing cisplatin/pemetrexed (CP) to cisplatin/gemcitabine (CG) in patients with lung adenocarcinomas (Scagliotti J Clin Oncol 2008). **Methods:** We created a system that can identify a patient cohort by extracting structured cancer and outcomes data from the EMR, algorithmically identifying chemotherapy regimens, and using natural language processing to extract functional and smoking status from physician notes. Using the earlier clinical trial's eligibility criteria, we identified a patient cohort and analyzed survival on an intent-to-treat basis. Our analysis relied on the extensive data warehouse of MSK's EMR information, which contains data on the care of over a million patients since 1989. **Results:** Our system successfully extracted structured data, and accurately categorized treatment regimens (F-measure = 0.985), functional status (F-measure = 0.998), and smoking status (F-measure = 0.993). 281 patients were automatically identified as eligible. The median overall survival (OS) of patients with lung adenocarcinomas receiving CP and CG was 14.7 and 12.6 months with a hazard ratio (HR) of 0.69 (95% CI: 0.52 - 0.90) favoring CP. These results are similar to those of the prospective trial (Table). **Conclusions:** Our system replicated the results of a prospective clinical trial. Highly-accurate computational tools to extract structured and textual data from the EMR are feasible and can help address pending clinical research questions. Future steps will focus on expanding data extraction capabilities to support a broader range of hypotheses within the EMR.

Metric	Virtual Trial	Clinical Trial
OS (months; CP, CG; % difference)	14.7, 12.6; 15.4%	12.6, 10.9; 14.5%
HR (95% CI)	0.69 (0.52 - 0.90)	0.81 (0.70 - 0.94)

8025 Poster Session (Board #347), Mon, 8:00 AM-11:30 AM

First-line monotherapy with nivolumab (NIVO; anti-programmed death-1 [PD-1]) in advanced non-small cell lung cancer (NSCLC): Safety, efficacy and correlation of outcomes with PD-1 ligand (PD-L1) expression. *First Author: Scott N. Gettinger, Yale Cancer Center, New Haven, CT*

Background: NIVO, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, has demonstrated durable responses and tolerability in heavily pretreated patients (pts) with advanced NSCLC. This phase I study evaluated the efficacy and safety of NIVO monotherapy in pts with chemotherapy naïve advanced NSCLC. **Methods:** Pts (N=52) with squamous (SQ) or non-SQ advanced NSCLC received NIVO 3 mg/kg IV Q2W until progression or unacceptable toxicity (post-progression treatment was permitted per protocol). Response (RECIST v1.1) was evaluated overall, by histology and by tumor PD-L1 expression (PD-L1$^+$: ≥5% tumor cells expressing PD-L1). **Results:** Objective response rate (ORR) was 21%, with 3 confirmed complete responses; 9/11 responders (82%) achieved response by first scan (wk 11). Median duration of response (mDOR) was not reached (NR; range, 7.6+, 85.6+ wks); 9 pts (82%) had ongoing responses at last tumor assessment, with a minimum follow-up of 8 mos in all pts. Two pts had unconventional immune-pattern responses with 35% and 43% maximum reductions in target lesions, respectively, and simultaneous appearance of new lesions (not reported as responders). Median overall survival (mOS) was 98.3 wks (range, 1.0, 104.4+). Objective responses were observed in both PD-L1$^+$ and PD-L1$^-$ pts, with ORR higher in pts with PD-L1$^+$tumors. Eight pts (15%) experienced grade 3–4 treatment-related adverse events, including rash (n=2), increased amylase/lipase, increased AST/ALT, hyperglycemia, cardiac failure, lung infection, and pneumonitis (n=1 each). **Conclusions:** First-line NIVO demonstrated durable responses, encouraging survival and a tolerable safety profile in pts with advanced NSCLC. Although response rates were higher in PD-L1$^+$ pts, OS was encouraging in both PD-L1$^+$ and PD-L1$^-$ pts. Updated OS and safety data will be presented. Clinical trial information: NCT01454102.

	ORR	mDOR	mOS
	n/N (%)	wks (range)	
All pts	**11/52 (21)**	**NR (7.6+, 85.6+)**	**98.3 (1.0, 104.4+)**
Non-SQ	**9/39 (23)**	**NR (7.6+, 85.6+)**	**NR (1.0, 104.4+)**
SQ	2/13 (15)	NR (46.9+, 77.3+)	73.1 (13.3, 87.3+)
PD-L1$^+$	8/26 (31)	NR (7.6+, 85.6+)	NR (1.0, 103.3+)
PD-L1$^-$	2/21 (10)	NR (13.0+, 24.1+)	98.3 (8.0, 104.4+)

8026 Poster Session (Board #348), Mon, 8:00 AM-11:30 AM

Optimizing PD-L1 as a biomarker of response with pembrolizumab (pembro; MK-3475) as first-line therapy for PD-L1–positive metastatic non-small cell lung cancer (NSCLC): Updated data from KEYNOTE-001. *First Author: Naiyer A. Rizvi, Columbia University Medical Center, New York, NY*

Background: Platinum doublets provide 6-mo PFS and 12-mo OS for treatment-naive, metastatic NSCLC without driver mutations. Preliminary data from KEYNOTE-001 revealed robust antitumor activity and manageable toxicity for the anti–PD-1 antibody pembro in treatment-naive NSCLC. In these patients (pts), PD-L1 positivity correlated with improved ORR, PFS, and OS. We explored the relationship between PD-L1 expression levels and efficacy in treatment-naive pts in KEYNOTE-001. **Methods:** 101 treatment-naive, PD-L1$^+$ metastatic NSCLC pts were randomized 1:1 to pembro 10 mg/kg Q2W or Q3W (11 pts randomized to 2 or 10 mg/kg Q3W). Pembro was given until unacceptable toxicity, PD, or pt/investigator decision. PD-L1 expression was assessed by IHC (22C3 antibody). Staining of tumor cells or stroma by a prototype assay was used for enrollment. In a prospectively defined validation set (n = 90), the percentage of PD-L1–stained tumor cells was determined with a clinical trial assay. Response was assessed centrally every 9 wk by RECIST 1.1. **Results:** There were no significant between-dose differences in ORR, PFS, or OS; 11% of pts experienced gr 3-5 drug-related AEs. In the validation set (38-wk median follow-up), ORR and DCR were highest and PFS was longest in pts with ≥50% PD-L1 tumor cell staining (Table); there was a trend toward longer OS (immature data). **Conclusions:** Pembro demonstrateddurable antitumor activity and manageable toxicity profile as first-line therapy for PD-L1$^+$ metastatic NSCLC, with the greatest efficacy observed in pts with PD-L1 staining in ≥50% of tumor cells. These data demonstrate that PD-L1 expression in tumor cells identifies those NSCLC pts most likely to respond to pembro. The efficacy and safety of pembro as first-line therapy for PD-L1$^+$NSCLC is being examined in ongoing, controlled clinical trials. Clinical trial information: NCT01295827.

PD-L1$^+$ Tumor Cells	n	ORR, % (95% CI)	DCR, % (95% CI)	Median, mo (95% CI)	
PFS	OS				
≥50%	17	47 (23-72)	77 (50-93)	NR (2.4-NR)	NR (NR-NR)
1%-49%	31	19 (8-38)	71 (52-86)	4.4 (3.6-6.4)	NR (8.6-NR)
<1%	7	14 (0.4-58)	57 (18-90)	3.4 (2.1-4.2)	7.3 (3.4-NR)
Total	90	24 (16-35)	68 (57-77)	6.0 (4.1-8.6)	NR (10.6-NR)

NR, not reached.

8027 Poster Session (Board #349), Mon, 8:00 AM-11:30 AM

Phase II studies of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients with advanced squamous (sq) or nonsquamous (non-sq) non-small cell lung cancer (NSCLC). *First Author: Makoto Nishio, Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: Nivolumab, a fully human IgG4, PD-1 immune-checkpoint inhibitor antibody, has shown durable clinical activity in phase I and II trials in several tumor types. Recently, a phase III study (CheckMate -017) demonstrated that nivolumab improved overall survival than docetaxel in second-line of sq NSCLC. Here, we report the results of two phase II studies to evaluate the efficacy and safety of nivolumab in previously treated advanced sq (JapicCTI-No.132072) and non-sq (JapicCTI-No.132073) NSCLC pts. **Methods:** Both studies require pts aged ≥ 20 years with ECOG status of 0 or 1, stage IIIB/IV, or recurrent NSCLC and at least one prior chemotherapy including platinum containing regimen.Pts received nivolumab 3 mg/kg IV Q2W until progression or unacceptable toxicity.The primary endpoint in both studies was the objective response rate (ORR) (RECIST v1.1).Planned sample size was 30 pts for Sq and 67 pts for Non-sq, respectively(P0=0.09, P1=0.26 , P0=0.09, P1=0.20 ; α=0.025 (one-side) , 1-β=0.8). **Results:** From April 2013 to April 2014, a total of 111 NSCLC pts were enrolled into two studies (35 pts with sq,76 pts with non-sq, male/female: 81/30; PS 0/1: 46/55; aged 31 to 84 [median: 65.0] years; Stage IIIB/Stage IV/recurrence: 6/86/19)Grade 3-4 drug related adverse events (G3AEs) were observed in 16.2 % (18/111) pts. Most common G3AEs were lymphocyte count decreased 3.6 % (4/111), hyponatremia 1.8 % (2/111), interstitial lung disease 1.8 % (2/111), pleural effusion 1.8 % (2/111). Any grade of Interstitial lung disease was observed in 4.5 % (5/111) pts. No grade 5 AEs were observed.Efficacy data were shown in table 1. Median follow-up was 10.4 months and 8.4 months, respectively. **Conclusions:** Nivolumab continues to demonstrate encouraging clinical efficacy in both sq and non-sq NSCLC with a manageable safety profile. Clinical trial information: 132072 and 132073.

	Sq	(n=35)	non-Sq	(n=76)
		(95% CI)		(95% CI)
ORR	25.7%	(14.2-42.1)	19.7%	(12.3-30.0)
mPFS	128 days	(44.0-215.0)	85 days	(43.0-102.0)
mDOR	NR	(135.0 -)	NR	(210.0 -)
mOS	NR	(378.0 -)	NR	(- -)

DOR : duration of response

8028 Poster Session (Board #350), Mon, 8:00 AM-11:30 AM

Clinical activity and safety from a phase II study (FIR) of MPDL3280A (anti-PDL1) in PD-L1–selected patients with non-small cell lung cancer (NSCLC). *First Author: David R. Spigel, Sarah Cannon Research Institute, Nashville, TN*

Background: MPDL3280A (anti-PDL1) has shown activity across a number of tumor types. In FIR, we assessed the efficacy of MPDL3280A in NSCLC pts based on PD-L1 expression. **Methods:** FIR is a single arm study of MPDL3280A in stage IIIB/IV NSCLC. Cohort 1 included chemo-naive pts, cohort 2 included ≥ 2L pts without brain metastases and cohort 3 included ≥ 2L pts with treated asymptomatic brain metastases. Pts received 1200 mg MPDL3280A IV q3w (last pt entered Jun 27, 2014). Here, we report investigator-assessed ORR per RECIST v1.1 (data cutoff Oct 23, 2014). PD-L1 expression was centrally assayed by an SP142 IHC antibody in archival or fresh tumor biopsies (required for cohorts 2 and 3) and scored as IC 0, 1, 2 or 3 and TC 0, 1, 2 or 3. Pts with PD-L1 TC 2/3 and/or IC 2/3 tumors were enrolled. **Results:** Of 1,009 pts screened, 205 pts were selected based on tumor PD-L1 status. Of the 138 pts that were enrolled, 137 pts were safety-evaluable. The median age was 66 y (range, 42-85 y) and 58% of pts were male. The AE profile was similar across cohorts. Treatment-related AEs occurred in 67% of pts, most often fatigue (26%), nausea (15%) and decreased appetite (14%). Related Grade 3-4 AEs occurred in 15% of pts, with one related death due to constrictive pericarditis. 114 pts were efficacy-evaluable with ≥ 3-mo follow up in cohort 1 and ≥ 6-mo follow up in cohorts 2 and 3. The highest ORR was seen in pts with PD-L1 TC3 or IC3 tumors (Table). The median DOR has not been reached in cohorts 1 and 2 (Table). **Conclusions:** MPDL3280A showed clinical efficacy in both chemo-naive and previously treated NSCLC. High PD-L1 expression (TC3 or IC3) was associated with a higher ORR. The safety profile of MPDL3280A in pts with NSCLC was consistent with previous reports. (NCT01846416) Clinical trial information: NCT01846416.

Efficacy results.

Pt population	Cohort 1[a]		Cohort 2[b]		Cohort 3[b]	
ORR (95% CI), %						
	n		n		n	
All	31	29 (13-45)	71	17 (8-26)	12	17 (0-38)
TC3 or IC3	7	29 (0-62)	26	27 (10-44)	8	25 (0-55)
DOR range, wk						
All	9	7-30+[c]	12	11+-69+[c]	2	-
TC3 or IC3	2	12-18+[c]	7	30+-69+[c]	2	-
24-wk PFS (95% CI), %						
All	31	39 (22-56)	71	35 (23-46)	12	-
TC3 or IC3	7	43 (6-80)	26	49 (30-69)	8	-

[a]Unconfirmed ORR. [b]Confirmed ORR. 2 pts had unknown IC/TC status. [c] Median not reached.

8029 Poster Session (Board #351), Mon, 8:00 AM-11:30 AM

Clinical activity, safety and predictive biomarkers of the engineered antibody MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC): update from a phase Ia study. *First Author: Leora Horn, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: NSCLC exhibits mutational complexity, which is associated with increased tumor immunogenicity. PD-L1 expression in the tumor microenvironment can inhibit antitumor immunity. MPDL3280A blocks PD-L1 and can restore tumor-specific T-cell immunity. **Methods:** In this dose-escalation and -expansion study, pts with NSCLC were enrolled from Oct 25, 2011 to Sep 24, 2013 and received MPDL3280A IV ≤ 20 mg/kg q3w (data cutoff Sep 2, 2014). ORRs were assessed by RECIST v1.1. PD-L1 expression on tumor-infiltrating immune cells (ICs) and tumor cells (TCs) was centrally evaluated by an IHC assay based on the SP142 antibody with pts scored as IC 0, 1, 2 or 3 and TC 0, 1, 2 or 3. **Results:** 88 NSCLC pts were safety- and efficacy-evaluable: 57% of pts were male, 28% were ECOG PS 0 and 72% were ECOG PS 1. The median age was 61 y (range, 24-84 y), and the majority of pts had 3 lines of therapy. Pts received MPDL3280A for a median duration of 15 wks (range, 0-129 wks). Treatment-related all grade AEs occurred in 73% of pts, most often fatigue (21%), nausea (15%) and decreased appetite (14%). 11% of pts had a related G3-4 AE, most often dyspnea, hypoxia, fatigue and hyponatremia (2% each). One related G5 AE due to cardio-respiratory arrest was seen. ORRs, DOR, PFS and OS were assessed by PD-L1 status (Table). Of note, pts with PD-L1 expression of TC3 or IC3 (n = 20) had an ORR of 45% (95% CI, 23-68%) vs 14% (95% CI, 6-25%) for pts with PD-L1 expression of TC 0/1/2 and IC 0/1/2 (n = 58). **Conclusions:** PD-L1 expression in the tumor microenvironment appeared to be a predictive biomarker for MPDL3280A clinical benefit with median OS not yet reached. Treatment with MPDL3280A was generally well tolerated. Phase III trials are ongoing. Clinical trial information: NCT01375842.

Efficacy results.

	Pts		
	TC0/1/2 and IC0/1/2	**TC3 or IC3**	**All[a]**
n	58	20	88
ORR (95% CI), %	14 (6-25)[b]	45 (23-68)[c]	21 (13-30)
24-wk PFS (95% CI), %	36 (24-49)	45 (23-67)	42 (32-53)
Median DOR (range), wk	108 (38+-110)	64 (31-80+)	67 (31-110)
1 y OS (95% CI), %[d]	78 (65-91)	89 (75-100)	82 (72-91)

[a]10 pts with unknown TC and IC status were included. [b]4 pts with missing or unevaluable response. [c]1 pt with missing or unevaluable response. [d] Median OS not yet reached for all groups.

8030 Poster Session (Board #352), Mon, 8:00 AM-11:30 AM

Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). *First Author: Stephen V. Liu, Georgetown Univ Hosp, Washington, DC*

Background: MPDL3280A, which preserves the PD-L2/PD-1 interaction to potentially diminish autoimmune lung toxicity, has promising activity in advanced NSCLC. Platinum-based doublet chemotherapy (chemo) remains standard first-line (1L) treatment for NSCLC with ORRs historically of ≈ 30%. Preclinical data show that chemo may prompt tumor antigen release and enhance MPDL3280A activity. Thus, we studied MPDL3280A + chemo in untreated NSCLC pts. **Methods:** This Ph Ib study evaluated MPDL3280A combined with carboplatin + either paclitaxel (Arm C), pemetrexed (Arm D) or weekly nab-paclitaxel (Arm E) in pts with chemona-ive locally advanced or metastatic NSCLC. Pts received MPDL3280A 15 mg/kg IV q3w with standard chemo dosing for 4-6 cycles followed by MPDL3280A maintenance therapy until progression. Unconfirmed ORRs were assessed by RECIST v1.1 in pts dosed by Jun 29, 2014 (data cutoff Sep 29, 2014). PD-L1 expression was centrally assayed using the SP142 IHC antibody. **Results:** 37 pts were safety evaluable (Arm C, 8; Arm D, 14; Arm E, 15). Across arms, 54% of pts were male, median age was 65 y (range, 40-82 y), 81% had non-squamous and 19% had squamous NSCLC. Median follow-up for safety was 154 d (range, 1-346 d). The most frequent all-grade AEs regardless of attribution across arms included those commonly associated with chemo, such as nausea (Arms C & D, 50%; Arm E, 73%), fatigue (Arm C, 38%; Arm D, 36%; Arm E, 73%) and constipation (Arm C, 25%; Arm D, 71%; Arm E, 27%). The most common MPDL3280A-related G3-4 AEs included anemia (Arms D & E, 7%), neutropenia (Arm C, 13%; Arm D, 7%) and thrombocytopenia (Arms D & E, 7%). No pneumonitis was seen. One MPDL3280A-related G5 AE due to candidemia after prolonged neutropenia was seen in Arm D. 30 pts were efficacy evaluable (Arm C, 5; Arm D, 12; Arm E, 13). Across all arms, the ORR (95% CI) was 67% (48%-82%): 60% (19%-92%) in Arm C (3 PRs), 75% (45%-93%) in Arm D (9 PRs) and 62% (33%-83%) in Arm E (6 PRs & 2 CRs). Responses were seen in each arm independent of PD-L1 expression. **Conclusions:** MPDL3280A + standard 1L chemo was well tolerated with no unexpected toxicities, showing promising clinical activity in advanced NSCLC pts. Ph III studies are ongoing. Clinical trial information: NCT01633970.

8031 Poster Session (Board #353), Mon, 8:00 AM-11:30 AM

Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 Cohorts A and C. *First Author: Vassiliki Papadimitrakopoulou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: As monotherapy, the anti–PD-1 antibody pembro has shown robust antitumor activity in advanced NSCLC patients (pts). KEYNOTE-021 evaluated the safety, tolerability, and clinical activity of pembro + PDC for treatment-naive advanced NSCLC. **Methods:** Pts with stage IIIB/IV NSCLC and no prior systemic therapy were randomized 1:1 to pembro 2 or 10 mg/kg Q3W plus carboplatin AUC 6 + paclitaxel 200 mg/m^2 (cohort A; any histology) or carboplatin AUC 5 + pemetrexed 500 mg/m^2 (cohort C; nonsquamous without *EGFR* sensitizing mutation or *ALK* translocation only). Pts received pembro + PDC for 4 cycles followed by pembro maintenance in A and pembro + pemetrexed in C. The dose-limiting toxicity (DLT) observation window was the first 3 wk after initial dosing. Key eligibility criteria included ECOG PS 0-1, measurable disease, and adequate tumor sample for PD-L1 assessment. Response was assessed every 6 wk until confirmed progression (RECIST v1.1, investigator review). **Results:** As of Dec 2014, 44 pts (20 in cohort A and 24 in cohort C) were treated. One DLT was reported (hospitalization for gr 3 rash, C [pembro 10 mg/kg]). Gr 3-4 treatment-related AE rate was 27% (15% in A, 38% in C); AEs were reversible transaminase elevation (n = 3 in C), anemia (n = 1 in A, 2 in C), rash (n = 1 in A, 1 in C), and colitis (n = 2 in C); no gr 3-4 febrile neutropenia was observed. One patient in C discontinued due to treatment-related gr 3 rash. No treatment-related deaths have occurred. Preliminary ORR (confirmed and unconfirmed) is 30% in A and 58% in C (Table). At the time of analysis, 16 pts in A and 21 pts in C remained on treatment. **Conclusions:** These data suggest that pembro + PDC has a reasonable safety profile and provides antitumor activity as front-line therapy for stage IIIB/IV NSCLC. Based on the promising ORR observed for pembro + carboplatin and pemetrexed, this combination is being evaluated in a larger cohort. Clinical trial information: NCT02039674.

	A (carboplatin/paclitaxel)		C (carboplatin/pemetrexed)	
	Pembro 10 n = 10	**Pembro 2 n = 10**	**Pembro 10 n = 12**	**Pembro 2 n = 12**
ORR (all PR)	3 (30%)	3 (30%)	8 (67%)	6 (50%)
SD	3 (30%)	5 (50%)	4 (33%)	5 (42%)
DCR (PR + SD)	6 (60%)	8 (80%)	12 (100%)	11 (92%)
PD	3 (30%)	1 (10%)	0	0
No assessment	1 (10%)	1 (10%)	0	1 (8%)

8032 Poster Session (Board #354), Mon, 8:00 AM-11:30 AM

Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). *First Author: Naiyer A. Rizvi, Columbia University Medical Center, New York, NY*

Background: MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity. PD-L1 is expressed in NSCLC tumors and may be associated with response to anti-PD-L1 treatment. This ongoing Phase 1/2, multicenter, open-label study (NCT01693562) evaluates the safety and clinical activity of M in patients (pts) with multiple solid tumor types including NSCLC. **Methods:** M is administered at 10 mg/kg IV every 2 wks (q2w) until unacceptable toxicity, disease progression, or for up to 12 months. Safety evaluations occur prior to each dose (toxicities graded by CTCAE v4.0). Response is based on investigator assessment (RECIST v1.1; includes confirmed/unconfirmed responses) at 6, 12, and 16 wks, then every 8 wks. Retreatment is permitted upon progression after 12 months of therapy. PD-L1 expression within the tumor is assessed using Ventana PD-L1 IHC (SP263). Data included represent a larger population with more mature follow up than previously reported.[1] **Results:** As of 31 Oct 2014, 198 pts (116 non-squamous and 82 squamous histology; mean age 64 [range 26–87]; ECOG PS 0 [24%] or 1 [76%]; 81% current/prior smokers; median 2.5 prior treatments [1–9]) have been treated with M 10 mg/kg q2w (median 6 doses; range 1–23). Drug-related AEs were reported in 48% of pts; most frequently fatigue (14%), decreased appetite (9%), and nausea (8%). Grade ≥ 3 drug-related AEs were reported in 6% of pts. Drug-related AEs led to study discontinuation in 2% of pts. Pneumonitis (Grade 1-2) occurred in 2 (1%) pts. In all, 149 pts were evaluable for response with ≥ 24 wks of follow-up; ORR was 14% (23% in PD-L1+), and DCR at 24 wks was 24%. ORR was higher in squamous (21%) than non-squamous pts (10%). Responses were durable with 76% ongoing (DoR range 0.1+ – 35+ wks). **Conclusions:** With more mature follow up, the safety profile of M in NSCLC is manageable and consistent with previous reports. Responses are durable; ORR appears to be higher in squamous NSCLC and PD-L1+ pts. A broad development program of M alone and in combination with other treatments is underway in NSCLC. Antonia S, et al. Poster presented at ESMO 2014, 1325P Clinical trial information: NCT01693562.

8033 Poster Session (Board #355), Mon, 8:00 AM-11:30 AM

Development of a PD-L1 companion diagnostic assay for treatment with MEDI4736 in NSCLC and SCCHN patients. *First Author: Marlon Rebelatto, MedImmune, Gaithersburg, MD*

Background: A high quality PD-L1 companion diagnostic may help predict which patients are more likely to respond to PD-1/PD-L1 antibody-based therapy. Here we describe a PD-L1 immunohistochemical (IHC) diagnostic test developed by Ventana Medical Systems for use with MEDI4736. **Methods:** An anti-human PD-L1 rabbit monoclonal antibody (SP263) was optimized for use with Ventana OptiView DAB IHC Detection Kit on the automated BenchMark ULTRA platform. The PD-L1 IHC assay was validated for use in formalin-fixed, paraffin-embedded samples of NSCLC and SCCHN in a series of studies addressing sensitivity, specificity, robustness, and precision. MEDI4736 is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity. A subset of clinical trial samples from a Phase 1/2 study of MEDI4736 (NCT01693562) was analyzed to determine optimal cut-off for enriching response to MEDI4736. Inter-reader precision was established by 3 pathologists who evaluated 81 NSCLC and 100 SCCHN samples across the range of expression levels. **Results:** The Ventana PD-L1 IHC (SP263) assay met all pre-defined acceptance criteria. The scoring algorithm was defined using statistical analysis of clinical response data and PD-L1 staining parameters observed in a set of NCT01693562 clinical trial samples. Samples of both cancer types are considered test positive when the membrane of ≥ 25% of tumor cells stain for PD-L1 at any intensity. Inter-reader precision in determining PD-L1 status resulted in an overall percentage agreement of 97% and 92% for NSCLC and SCCHN, respectively. For both NSCLC and SCCHN, PD-L1+ patients identified by the scoring algorithm had a higher response rate than PD-L1- patients. **Conclusions:** These results highlight the robustness and reproducibility of the PD-L1 IHC (SP263) assay in a clinical setting. In NSCLC and SCCHN patients treated with MEDI4736, PD-L1+ patients identified by the scoring algorithm had a higher response rate than PD-L1- patients. The clinical utility of the PD-L1 diagnostic assay will be further validated in a prospective manner using additional patients in this study and in other MEDI4736 studies. Clinical trial information: NCT01693562.

8034 Poster Session (Board #356), Mon, 8:00 AM-11:30 AM

Avelumab (MSB0010718C), an anti-PD-L1 antibody, in advanced NSCLC patients: A phase 1b, open-label expansion trial in patients progressing after platinum-based chemotherapy. *First Author: James L. Gulley, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against cancer. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody being investigated in clinical trials. We report safety and clinical activity in patients (pts) with advanced NSCLC progressing after platinum-based chemotherapy (NCT01772004). **Methods**: Pts were treated with avelumab at 10 mg/kg Q2W until progression, confirmed complete response (CR), or toxicity. A prespecified analysis of 184 pts with ≥ 3 months follow-up (range 3-13) was performed. Tumors were assessed every 6 weeks (w) (RECIST 1.1) and unconfirmed best overall response (BOR) was evaluated. Tumor PD-L1 expression was assessed by immunohistochemistry. **Results**: Median age was 65y (range 31-83) and ECOG PS was 0 (30%) or 1 (70%). Histology was adenocarcinoma (62%), squamous cell carcinoma (29%), or other (9%). Any grade drug-related treatment-emergent adverse events (TEAEs) occurred in 139 (75.5%) pts; the most common (> 5%) were fatigue, nausea, infusion-related reactions (IRRs), chills, decreased appetite, and diarrhea. Drug-related grade ≥ 3 TEAEs occurred in 22 (12%) pts, including 4 IRRs. Drug-related deaths were reported (n = 3; radiation pneumonitis, acute respiratory failure, and disease progression). Objective responses (OR) were observed in 22 (12%) pts (95% CI: 7.6, 17.5; 1 CR, 21 partial responses; 18 were ongoing at data cutoff). BOR of stable disease was observed in 70 pts (38%). Median progression-free survival (PFS) was 11.6 w (95% CI: 8.4, 12.1) and the PFS rate at 24 w was 25.4% (95% CI: 18.3, 33.2). Tumors were PD-L1(+) in 86% of evaluable pts (1% cutoff). The ORR in PD-L1(+) pts (n = 118) was 14.4% and 10.0% in PD-L1(-) pts (n = 20). Median PFS in PD-L1(+) pts was 11.7 w vs 5.9 w in PD-L1(-) pts. **Conclusions**: In pts with previously treated NSCLC, avelumab was administered safely with a toxicity profile similar to other anti-PD-1/anti-PD-L1 agents. A trend of greater activity in pts with PD-L1(+) tumors was observed. A randomized phase 3 trial of avelumab in pts with advanced NSCLC is planned. *Proposed INN. Clinical trial information: NCT01772004.

8035 Poster Session (Board #357), Mon, 8:00 AM-11:30 AM

Activity and safety of pembrolizumab in patients with metastatic non-small cell lung cancer with untreated brain metastases. *First Author: Sarah B. Goldberg, Yale Cancer Center, New Haven, CT*

Background: Brain metastases (BrMs) are common among patients (pts) with advanced non-small cell lung cancer (NSCLC) and local therapy such as surgery and radiation can add toxicity and delay systemic treatment. Pembrolizumab is a monoclonal anti-programmed death 1 (PD-1) antibody that relieves inhibition of anti-tumor immunity. In a Phase I trial of pembrolizumab, pts with advanced NSCLC showed a 21% response rate with good tolerability and durable responses, however pts were required to have local therapy to BrMs prior to enrollment. This trial aims to determine the activity and safety of pembrolizumab in patients with advanced NSCLC and untreated BrMs. **Methods:** This is a Phase II trial with 2 independent arms: one for pts with advanced NSCLC (reported here) and the other for pts with metastatic melanoma (NCT02085070). Pts are eligible if they have ≥ 1 BrM that is previously untreated or progressing after prior local therapy. BrMs must be between 5mm and 20mm, asymptomatic, and not requiring immediate local therapy or corticosteroids. Tumor biopsy demonstrating PD-Ligand 1 (PD-L1) expression is required. Pts are treated with pembrolizumab 10mg/kg intravenously every 2 weeks. Extra-cerebral response is determined by RECIST 1.1, and BrM response is determined by modified RECIST (mRECIST), in which brain lesions ≥ 5mm are considered measurable and up to 5 target lesions are allowed. The primary endpoint is BrM response rate (RR) by mRECIST. **Results:** Ten NSCLC pts were accrued between April and December 2014, 9 of whom were evaluable for response. BrM RR was 44% (4/9 partial responses, 2 unconfirmed due to limited follow-up time); 34% (3/9) had progressive disease (PD) as their best BrM response, and 22% were unevaluable in the brain due to rapid systemic progression. Systemic RR was 34% (3/9, 1 unconfirmed); only 1 pt who responded systemically had PD in the brain. There were no grade ≥ 3 adverse events that were considered treatment-related or attributed to BrMs. **Conclusions:** Pembrolizumab shows promising clinical activity in patients with NSCLC and untreated BrMs with a favorable safety profile. Recruitment for this Phase II trial and correlative analysis from tumor tissue is ongoing. Clinical trial information: NCT02085070.

8036 Poster Session (Board #358), Mon, 8:00 AM-11:30 AM

Validation of ERCC1 (E1) for response prediction to platinum-gemcitabine. *First Author: Gerold Bepler, Karmanos Cancer Institute, Detroit, MI*

Background: E1 had been suggested as a predictive marker for platinum drugs. However, it has 4 different isoforms with differential DNA repair functions, antibodies used for quantitation lack specificity, and a phase 3 trial designed to validate E1's predictive power failed to demonstrate the anticipated benefit (trial A). We investigated the interaction of E1 mRNA levels with therapeutic benefit from various therapeutic doublets in pts with advanced NSCLC. **Methods:** FFPE specimens from trial A were microdissected; RNA was extracted, and analyzed for E1 levels using commercially validated primers and probes. Median and optimized cut-offs were investigated for interaction of E1 levels with survival and validated using a second randomized phase 3 trial (trial B, Ann Oncol 25: 2147–55, 2014). **Results:** E1 expression analysis on 84 pts in trial A, 38 treated with PG and 46 with other doublets, showed a significant ($p = 0.044$), inverse association between E1 mRNA levels and disease response in pts treated with PG; i.e., the higher the E1 levels the worse the tumor response. An analysis for treatment interaction (PG vs others) using the optimized E1 cut-off level of 1.44 showed E1 was highly predictive of OS and PFS in pts on PG, with high levels predicting short survival (Cox model interaction $p = 0.002$ for OS and 0.003 for PFS). Using the median E1 level of 1.73, the interaction p-value was 0.028. E1 levels were not associated with histology, sex, age, and smoking status. Specimens from 86 pts in trial B yielded sufficient RNA for a successful E1 analysis. 19 pts had been treated with PG, 55 with P-docetaxel, and 12 with docetaxel. E1 values were similar to those in trial A. Using the optimized E1 cut-off level of 1.44 from trial A, we found a log-rank p-value of 0.029 for PFS, with high levels predicting short survival for pts treated with PG. A 2ndvalidation on pts treated with PG in Torino, Italy is in progress. We also attempted to develop an RTPCR assay specific for the E1-202 isoform. Despite optimized primer/probe designs and validation using in vitro samples, the majority of FFPE samples failed analysis. **Conclusions:** E1 mRNA levels, as determined by a commercially available and CLIA/CAP certified assay, are predictive of treatment benefit from PG in advanced NSCLC.

8037 Poster Session (Board #359), Mon, 8:00 AM-11:30 AM

Pre-treatment 5-methyltetrahydrofolate levels and response to pemetrexed in stage IV adenocarcinoma of the lung. *First Author: Stephen Joseph Bagley, University of Pennsylvania, Philadelphia, PA*

Background: The anti-folate drug pemetrexed (PMX) is used in treatment regimens for non-small cell lung cancer (NSCLC). Recent evidence suggests that differences in cellular folate metabolism may confer variation in tumor response to PMX. We investigated whether the pre-treatment intra-erythrocyte (RBC) level of 5-methyltetrahydrofolate (5-MTHF), a key component of folate metabolism, is associated with response to PMX-based chemotherapy in stage IV lung adenocarcinoma. **Methods:** We conducted a single-center, prospective cohort study of patients with newly diagnosed stage IV lung adenocarcinoma receiving first-line chemotherapy with a PMX-containing regimen. RBC 5-MTHF levels were quantified using a mass spectrometry-based method from blood drawn prior to initiation of chemotherapy. Clinical response was assessed by determining radiographic tumor response after 4-6 cycles of PMX-based chemotherapy and categorized as partial response, stable disease, or progression. We explored the relationship between pre-treatment RBC 5-MTHF levels and response to PMX-based chemotherapy. A log-binomial model was used to adjust for age and sex. **Results:** 54 patients were enrolled; the median age was 61 (IQR 55-68) and 29 (54%) were female. RBC 5-MTHF ranged from 37 to 1,667 nM (mean 588, median 518). Following 4-6 cycles of chemotherapy, 23 patients (43%) had an objective radiographic response and 15 (28%) had stable disease. The remaining 16 patients (29.6%) had progression (7 during cycles 1-3, 9 during cycles 4-6). Patients with 5-MTHF levels in the lowest quartile were significantly less likely to achieve radiographic response compared to patients in the highest three quartiles (response rate 8% vs. 54%; risk difference 0.46, 95% CI 0.25-0.67). After controlling for age and sex, there remained a significantly higher likelihood of lack of response to PMX for patients in the lowest 5-MTHF quartile (RR 6.86, 95% CI 1.01 – 46.92). **Conclusions:** Low pre-treatment RBC 5-MTHF levels are associated with an inferior response to PMX-based chemotherapy in stage IV lung adenocarcinoma. Multicenter prospective studies are needed to validate RBC 5-MTHF as a predictive marker of response to PMX in NSCLC.

8038 Poster Session (Board #360), Mon, 8:00 AM-11:30 AM

Smoking status to predict sensitivity to PARP inhibitor, veliparib, in patients with advanced NSCLC. *First Author: Suresh S. Ramalingam, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Tobacco-related non-small cell lung cancer (NSCLC) is associated with reduced survival and greater genomic instability. Veliparib (V) is a PARP inhibitor that augments platinum-induced DNA damage in preclinical studies, and a recent Ph 2 trial of advanced NSCLC trended to improved survival (HR 0.80; CI 0.54–1.18) when V was added to carboplatin (C) and paclitaxel (P). Here we report outcomes based on smoking status from a randomized Ph 2 study of CP with either V or placebo in advanced NSCLC. **Methods:** Patients (pts) with previously untreated advanced/metastatic NSCLC were randomized 2:1 to CP with either V at 120 mg BID or placebo (pre-specified stratification by histology and smoking history). Cotinine (COT) was measured in pt plasma samples as an index of recent tobacco use. **Results:** Of 158 pts, 68% were male, and 49% had squamous NSCLC. At study entry, 60% of pts were self-reported current smokers (CS), 27% former smokers, and 13% never smoked. There were no significant differences in V PK parameters between the COT-high and low pts.Most common AE in CS were neutropenia (41% VCP; 27% CP), alopecia (36%; 33%), and anemia (31%; 40%). G3/4 AEs were elevated in CS treated with VCP vs CP (66% vs. 40%, p=0.026); all-grade AEs and SAEs were similar between the two groups. In a COT sensitivity analysis of OS, HR VCP/CP for COT-high was 0.52 (0.29–0.92) and COT-low was 1.07 (0.63–1.81). **Conclusions:** Smoking status was a strong predictor of efficacy for veliparib-chemotherapy combination in advanced NSCLC. No differences in PK of V were seen based on plasma COT; toxicity of VCP was acceptable regardless of smoking history. A Ph 3 study has been initiated in pts with smoking history. Clinical trial information: NCT01560104.

Median months (95% CI)		CP CS, n=31 Former, 14 Never, 8	VCP CS, n=64 Former, 28 Never, 13	HR VCP/CP	HR_{adj} VCP/CP (Adjusted for gender and ECOG PS)
PFS	CS	3.3 (1.4–4.2)	5.6 (4.1–7.0)	0.38 (0.21–0.67)	0.37 (0.21–0.68)
	Former	NA (3.3–NA)	6.0 (2.4–NA)	2.10 (0.66–6.65)	0.77 (0.20–3.06)
	Never	5.6 (1.4–8.2)	6.4 (1.0–NA)	1.03 (0.27–3.85)	0.96 (0.21, 4.46)
OS	CS	5.4 (3.8–8.8)	12.5 (9.9–16.6)	0.43 (0.26–0.70)	0.45 (0.27–0.76)
	Former	14.6 (9.2–NA)	8.6 (5.9–17.5)	1.62 (0.73–3.6)	0.72 (0.27–1.92)
	Never	NA (3.6–NA)	13.2 (5.0–NA)	1.34 (0.40–4.44)	0.71 (0.18–2.74)

8039 Poster Session (Board #361), Mon, 8:00 AM-11:30 AM

An open-label, randomized, multicenter, phase III study of S-1 and cisplatin versus docetaxel and cisplatin in patients with untreated advanced non-small-cell lung cancer. *First Author: Jianxing He, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou,Guangdong Province, China*

Background: Platinum-based doublet chemotherapy is the standard chemotherapy regimen for treatment-naïve advanced Non-Small-Cell Lung Cancer (NSCLC). S-1, an oral fluoropyrimidine, combined with carboplatin or cisplatin (CDDP) has shown no less efficacy than standard platinum doublet chemotherapy in Japanese NSCLC patients. However, the effectiveness in Chinese NSCLC patients is uncertain. We aimed to compare the efficacy and safety of these chemotherapy regimens in Chinese NSCLC patients. **Methods:** In this study, we recruited patients aged 18-70 years with stage IIIB, IV or recurrence, histologically or cytologically confirmed NSCLC, ECOG performance status of 0-1, have at least one measurable lesion, and adequate organ function. Patients were randomized in 1:1 ratio to receive either S-1 (80–120 mg/day, PO, BID, days 1 to 21) with 60 mg/m^2 CDDP on day 8 every 5 weeks (SP) or docetaxel and CDDP (both 75 mg/m^2) on day 1 every 3 weeks (DP), for up to 6 cycles. The primary endpoint was progression-free survival (PFS) and all CT scans were extramurally reviewed by Independent Review Committee (IRC). Non-inferiority study design was employed as upper confidence interval (CI) limit for hazard ratio (HR) < 1.33. **Results:** Between March 2011 and November 2012, 246 patients from 21 institutions in China were randomly assigned and received SP or DP treatment (124 vs 122) with 18-month follow-up period from the last patient randomized. In the SP and DP group, median PFS was 5.9 and 5.7 months (HR = 0.68; 95% CI, 0.48 to 0.96) respectively, median overall survival was 19.1 and 14.8 months, respectively (HR = 0.84; 95% CI, 0.61 to 1.14). The most common grade 3 or worse adverse events in both treatment groups were neutropenia 3.3% vs 55.1%, leukopenia 1.7% vs 39.0%, and febrile neutropenia 0.8% vs 5.9%, of 121 patients in the SP group and of 118 patients in the DP group, respectively. **Conclusions:** The efficacy of SP was non-inferior to DP. Well-tolerated safety could be provided by SP regimen. SP would be a new first-line chemotherapy regimen for Chinese patients with advanced NSCLC. Clinical trial information: Japic CTI-111479.

8040 Poster Session (Board #362), Mon, 8:00 AM-11:30 AM

SWOG 0709: A randomized phase II "pick-the-winner" trial of erlotinib (ERL) vs. ERL plus carboplatin/paclitaxel (C/T) in patients (pts) with advanced non-small cell lung cancer (NSCLC) and impaired performance status (PS 2) as selected by serum proteomics. *First Author: Primo Lara, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Advanced NSCLC pts with Zubrod PS2 are often excluded from clinical trials and platinum-based therapy. In SWOG 0341, ERL in PS 2 pts yielded progression-free (PFS) and overall survival (OS) of 2.1 and 5 months respectively. In a trial of ERL versus C/T in PS2 pts (Lilenbaum, JCO 2008), PFS for ERL and C/T were 1.9 and 3.5 months. Early reports suggested a potential role for serum proteomics in predicting ERL benefit beyond that of EGFR mutational status. We conducted a trial in PS2 pts enriched by serum proteomics (Veristrat-good). **Methods:** NSCLC pts with PS2 and Veristrat-good status were randomized to either Arm A (ERL 150 mg po QD) or Arm B (ERL 150 mg po QD d2-16 + carbo AUC 5 IV day 1, paclitaxel 200 mg/m2 IV d1 x 4 cycles, then ERL 150 mg QD). Cycles were q3 weeks. Arm B agents were pharmacodynamically separated to mitigate potential antagonism. The arm with superior observed median PFS would be selected for further evaluation, but only if ≥ 3 months. A sample size of 98 pts was based on a variety of assumed PFS probabilities for each arm. The trial prematurely closed after the FDA determined an IDE application was required for VeriStrat; however SWOG had limited resources available for such filing. **Results:** Of 156 pts screened, 83 (59%) were Veristrat-good, of which 59 (60%) met trial eligibility & were randomized. Treatment-related grade 4 adverse events were seen in 2 pts in Arm A (DVT, hypoMg+); 5 pts in Arm B (neutropenia 5, febrile neutropenia 1, leukopenia 1). **Conclusions:** In PS2 pts with advanced NSCLC and Veristrat-good status, ERL + C/T (vs. ERL alone) had better observed median PFS/OS and surpassed the protocol-specified benchmark of PFS >= 3 months required for further study. Clinical trial information: NCT00661193.

	Arm A: ERL (N=33)	Arm B: ERL + C/T (N=26)	p-value
Characteristics (n,%)			
Median age (years)	75	71	
Male sex	14 (42%)	10 (38%)	
Adenocarcinoma	27 (82%)	23(88%)	
Never smoker	6 (18%)	6 (23%)	
Efficacy			
Response rate* (n, %)	2/32 (6%)	6/26 (23%)	0.06
DCR* (n, %)	13/32 (41%)	20/26 (77%)	0.0046
PFS (median, months)	1.6	4.6	0.06
OS (median, months)	6	11	0.27

*Subset w/ measurable disease at baseline.

8041 Poster Session (Board #364), Mon, 8:00 AM-11:30 AM

A randomized Phase 3 study comparing first-line pemetrexed plus cisplatin followed by gefitinib maintenance (PC/G) with gefitinib monotherapy (G) in East Asian patients (pts) with locally advanced or metastatic nonsquamous non-small cell lung cancer (nSqNSCLC): Final survival results. *First Author: James Chih-Hsin Yang, Department of Oncology, National Taiwan University Hospital; Graduate Institute of Oncology & Cancer Research Center, National Taiwan University, Taipei, Taiwan*

Background: The primary analysis of this open-label, randomized, multicenter study found no significant difference in progression-free survival (PFS) between PC/G and G in pts with nSqNSCLC and unknown epidermal growth factor receptor (EGFR) mutation status, although the unadjusted hazard ratio (HR, PC/G vs G) favored PC/G (0.85, 95% CI: 0.63–1.13). Final overall survival (OS) data are reported here. **Methods:** Eligible pts were chemonaïve, East Asian light ex-smokers/never-smokers aged ≥18 years with advanced nSqNSCLC, ECOG PS 0/1 and unknown EGFR mutation status. Pts (N = 236) were randomized (1:1) to PC/G (pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 for six 21-day cycles then gefitinib 250 mg/day) or G (gefitinib 250 mg/day). EGFR mutation status was determined for 76 pts; 52 (68.4%) had mutations. OS was analyzed (intent-to-treat population) by unadjusted Cox regression analysis. **Results:** Baseline characteristics were similar between groups (both N = 118). Median OS was similar in the PC/G and G groups in the overall population, but longer in the G group in the subgroups with EGFR mutations (EGFR-mutated, Ex19del, L858R; Table). Postdiscontinuation therapy (PC/G: 60.2%; G: 72.0%) included chemotherapy (PC/G: 34.7%; G: 61.9%) and rechallenge with an EGFR tyrosine kinase inhibitor (PC/G: 22.9%; G: 7.6%). **Conclusions:** There was no significant difference in OS between PC/G and G in the overall population. As reported for PFS, there appeared to be better outcomes with G in the EGFR mutation subgroups (especially Ex19del) and with PC/G in the EGFR wild-type subgroup. Clinical trial information: NCT01017874.

	OS (mo) Median (95% CI)		
Population (n)	**PC/G**	**G**	**PC/G vs G HR (95% CI; *P* value)**
Overall (236)	26.87 (20.76–35.12)	27.86 (21.26–32.36)	0.94 (0.68–1.31; 0.717)
EGFR wild-type (24)	28.35 (11.27–50.63)	8.94 (0.69–NE)	0.62 (0.22–1.72; 0.356)
EGFR-mutated (52)	32.39 (19.29–NE)	45.70 (25.76–NE)	1.57 (0.72–3.39; 0.255)
Ex19del (26)	32.39 (15.15–NE)	45.70 (18.66–NE)	2.36 (0.70–7.92; 0.166)
L858R (24)	35.65 (1.25–NE)	41.26 (13.60–NE)	1.23 (0.41–3.67; 0.709)

NE: not estimable.

8042 Poster Session (Board #365), Mon, 8:00 AM-11:30 AM

Intercalating and maintenance use of gefitinib plus chemotherapy versus chemotherapy alone in selected advanced NSCLC(ISCAN,CTONG-1102): A multicentre, open-label, randomised, phase 3 study. *First Author: Shun Lu, Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China*

Background: This study investigated whether intercalating and maintenance use of gefitinib and chemotherapy improves clinical outcomes versus chemotherapy alone in selected patients with advanced NSCLC after receiving two cycles of chemotherapy with stable disease. **Methods:** We undertook an open-label, randomized, phase 3 trial at 14 centers in China. We assigned previously untreated patients in China who had stage IIIB or IV pulmonary adenocarcinoma and who were nonsmokers and EGFR mutation status unknown to firstly receive two cycles of gemcitabine plus carboplatin(GC). The patients with stable disease were randomly assigned (1:1) to receive gefitinib on days 15 to 25 of a 4-week cycle of GC or a 4-week cycle of GC alone. In the absence of disease progression, chemotherapy was continued for a maximum of four cycles, after which time patients continued to receive gefitinib or observation until disease progression or unacceptable toxicity. The primary end point was progression-free survival. Secondary end points included overall survival and safety. The trial is registered at ClinicalTrials.gov, number NCT01404260, and has completed enrolment. **Results:** 109 patients were randomly assigned to receive intercalating and maintenance use of gefitinib plus chemotherapy and 110 to receive chemotherapy alone. 109 in the intercalating and maintenance group and 109 in the chemotherapy alone group were included in analysis of the primary endpoint. Median progression-free survival was significantly longer in intercalating and maintenance use of gefitinib-treated patients than in those on chemotherapy alone(10.0 vs 4.4 months; hazard ratio 0.475, 95% CI 0.349-0.646; p < 0.0001). The addition of gefitinib to chemotherapy was well tolerated. **Conclusions:** Intercalating and maintenance use of gefitinib plus gemcitabine/carboplatin led to a significant improvement in PFS for advanced pulmonary adenocarcinoma Chinese patients with nonsmoking and EGFR mutation status unknown after receiving two cycles of gemcitabine/ carboplatin with stable disease. Clinical trial information: NCT01404260.

8043 Poster Session (Board #366), Mon, 8:00 AM-11:30 AM

Maintenance therapy with gefitinib (G)/pemetrexed (P) versus P alone after induction therapy with P/platinum for metastatic lung adenocarcinoma (MLADC) harboring no sensitizing epidermal growth factor receptor mutation (sEGFRm): A phase II multicenter randomized open-label study (GENIUS trial). *First Author: Chun-Ming Tsai, Division of Thoracic Oncology, Department of Chest Medicine, Taipei Veterans General Hospital & Department of Medicine, National Yang-Ming University, Taipei, Taiwan*

Background: Synergistic EGFR-tyrosine kinase inhibitor (TKI)-chemotherapeutic interaction in lung cancer cells has 3 basics: no platinum, cells not sensitive to EGFR-TKI, and using a synergistic chemo partner, e.g., pemetrexed (Tsai, et al. Lung Cancer 82:305, 2013). **Methods:** GENIUS (NCT01579630) was a prospective trial comparing maintenance G/P v P in patients (pts) with MLADC harboring no sEGFRm detected by high sensitivity methods following a 4-cycle P/Platinum induction therapy in frontline setting. Pts with no disease progression (PD) were 1:1 randomized to receive P (500mg/m^2, 3-week cycle) ± G (250mg, daily) until PD or treatment failure, and stratified by center and response. The primary endpoint was progression free survival (PFS) by both independent radiologist review (IRR) and investigator assessment (IA), secondary endpoints included time to treatment failure (TTF), overall survival, safety and toxicity profile. **Results:** Between 03/2011 and 11/2013, 55 pts were randomized, G/P 26, P 29. Baseline characteristics were balanced between arms (age 57; female 42%; never smoker 55%; ECOG1 91%; ≥ 2 metastatic sites 38.2%; ALK+ 16%). Median follow-up was 15.9 mo. Median cycle of treatment was G/P 8.5 (range 1-27) and P 4 (2-17). Median PFS was substantially longer for G/P than P, both by IRR (3 deemed as PD at randomization were excluded; n = 25 v 27): 8.4 v 3.8 mo; HR [95% CI] 0.35 [0.18-0.68]; p = 0.0014, and by IA: 8.5 v 2.9 mo; HR 0.34 [0.18-0.64], p = 0.0005. Response with induction therapy, age, and smoker had interactions with treatment for PFS. Median TTF: 7.0 v 2.9 mo; HR 0.43 [0.24-0.79], p = 0.005. There were more treatment-related diarrhea, liver and skin toxicities on G/P v P, but generally mild. 2 G/P pts were off-study due to liver toxicity. Death occurred in 8 G/P and 14 P pts. **Conclusions:** GENIUS is the first prospective trial to show robust PFS benefit of EGFR-TKI plus chemo in the maintenance phase of 1st line treatment for MLADC with no sEGFRm and proved our concept. This strategy deserves phase III study to confirm. Clinical trial information: NCT01579630.

8044 Poster Session (Board #367), Mon, 8:00 AM-11:30 AM

Pharmacodynamic separation (PDS) of pemetrexed (Pem) and erlotinib (Erl) in patients (pts) with advanced, EGFR wild-type (wt) Non-Small Cell Lung Cancer (NSCLC): A randomized phase II trial. *First Author: Tianhong Li, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: We previously reported that PDS of Pem and Erl (Pem 500 mg/m^2 IV on day 1 and Erl 150 mg po QD on days 2-17 of a 21-day cycle) as 2nd-line therapy has promising clinical activity over Pem alone in 75 unselected pts with advanced non-squamous NSCLC (NCT00950365; Li et al., ASCO 2013). Given pts with EGFR mutant NSCLC usually have better clinical response to Pem or Erl monotherapy, we updated the efficacy analysis restricted to those pts with confirmed EGFR wt NSCLC. **Methods:** EGFR genotype status was determined by the Clinical Laboratory Improvement Amendments-certified RT-PCR, direct sequencing, and/or Sequenom multiplex genotype tests using archival formalin fixed, paraffin embedded tumor specimens or plasma circulating tumor DNA from study pts. For those pts with only blood samples, a repeat or alternative test was used to confirm the status of EGFR wt genotype. The parent study was designed to detect an increase in median progression-free survival (mPFS) by 50%, i.e., a hazard ratio (HR) of $\leq$ 0.67. **Results:** 59 (79%) of 75 eligible pts had confirmed EGFR wt (N=52) or EGFR-mutant (N=7) genotype. The results are summarized in Table 1. Longer PFS was observed in pts with EGFR WT NSCLC treated with the combination (Arm B). **Conclusions:** PDS of Pem and Erl as 2nd-line therapy appears to have promising clinical activity in pts with advanced, EGFR wt non-squamous NSCLC, which comprises of 85% of non-Asian NSCLC pts, and warrants further confirmation. (UL1 RR024146, P30CA093373, Astellas, Eli Lilly). Clinical trial information: NCT00950365.

Clinical efficacy in pts with EGFR wt NSCLC.

Treatment Arm (Pt No)	Median Age	Female	Smoking hx (< 15 PY)	mPFS: mo (95% CI)	Median OS: mo (95% CI)	ORR: % (95% CI)	DCR 3mo: % (95% CI)	DCR 6mo: % (95% CI)	DCR 12mo: % (95% CI)
A: Pem (N = 21)	64	57.1%	23.8%	3.5 (1.6-5.5)	9.2 (3.3-11.8)	10% (0-22%)	52% (31%-74%)	29% (9%-48%)	10% (0-22%)
B: Pem + Erl (N = 31)	62	54.8%	25.8%	5.3 (3.6-7.6)	9.9 (6.6-20.0)	29% (13%-45%)	71% (55%-87%)	45% (28%-63%)	23% (8%-37%)
p value	0.23$	0.87&	0.87& HR (95% CI)	0.11* 0.63 (0.4-1.1)	0.44* 0.77 (0.4-1.4)	0.17#	0.24#	0.26#	0.28#

$t-test; &chi-square; *Log-rank test; #Fisher's exact test.

8045 Poster Session (Board #368), Mon, 8:00 AM-11:30 AM

A phase 1b study of the anti-cancer stem cell agent demcizumab (DEM), pemetrexed (PEM) & carboplatin (CARBO) in pts with 1st line non-squamous NSCLC. *First Author: Dusan Kotasek, Adelaide Cancer Centre, Kurralta Park, Australia*

Background: Delta-like ligand 4 (DLL4) activates the Notch pathway & is important for cancer stem cell (CSC) survival. DEM is a humanized IgG$_2$anti-DLL4 antibody that has been shown to inhibit tumor growth, decrease CSC frequency & cause dysfunctional sprouting of new vessels resulting in an antiangiogenic effect in human tumor xenograft models. **Methods:** Pts received DEM (2.5 or 5 mg/kg), PEM 500 mg/m^2 & CARBO (AUC = 6) every 3 weeks X 6 cycles followed by maintenance DEM (cohorts 1-4) or truncated DEM (5 or 7.5 mg/kg), PEM 500 mg/m^2& CARBO (AUC = 6) every 3 weeks X 4 cycles followed by maintenance PEM (cohorts 5 & 6). The objectives were to determine the MTD, safety, efficacy, immunogenicity, pharmacokinetics & biomarkers of Notch signaling. **Results:** Thirty-nine pts were enrolled; 6 received 2.5 mg/kg, 20 received 5 mg/kg, 6 received 7.5 mg/kg of truncated DEM & 7 received 5 mg/kg of truncated DEM. Related AEs in $>$ 20% of pts were: nausea (51%), fatigue (46%), hypertension (46%), vomiting (31%), edema (26%), neutropenia (26%), increased B-type natriuretic peptide (BNP) (26%) & anemia (21%). Increased BNP values are an early indicator of the cardiac effects of DEM & mildly elevated values are being used to initiate cardioprotective therapy with an ACE inhibitor or carvedilol. Two pts receiving 5 mg/kg developed reversible pulmonary hypertension & heart failure on days 167 & 183, respectively. As a result, DEM treatment was limited to 63 days in cohorts 5 & 6. One of 33 (3%) evaluable pts had a RECIST CR, 15 (45%) had a PR & 13 had SD. The Kaplan Meier estimated median progression free survivals for the 2.5, 5, truncated 5 & truncated 7.5 mg/kg pts were 4.3, 5.3, not yet reached & 4.4 months, respectively. Eight pts who discontinued the study for a reason other than progression (6 continued to receive CARBO &/or PEM off-study) were progression-free through Days 314+, 408+, 448+, 456+, 546+, 677+ 680+ & Day 850. **Conclusions:** This therapy was generally well tolerated with nausea, fatigue & hypertension being the most common drug related toxicities. Encouraging early clinical activity has been observed. Biomarker data showed modulation of the Notch pathway. Final data will be presented. Clinical trial information: NCT01189968.

8046 Poster Session (Board #369), Mon, 8:00 AM-11:30 AM

A phase Ib study of selumetinib in patients (pts) with previously untreated metastatic Non-Small Cell Lung Cancer (NSCLC) receiving standard chemotherapy: NCIC Clinical Trials Group IND.215. NCT01783197. *First Author: Garth Andrew Nicholas, Ottawa Hospital Regional Cancer Centre, Ottawa, ON, Canada*

Background: Selumetinib (AZD6244, ARRY-142886, S) is a potent inhibitor of MEK, with promising activity with docetaxel in pts with previously treated NSCLC. Non-clinical data suggest potential negative interaction with platin. We conducted a phase Ib study testing continuous or intermittent S with either cisplatin/pemetrexed (CPe; non-squamous) or carboplatin/paclitaxel (CPa) in previously untreated NSCLC. **Methods:** Pts received CPa (C AUC 6; Pa 200mg/ m2) or CPe (C 75mg/ m2 ; Pe 500mg/ m2) or for 4-6 21day cycles; single-agent S continued. A 3+ 3 design was used, dose levels (DL) were: DL1 50mg bid d2-19, DL2 75 mg bid d2-19, DL3 75 mg bid d1-21 (continuous) with an expansion cohort at RP2D. DLTs were assessed in cycle 1. **Results:** 30 pts were enrolled and 27 currently evaluable for adverse events (AE). In both cohorts, the most common S related toxicities were mild GI and skin. For CPa, 11 pts were treated, and no DLTs were seen at any DL. CPa related AEs were as expected. 2 pts had dose reductions of S (1 each of fatigue, skin toxicity). Most AEs related to S were grade (G) 1-2 and included gastrointestinal and skin. 4 pts had $\geq$ G3 AEs considered related to S (includes 1 pt with fatal lung infection also related to CPa and 1 pt with fatal stroke also related to disease & CPa). 2 pts had G3 neutropenia; 1 pt had G4 thrombocytopenia; 1 pt had G3 LFTs. For CPe, 16 pts are currently evaluable; 2 possible DLTs were seen at the continuous DL (vomiting but inadequate antiemetics). Expansion to that DL ongoing. CPe related AEs were as expected. 3 pts had dose reductions of S (1 each of CPK, fatigue, dehydration). 3 additional pts had G3 AE (retinal vascular disorder, thromboembolism, diarrhea/ dehydration/ hypertension) related to S. There were no S related G5 events. There were no G4 hematologic toxicities. One pt had a G3 increase in CPK. **Conclusions:** S can be given in combination with CPe or CPa at full single agent doses, with generally mild incremental GI and skin toxicity. Patients continue to be enrolled to the RP2D expansion cohorts at a dose of 75 mg bid d1-21. NCIC CTG plans further P2 studies of CPe with S in NSCLC. Clinical trial information: NCT01783197.

8047 Poster Session (Board #370), Mon, 8:00 AM-11:30 AM

A phase Ib study of abemaciclib in combination with multiple single agents in stage IV NSCLC. *First Author: Edward S. Kim, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC*

Background: Abemaciclib, a cell cycle kinase inhibitor of CDK4/CDK6, demonstrated acceptable safety and early clinical activity in metastatic NSCLC, given orally as monotherapy on a continuous schedule. In preclinical models of KRAS-mutant NSCLC, combinations of abemaciclib with other agents showed greater antitumor activity compared with monotherapy. Primary aim in study NCT02079636 was safety and tolerability of combination therapy with abemaciclib; secondary aims were pharmacokinetics (PK), antitumor activity, and patient (pt) reported outcomes. **Methods:** In this phase Ib open-label 3 + 3 dose-escalation study with expansion cohorts, pts received abemaciclib in combination with pemetrexed (Part A, nonsquamous), gemcitabine (Part B), ramucirumab (Part C), or LY3023414 (dual PI3K-mTOR inhibitor, Part D). Pts with stage IV NSCLC, ECOG PS $\leq$ 1, and 1-3 prior therapies were eligible. In escalation, pts were dosed continuously until progression with abemaciclib at 150 mg or 200 mg orally Q12H. Doses for other agents were: pemetrexed (500 mg/m^2 IV day 1), gemcitabine (1250 mg/m^2 IV days 1 and 8), ramucirumab (8 mg/kg IV days 1 and 8, or 10 mg/kg IV day 1) (Q21). In Part D, pts will receive LY3023414 at 100 mg, 150 mg or 200 mg orally Q12H. **Results:** Asof 27-OCT-2014, 40 pts received $\geq$ 1 dose of treatment; 15 pts at 150 mg and 25 pts (including all 10 pts in expansion) at 200 mg Q12H abemaciclib. In escalation, 3 dose-limiting toxicities were observed: 2 in Part A (150 mg: G4 neutropenia, 200 mg: G4 febrile neutropenia), and 1 in Part C (200 mg: G3 diarrhea). Possibly related G3/4 TEAEs in $\geq$ 2 pts (% Parts A, B, C) were: neutropenia (38, 15, 9), leukopenia (19, 8, 9), diarrhea (0, 8, 18), fatigue (13, 8, 0), anemia (13, 8, 0), and thrombocytopenia (0, 8, 9). Among 25 pts remaining on treatment, 5 pts (3 in Part A; 2 in Part C) received treatment $\geq$ 4 cycles. In Part C, 2 pts had unconfirmed PRs (RECIST v1.1), 1 pt (150 mg) with nonsquamous histology and KRAS mutation, and 1 pt (200 mg) with squamous histology and unknown KRAS status. **Conclusions:** Abemaciclib could be combined with other agents in NSCLC. Toxicities of combinations were consistent with those of the single agents. Findings will be reviewed with PK to support the recommended dose for each combination. Clinical trial information: NCT02079636.

8048 Poster Session (Board #371), Mon, 8:00 AM-11:30 AM

Individual patients data analysis (IPD) of three randomized studies comparing erlotinib (E) with chemotherapy (CT) in patients with advanced wild-type epidermal growth factor receptor (wtEGFR) non-small cell lung cancer (NSCLC). *First Author: Valter Torri, IRCCS-Mario Negri Institute, Milano, Italy*

Background: While the benefit of EGFR tyrosine kinase inhibitors in EGFR mutated NSCLC patients (pts) is undisputed, their usefulness in wtEGFR pts is still questioned. The TAILOR, DELTA and PROSE trials singularly showed a significant gain in Progression-Free Survival (PFS) favoring CT. We present here the mature results from the IPD analysis of the three studies. **Methods:** In each trial, pts with wtEGFR stage IIIB/IV NSCLC, progressing after first line platinum-based therapy, were randomized 1:1 to receive either E or CT at standard doses. Primary endpoints of this IPD were PFS and Overall Survival (OS); summary measures were Hazard Ratio (HR) and Difference in Mean Survival Time (DMST), which is the difference in the areas under the Kaplan-Meier curves of two treatment arms. Cox regression analyses were used to estimate the HR. All analyses were stratified by trial. **Results:** The analysis included all 587 pts randomized into the trials (Overall E/CT 303/284; TAILOR 109/110; DELTA 109/90; PROSE 85/84); 464 deaths and 570 progressions or deaths were observed. Compared with CT, E treatment was associated to an increased risk of both progression (40%) and death (12%) (HR-PFS: 1.40, 95%CI: 1.18-1.65, $p < 0.0001$; HR-OS: 1.12, 95%CI: 0.93-1.35; $p = 0.221$). Importantly, patients treated with CT gained 1.6 and 1.5 months, in progression-free and life-time respectively (DMST-PFS 95%CI: 0.6-2.1; DMST-OS 95%CI: -0.5-3.4). Results were preserved after adjustment by age, gender, smoking habit, performance status and histotype. **Conclusions:** The IPD analysis of TAILOR, DELTA and PROSE conclusively confirm the superiority of CT over E in the disease control of wtEGFR NSCLC patients, and corroborate the original results of each single trial.

8049 Poster Session (Board #372), Mon, 8:00 AM-11:30 AM

Randomized phase III trial of erlotinib vs. docetaxel in patients with advanced squamous cell non-small cell lung cancer (SqNSCLC) failing first line platinum based doublet chemotherapy stratified by VeriStrat Good vs VeriStrat Poor: The European Thoracic Oncology Platform (ETOP) EMPHASIS trial. *First Author: Solange Peters, University Hospital of Lausanne (CHUV), Lausanne, Switzerland*

Background: Docetaxel (D) or Erlotinib (E) are registered second-line treatments for *EGFR* wild type NSCLC. Previous studies suggested a predictive value of the serum proteomic VeriStrat test (VS), assigning a good (VSG) or poor (VSP) classification in second-line therapy of patients (pts.) with NSCLC. EMPHASIS aimed at exploring a predictive interaction in SqNSCLC pts. The trial closed prematurely due to low accrual. **Methods**: EMPHASIS is a randomized phase III multicenter trial exploring the differential activity of second line E vs D on progression-free survival (PFS) in VSG vs VSP SqNSCLC. The expected hazard ratio (HR) of E vs D was 0.675 for the VSG patients (median PFS, E: 4.0 and D: 2.7 mo.), and 1.23 for the VSP patients (median PFS, E: 2.2 and D: 2.7 mo.). A sample size of 500 was needed to achieve 86% power for testing the expected interaction HR of 1.82 at a two-sided p-value of 0.05. Pts were randomized to receive treatment E150 mg p.o. daily or D 75 mg/m2 i.v. on day 1 of each 21 day cycle. **Results**: From 1/2013 to 1/2014, a total of 80 patients were randomized to the study, with 72.5% categorized as VSG. Median age was 69 years with the majority being male (83%), smokers (94%), and having good performance status (91%). No unexpected serious adverse events (SAEs) were observed in either treatment arm. All pts are off treatment (median time to treatment failure: 2.1 mo.), while 73 progression events (median PFS: 2.7 mo.) and 56 deaths (median OS: 7.1 mo.) were observed. Median PFS for VSG is 4.1 and 1.6 mo. under D and E respectively, and 1.9 and 2.1 mo. for VSP pts (HR = 1.04, interaction p-value = 0.94). Median OS for VSG is 7.8 and 8.4 mo. for D and E and 4.4 and 5.2 mo. for VSP. **Conclusions**: The final analysis of EMPHASIS did not show a differential activity on PFS of E vs D in SqNSCLC pts stratified by VS status. These results are at variance with trial assumptions and previous studies. In addition to the EMPHASIS results (PFS & OS), we will present a combined PFS/OS analysis with the subgroup of SqNSCLC from the PROSE study. **EudraCT number: 2012-001896-35.** Clinical trial information: NCT01652469.

8051 Poster Session (Board #374), Mon, 8:00 AM-11:30 AM

Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin in advanced non-small cell lung cancer (NSCLC) patient. *First Author: Markus Joerger, Cantonal Hospital, St. Gallen, Switzerland*

Background: Variability of chemotherapy exposure may cause severe toxicity or lack of efficacy. Paclitaxel (PTX) exposure (time above a plasma concentration of 0.05mM, Tc > 0.05) has been shown to predict toxicity. Whereas carboplatin dose is adapted to kidney function, PTX dosing only accounts for body-surface area. We developed a PTX dosing algorithm for avoidance of supra- or subtherapeutic PTX exposure based on Tc > 0.05 determined from a single blood sample drawn 18-30 hours after starting PTX infusion. This study was initiated to validate PK-guided PTX dosing in advanced NSCLC patients. **Methods:** 304 patients with advanced NSCLC were randomly assigned to receive up to 6 cycles of first-line 3-weekly carboplatin AUC 6 combined with PTX either at a standard dose of 200mg/m^2 (Arm A) or at a PK-guided dose (Arm B). Initial PTX dose in Arm B was between 150 to 200 mg/m^2 based on age and sex, and subsequent PTX doses were adjusted according to the previous cycle PTX Tc > 0.05 to target a Tc > 0.05 between 26 and 31 hours. Dose reductions were permitted in both arms for chemotherapy-associated toxicity. The study had a power of 90% to detect a 11% reduction of grade 4 neutropenia with PK-guided PTX dosing. **Results:** Major patient characteristics were male gender in 67%, current smokers in 38%, ≥ 65 years of age in 50%, performance status of 2 in 8%, squamous-cell histology in 21%.Compared to standard dosing, PK-guided dosing of PTX reduced the incidence of grade 4 neutropenia (measured on day 15 of each cycle) (15% v 21%, P = 0.029), grade ≥ 2 neuropathy (14% v 27%, P < 0.001), and grade ≥ 3 neuropathy (1% v 8%, P < 0.001). Median PTX dose at cycle 6 was significantly lower with PK-guided dosing (132 v 197 mg/m^2, P < 0.001), and the proportion of patients with supratherapeutic PTX exposure was reduced from 41% in cycle 1 to 2% in cycle 6. Objective response rate was 32% and 29% in Arms A and B (P = 0.70). Progression-free survival was 5.2 and 4.7 months in Arms A and B (hazard ratio 1.1, 95% CI 0.8-1.4, P = 0.54). **Conclusions:** PK-guideddosing of PTX improves the risk-benefit profile in patients with advanced NSCLC, primarily by a substantial reduction of PTX-associated neuropathy. Clinical trial information: 2010-023688-16.

8052 Poster Session (Board #375), Mon, 8:00 AM-11:30 AM

Paclitaxel (PTX) dose individualization by exposure optimization in Chinese patients with advanced non small-cell lung cancer (NSCLC) receiving first-line paclitaxel-carboplatin (PC) chemotherapy. *First Author: Jie Zhang, Department of Oncology, Shanghai Pulmonary Hospital, Tongji University, School of Medicine, Shanghai, China, Shanghai, China*

Background: PC chemotherapy is complicated by febrile neutropenia in up to 5% of patients with advanced NSCLC. PTX pharmacokinetic (PK) variability is a major factor in severe neutropenia. The time above a PTX plasma concentration of 0.05μmol/L ($T_{C > 0.05}$) is the key PK parameter to measure systemic exposure to the drug and is a predictor of severe neutropenia. Optimization of an individual's dose by exposure measures may improve PTX safety and efficacy. A randomized controlled study in Chinese NSCLC patients was performed to assess impact of PK-guided PTX dosing on safety and efficacy. **Methods:** To date, 141 stage IIIB/IV NSCLC patients receiving first-line PC chemotherapy have been enrolled. Patients are randomized to receive 4-weekly carboplatin (AUC = 5) plus paclitaxel at a starting dose of 175 mg/m^2 with subsequent PTX dosing based on body surface area (BSA) or PK-guided dosing to target a PTX $T_{C > 0.05}$ between 26 and 31 hours. Primary objective is to compare severe toxicities and response rates between BSA and PK arms. **Results:** Exposure values from 1st cycle in 90 patients show great PTX PK variability, with a mean $T_{C > 0.05}$ of 36 hr (range = 26 - 46 hr, CV = 27%). 14% of these patients had PTX exposure values within the target range (26 to 31 hr) while 86% were above target exposure. No patient showed PTX exposure below target at standard PTX dose of 175mg/m^2. Severe neutropenia rate for patients above exposure target was higher than those in target (grade 3 & 4 neutropenia of 31% vs 60%, grade 4 neutropenia of 0% vs 18%, respectively). Exposure optimization of PTX in PK arm leads to an overall 21% dose reduction. In 51 patients with 4 cycles of chemotherapy completed, severe neutropenia rate in PK arm at cycle 4 was 39% compared to 61% in BSA arm (p = 0.026). Response rate was also evaluated and showed no negative impact (24% PR rate in PK arm vs 16% in BSA arm). A higher neuropathy rate was observed in BSA arm (77%) compared to PK arm (42%). **Conclusions:** With exposure optimized PTX dose, severe neutropenia can be significantly reduced with no negative impact to clinical outcome.

8053 Poster Session (Board #376), Mon, 8:00 AM-11:30 AM

Exposure-response relationship for ramucirumab (RAM) from the randomized, double-blind, phase III REVEL trial (docetaxel [DOC] vs DOC plus RAM) in second-line treatment of metastatic non-small cell lung cancer (NSCLC). *First Author: Egbert F. Smit, Cancer Center Amsterdam, Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, Netherlands*

Background: An exploratory exposure-response analysis for RAM was performed using data from the REVEL trial (NCT01168973). **Methods:** Patients received RAM (10 mg/kg) or placebo (PL) + DOC (75 mg/m^2) every 3 weeks (q3w). Sparse pharmacokinetic (PK) samples were collected; a population PK (PopPK) analysis was conducted. PopPK model-predicted RAM exposure parameters ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) were used to evaluate the relationship between RAM exposure and measures of efficacy and safety. $C_{min,1}$ and $C_{ave,ss}$ are presented. Kaplan-Meier, Cox regression, and ordered categorical analyses evaluated these relationships. **Results:** Analyses included 376 RAM+DOC pts and 366 PL+DOC pts. Similar trends were seen for all four exposure parameters. As RAM exposure increased, greater improvements (smaller HRs) were seen in OS and PFS (table below). A statistically significant correlation was also seen for RAM exposure and grade ≥ 3 febrile neutropenia and hypertension. **Conclusions:** Results from exposure-response analyses suggest improvements in efficacy and increased toxicity may occur with increasing RAM exposure. RAM at a dose of 10 mg/kg q3w in combination with DOC is appropriate for the NSCLC indication. Clinical trial information: NCT01168973.

		Median (months)	Hazard ratio (95% CI)[a]
OS[b]			
PL+DOC		13.3	
RAM+DOC $C_{min,1}$	Q1	11.1	1.19 (0.89, 1.59)
	Q2	14.6	0.80 (0.58, 1.08)
	Q3	12.6	0.85 (0.63, 1.14)
	Q4	17.1	0.67 (0.48, 0.93)
PFS[b]			
PL+DOC		5.5	
RAM+DOC $C_{min,1}$	Q1	5.6	0.92 (0.72, 1.18)
	Q2	7.0	0.71 (0.55, 0.90)
	Q3	5.7	0.84 (0.67, 1.07)
	Q4	7.0	0.71 (0.55, 0.90)
Grade ≥3 AE[c]		Hypertension (%)	Febrile Neutropenia (%)
PL+DOC		2.8	11.8
RAM+DOC $C_{ave,ss}$	Q1	4.3	7.5
	Q2	5.3	19.1
	Q3	13.8	22.3
	Q4	6.4	21.3

[a]Adjusted for significant prognostic factors. [b]RAM+DOC pts stratified by $C_{min,1}$ quartile (μg/mL) (n = 94 for each): Q1 ≤ 15.7; Q2 > 15.7 ≤ 20.7; Q3 > 20.7 ≤ 27.9; Q4 > 27.9; compared to PL+DOC pts. [c]RAM+DOC pts stratified by $C_{ave,ss}$ quartile (μg/mL) (n = 94 for each): Q1 ≤ 79.3; Q2 > 79.3 ≤ 97.4; Q3 > 97.4 ≤ 118; Q4 > 118; compared to PL+DOC pts.

8054 Poster Session (Board #377), Mon, 8:00 AM-11:30 AM

Docetaxel + ramucirumab (DR) versus docetaxel + placebo (D) as second-line treatment for advanced non-small cell lung cancer (NSCLC): A randomized, phase II, double-blind, multicenter trial in Japan. *First Author: Yukio Hosomi, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan*

Background: A randomized global phase III trial (REVEL) demonstrated statistically significant improvement in OS and PFS for DR versus D in patients (pts) with advanced NSCLC; a limited number of East Asian pts were given docetaxel (DOC) at 75 mg/m^2, higher than 60 mg/m^{2}recommended in Japan. **Methods:** A similar phase II study was conducted in Japan to evaluate the efficacy of DR for stage IV NSCLC following disease progression during or after prior platinum-based chemotherapy. Pts with EGFR mutant NSCLC who received prior EGFR tyrosine kinase inhibitor (TKI) therapy were enrolled as exploratory. Eligibility criteria included ECOG PS 0-1, age ≥ 20 years, and adequate organ function. Pts were randomized 1:1 to receive DOC 60 mg/m^2+ramucirumab 10 mg/kg IV or placebo on Day 1 of a 21-day cycle until disease progression. Stratification factors: PS, gender, prior maintenance therapy. The primary endpoint was PFS to be analyzed after observing 134 PFS events for pts without prior EGFR-TKI therapy (primary population). The number was designed to show a high likelihood of observing PFS HR < 1. Secondary endpoints: safety profile, OS, objective response rate (ORR), disease control rate (DCR), patient-reported outcomes. We report the results of the primary population. **Results:** 157 pts (DR 76; D 81) were randomized and treated. Pts characteristics were balanced between arms. The median PFS was 5.2 months (m) [95%CI 3.52, 6.97] for DR and 4.2m [2.83, 5.62] for D; hazard ratio (HR) 0.83 [0.59, 1.16]. ORR: 28.9% (DR), 18.5% (D). DCR: 78.9% (DR), 70.4% (D). The median OS at the time of primary PFS analysis was 15.2m for DR and 14.0m for D (data are immature). Main Grade3/4 toxicites (DR vs D) were neutropenia (90% vs 86%), leukopenia (70% vs 68%), febrile neutropenia (33% vs 20%) and anorexia (7% vs 5%). The Grade3/4 febrile neutropenia did not lead to any fatal events and incidence of Grade ≥ 3 infections were 1% vs 10%. **Conclusions:** Efficacy results were consistent with those from REVEL. DR has shown clinical benefit over D in terms of PFS, ORR, and DCR in Japanese NSCLC pts. DR was well tolerated, with manageable toxicity. Clinical trial info: NCT01703091. Clinical trial information: NCT01703091.

8055 Poster Session (Board #378), Mon, 8:00 AM-11:30 AM

Exploratory analysis of safety by histology and efficacy in a nonsquamous NSCLC subgroup in REVEL: A randomized phase III study of ramucirumab (RAM) plus docetaxel (DOC) vs DOC for second-line treatment of stage IV non-small-cell lung cancer (NSCLC). *First Author: Luis Paz-Ares, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: REVEL, a study inclusive of nonsquamous (NSQ) and squamous (SQ) NSCLC, led to FDA approval of second-line RAM+DOC for patients (pts) with metastatic NSCLC based on improved survival. Neutropenia, febrile neutropenia, gastrointestinal and pulmonary hemorrhage events were similar across histologies. Additional outcomes are presented. **Methods**: A total of 1,253 pts with SQ or NSQ NSCLC received DOC (75 mg/m^2) plus RAM (10 mg/kg; N = 628) or placebo (N = 625) after disease progression on platinum-based therapy (NCT01168973). Endpoints evaluated in specified histologic subgroups were OS, PFS, response rates, safety, and QoL. OS and PFS were analyzed using Kaplan-Meier (KM) method and Cox proportional hazard model. Response was compared using the Cochran-Mantel-Haenszel test. The primary QoL analysis was time to deterioration (TtD) of the Lung Cancer Symptom scale (LCSS) using the KM method. **Results**: Of the 73% (N = 912) of NSQ tumors, the majority were adenocarcinoma (79%; N = 725). Efficacy outcomes for pts with adenocarcinoma were similar to the NSQ population (see table). Incidences of pts with ≥ 1 treatment-emergent adverse event (TEAE), ≥ 1 serious adverse event, TEAEs grade ≥ 3, and TEAEs leading to dose adjustment or discontinuation were similar between treatment arms and across NSQ and SQ histologies. The TtD for total LCSS score was similar between treatment arms in NSQ and SQ subgroups. **Conclusions**: REVEL demonstrated an acceptable benefit/risk profile for RAM+DOC, with favorable efficacy and manageable safety outcomes seen across the major histologic subtypes of NSCLC. Clinical trial information: NCT01168973.

	NSQ ITT			NSQ Adenocarcinoma		
	RAM+DOC (N = 465)	PBO+DOC (N = 447)	HR (95% CI)	RAM+DOC (N = 377)	PBO+DOC (N = 348)	HR (95% CI)
Median OS, mos	11.1	9.7	0.83 (0.71, 0.97)	11.2	9.8	0.83 (0.69, 0.99)
Median PFS, mos	4.6	3.7	0.77 (0.67, 0.88)	4.5	3.9	0.75 (0.64, 0.88)
DCR (CR+PR+SD), %	66	55		65	56	
ORR (CR+PR), %	22	15		19	15	

CR = complete response; DCR = disease control rate; HR = hazard ratio; ITT = intent-to-treat; ORR = overall response; PBO = placebo; PR = partial response; SD = stable disease.

8056 Poster Session (Board #379), Mon, 8:00 AM-11:30 AM

Bevacizumab beyond disease progression after first-line treatment with bevacizumab plus chemotherapy in advanced nonsquamous non–small cell lung cancer (WJOG 5910L): An open-label, randomized, phase II trial. *First Author: Masayuki Takeda, Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka-Sayama, Japan*

Background: Bevacizumab combined with platinum-based chemotherapy has been established as a standard treatment option in the first-line setting for advanced nonsquamous non–small cell lung cancer (NSCLC). However, there have been no evidence-based studies to support the use of bevacizumab beyond disease progression in NSCLC patients receiving such treatment. **Methods:** WJOG 5910L was designed as a multicenter, open-label, randomized, phase II trial of docetaxel (60 mg/m^2) versus docetaxel (60 mg/m^2) plus bevacizumab (15 mg/kg) every 3 weeks in patients with recurrent or metastatic nonsquamous NSCLC whose disease has progressed after first-line treatment with bevacizumab plus a platinum-based doublet. The primary end point was progression-free survival (PFS). **Results:** One hundred patients were randomly assigned to receive docetaxel (Doc, $n = 50$) or docetaxel plus bevacizumab (Doc+Bev $n = 50$). The median PFS was 4.4 months for the Doc+Bev group and 3.4 months for the Doc group, with a hazard ratio (HR) of 0.71 (95% confidence interval [CI], 0.47–1.09) and stratified log-rank P value of 0.058, which met the predefined value for statistical significance ($P < 0.2$). The median overall survival also tended to be longer in the Doc+Bev group (13.1 months; 95% CI, 10.6–21.4) than in the Doc group (11.0 months; 95% CI, 7.6–16.1), with a HR of 0.74 (95% CI, 0.46–1.19; stratified log-rank $P = 0.11$). Frequent adverse events of grade ≥ 3 included neutropenia (90% in the Doc+Bev group vs. 82% in the Doc group), leukopenia (64% vs. 52%, respectively), and febrile neutropenia (26% in both groups). There were two treatment-related deaths (one in each group). **Conclusions:** The addition of bevacizumab to docetaxel in the second-line setting shows promising efficacy with regard to PFS for patients with nonsquamous NSCLC whose disease has progressed while receiving bevacizumab plus a platinum-based doublet. The addition of bevacizumab was associated with a slight increase in toxicity, although the combination regimen was tolerable. Phase III studies of this combination are warranted. Clinical trial information: 000004715.

8057 Poster Session (Board #380), Mon, 8:00 AM-11:30 AM

Efficacy and safety of BCD-021, bevacizumab biosimilar candidate, compared to Avastin: Results of international multicenter randomized double blind phase III study in patients with advanced non-squamous NSCLC. *First Author: Olga Filon, CJSC BIOCAD, St. Petersburg, Russia*

Background: BCD-021 demonstrated equivalence to Avastin in a comprehensive comparability exercise that included physicochemical, PK and PD studies, as well as phase I PK clinical study in patients with non-squamous NSCLC. **Methods:** 138 patients with advanced non-squamous NSCLC (stage IIIb/IV) were randomly assigned into 2 groups at a ratio of 1:1 to receive BCD-021 or Avastin at a dose of 15 mg/kg in combination with paclitaxel (175 mg/m^2) and carboplatin (AUC 6 mg/ml×min) every 3 weeks up to 6 cycles of therapy or until progression or unbearable toxicity. **Results:** ORR (primary endpoint) in both groups had no statistically significant differences: 42.59 % (95% CI 30.33 – 55.83) in BCD-021 group and 39.29% (95% CI 27.58 – 52.27%) in Avastin group. The lower limit of 95% CI for ORR difference between the groups (-14.96%) did not exceed the non-inferiority margin, hence BCD-021 is non-inferior to Avastin. There were also no differences between the groups for all other efficacy parameters: CR (1.85% *vs* 1.79%), PR (40.74% *vs* 37.50%), stable disease (51.85% *vs* 51.79%) and progression rate (5.56% *vs* 8.93%) in BCD-021 and Avastin group, respectively. AEs profiles of BCD-021 and Avastin were equivalent. Rate of all observed AEs including severe AEs had no statistically significant difference between the groups. Most AEs were associated with chemotherapy : neutropenia (85.29% *vs* 78,7%), anemia (88.24% *vs* 84.85%), leukopenia (79.41% *vs* 75.76%), thrombocytopenia (69.12% *vs* 62.12%), hyperglycemia (61.76 *vs* 56.06), LDH increase (48.53 *vs* 37.88), ALP increase (35.29% *vs* 30.30), ALT increase (26.47% *vs* 28.79%), alopecia (30.88% *vs* 24,24%), etc. Reactions specific for bevacizumab included: arterial hypertension (26,47% *vs* 22,73%), weakness (17.65 *vs* 16.67), lung bleeding (5.88% *vs* 3.03%), proteinuria (2.94% *vs* 0%), GIT perforation (0% *vs* 1.52%) and VTE (0% *vs* 1.52%). Binding and neutralizing antibodies were transient and detected only in 1 patient in each group that indicated to low immunogenic potential of both drugs. **Conclusions:** BCD-021 demonstrated non-inferiority to Avastin in patients with NSCLC. Clinical trial information: NCT01763645.

8058 Poster Session (Board #381), Mon, 8:00 AM-11:30 AM

Comparative efficacy of ceritinib and crizotinib in previously treated crizotinib-naïve anaplastic lymphoma kinase-positive (ALK+) advanced or metastatic non-small cell lung cancer (NSCLC): An adjusted indirect comparison. *First Author: Daniel Shao-Weng Tan, National Cancer Centre Singapore, Singapore, Singapore*

Background: Ceritinib (CER) has been studied in previously treated, crizotinib (CRZ)-naïve patients (pts) in two clinical trials (ASCEND-1: NCT01283516; ASCEND-3: NCT01685138). No randomized controlled trial has compared CER and CRZ. This analysis indirectly compared the efficacy of CER and CRZ among previously treated, CRZ-naïve pts with advanced/metastatic ALK+ NSCLC. **Methods:** Individual pt data for CER-treated pts were pooled from two single-arm trials (ASCEND-1, ASCEND-3); published summary data for CRZ-treated pts were extracted from three trials (PROFILE 1001, 1005 and 1007). To adjust for cross-trial differences, CER-treated pts were re-weighted to match their mean baseline characteristics to those reported for the CRZ-treated pts, including age, gender, race, ECOG PS, number of prior regimens and tumor histology. Progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) were compared between the treatment groups after matching. **Results:** Before matching, CER pts (N = 189) were significantly different from CRZ pts (N = 557) in the distribution of race (Asian: 55% vs. 38%; P < .001) and the number of prior regimens (1/2/ ≥ 3: 49%/28%/23% vs. 45%/22%/33%; P = .028). After matching, all available baseline characteristics were balanced. Compared to CRZ, CER was associated with longer PFS (median: 13.8 vs. 8.3 months; hazard ratio (HR): 0.52; 95% CI, 0.44–0.62) and OS (HR: 0.59; 95% CI, 0.46–0.75). The 12-month OS rate was 83% with CER and 66% with CRZ. **Conclusions:** In this adjusted indirect comparison, CER was associated with prolonged PFS and OS compared to CRZ among previously treated CRZ-naïve ALK+ NSCLC.

Endpoint, 95% CI		CER	CRZ	HR	P-value
PFS	Median, mo	13.8 (11.1–NE)	8.3 (7.3–9.3)	0.52 (0.44–0.62)	< .001
	12-mo rate, %	58 (48–71)	37 (33–42)	—	< .001
OS	Median, mo	NE (19.6–NE)	20.5 (19.9–29.6)	0.59 (0.46–0.75)	< .001
	12-mo rate, %	83 (75–91)	66 (62–70)	—	< .001
ORR	rate, %	68 (61–76)	61 (57–65)	—	.102

Notes: NE = not estimable. P-values for HR were calculated by weighted Cox proportional hazards model; P-values for rate were calculated by weighted t-tests.

8059 Poster Session (Board #382), Mon, 8:00 AM-11:30 AM

ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ). *First Author: Tony Mok, Chinese University of Hong Kong, Shatin, Hong Kong*

Background: In the ASCEND-1 study ceritinib showed clinical activity in pts with ALK+ NSCLC, including in brain metastases (BM). ASCEND-2 (NCT01685060) evaluated efficacy and safety of ceritinib in ALK+ NSCLC pts pre-treated with chemotherapy (≥ 1 platinum doublet) who progressed ≤30 days from last treatment with CRZ. **Methods:** At August 2014 data cut-off, 140 pts receiving oral ceritinib 750 mg daily had enrolled worldwide. Whole body (WB) and intracranial (I) responses were assessed by investigator; Lung Cancer Symptom Scale (LCSS) and EORTC (QLQ-C30) surveys assessed patient reported outcomes. **Results:** Of 140 pts: median age (range) 51 (29–80) years; 50.0% male; 60.0% Caucasian; 37.9% Asian; 71.4% with BM, of which 28.0% had no prior brain radiation (BRT). Median duration of exposure and follow-up time were 8.8 (0.1–19.4) and 11.3 (0.1–18.9) mos, respectively. At baseline, 20 pts had investigator-assessed measurable brain lesions (MBL); IDCR was 80.0% (95% CI: 56.3, 94.3); in 5 of 6 pts with MBL and no prior brain radiation, brain responses (2 CR, 3 PR) matched or exceeded WB response. Most common AEs (mostly Grade 1/2) were nausea (81.4%), diarrhea (80.0%), vomiting (62.9%). Eleven (7.9%) pts discontinued due to AEs, with no one AE predominating. LCSS showed improvement in symptom burden (-1.4 to -6.2). Global quality of life score (QLQ-C30) was maintained on treatment, with no substantial change from baseline (-1.5 to +4.6). **Conclusions:** Ceritinib provided durable responses and safety outcomes in CRZ-pretreated patients with or without BM consistent with those seen in ASCEND-1. Clinical trial information: NCT01685060.

Investigator-assessed efficacy outcomes.

	BM N=100	No BM N=40	All N=140
WB ORR (CR+PR), n (%) [95% CI]	33 (33.0) [23.9, 43.1]	21 (52.5) [36.1, 68.5]	54 (38.6) [30.5, 47.2]
WB DCR (CR+PR+SD), n (%) [95% CI]	74 (74.0) [64.3, 82.3]	34 (85.0) [70.2, 94.3]	108 (77.1) [69.3, 83.8]
Median Duration of Response, Mos [95% CI]	9.2 [5.5, 11.1]	10.3 [7.4, 16.6]	9.7 [7.1, 11.1]
Median Progression Free Survival (PFS) Mos [95% CI]	5.4 [4.7,7.2]	11.3 [5.7,15.6]	5.7 [5.4, 7.6]

8060 Poster Session (Board #383), Mon, 8:00 AM-11:30 AM

ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC). *First Author: Enriqueta Felip, Vall d'Hebron University, Barcelona, Spain*

Background: Ceritinib demonstrated clinical activity in ALKi-pretreated and -naïve pts with ALK+ NSCLC, including those with brain metastases (BM; pivotal ASCEND-1 study). ASCEND-3 (NCT01685138) evaluated efficacy and safety of ceritinib in ALKi-naïve pts. **Methods:** At 27June 2014 data cutoff, 124 pts enrolled worldwide received oral ceritinib 750 mg/d. Whole body (WB) and intracranial (I) responses were assessed by investigator. Prior chemotherapy (≤3 lines) was permitted. **Results:** Median age of enrolled pts was 56 (27–82); 40.3% were male, 59.7% Asian and 38.7% Caucasian; 40.3% had BM, of which 46% had no prior brain radiation (BRT). Median time from initial diagnosis to treatment start was 13.5 (1.0–283.1) mos; median exposure duration was 8.0 (0.1–16.2) mos; median follow-up (range) was 8.3 (0.6-16.3) mos. Investigator-assessed efficacy outcomes are located in the table below. At baseline 10 pts had investigator-assessed measurable brain lesions (MBL); IDCR was 80.0% (95% CI: 44.4, 97.5); in 6 pts with MBL and no prior BRT, all responses in brain (2 PR) matched or exceeded WB response. Most common AEs (mostly Grade 1/2) were gastrointestinal: diarrhea (82.3%), nausea (74.2%), and vomiting (66.9%); 7.3% pts discontinued due to AEs, with no one AE predominating. **Conclusions:** Ceritinib achieved robust ORR and promising DOR/PFS in pts with and without baseline BM. Ceritinib showed brain responses even in pts with no prior BRT. Safety outcomes were similar to the ASCEND-1 trial. Clinical trial information: NCT01685138.

	BM N=50	No BM N=74	All N=124
WB ORR (CR+PR), n (%) [95% CI]	29 (58.0) [43.2, 71.8]	50 (67.6) [55.7, 78.0]	79 (63.7) [54.6, 72.2]
WB DCR (CR+PR+SD), n (%) [95% CI]	43 (86.0) [73.3,94.2]	68 (91.9) [83.2,97.0]	111 (89.5) [82.7, 94.3]
Median Duration of Response (DOR), Mos [95% CI]	9.1 [7.5, NE]	10.8 [9.3, 10.8]	9.3 [9.1, NE]
Median Progression Free Survival (PFS)* Mos [95% CI]	10.8 [7.3, NE]	11.1 [9.2, 12.8]	11.1 [9.3, NE]

NE = Not Estimable *Follow-up ongoing: 84 (67.7%) pts censored; 77 (62.1%) ongoing without event.

8061 Poster Session (Board #384), Mon, 8:00 AM-11:30 AM

A phase I/II study with a CNS-penetrant, selective ALK inhibitor alectinib in *ALK*-rearranged non-small cell lung cancer (*ALK*+ NSCLC) patients (pts): Updates on progression free survival (PFS) and safety results from AF-001JP. *First Author: Yuichiro Ohe, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Alectinib, a CNS-penetrant, selective ALK inhibitor with a novel scaffold, was granted approval in Japan 2014, since it showed good efficacy and tolerability in *ALK*+ NSCLC pts without previous ALK inhibitor treatment (CMSTO2014). This report describes the updated data of the 46 pts enrolled in phase II part of AF-001JP. **Methods:** *ALK*+ NSCLC pts without previous ALK inhibitor treatment were given alectinib at 300 mg b.i.d to investigate the efficacy and safety until no further clinical benefits as assessed by investigator. **Results:** Alectinib showed good tumor response to *ALK*+ NSCLC in AF-001JP study and has been already approved in Japan. Further evaluation is ongoing for PFS and OS. 28 of 46 pts were on treatment with alectinib as of October 31, 2014. In spite of the fact that median follow-up duration had passed 30 months (range: 1-36) as of then, progressive disease (PD) was confirmed in only 12 pts (26.1%) (CNS progression: 4 pts, Non-CNS progression: 8 pts).Of them, 3 pts received alectinib later than PD. Though median PFS had not been reached then, it is expected to be at least longer than 29 months. 7 of 14 pts with baseline brain metastasis still remained in the study without CNS or systemic progression at that time. PFS with brain metastasis was similar to the one without brain metastasis. There were no treatment-related Grade 4 or 5 AEs. Since safety profile was consistent with the one in the previous reports, high tolerability of long term administration of alectinib was observed. The results suggested that alectinib showed high efficacy and safety for longer period. **Conclusions:** Alectinib is a novel therapeutic option for the treatment of *ALK*+ NSCLC, since in *ALK*+ NSCLC pts without previous ALK inhibitor treatment, alectinib demonstrated excellent efficacy and tolerability for longer administration. Clinical trial information: JapicCTI-101264.

8062 Poster Session (Board #385), Mon, 8:00 AM-11:30 AM

Safety and efficacy of brigatinib (AP26113) in advanced malignancies, including ALK+ non–small cell lung cancer (NSCLC). *First Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

Background: Brigatinib is an investigational oral tyrosine kinase inhibitor with preclinical activity against rearranged ALK and clinically identified crizotinib-resistant mutants. **Methods:** A phase (ph) 1/2 single-arm, open-label, multicenter study in patients (pts) with advanced malignancies is ongoing. Pts received brigatinib (30–300 mg/d total daily dose, ph 1; 90 mg/d, 180 mg/d, or 90 mg/d for 7 d followed by 180 mg/d, ph 2). Safety was evaluated in all 137 treated pts; efficacy was evaluated in all 79 ALK+ NSCLC pts. NCT01449461. **Results:** Median age: 57 y; 58% female. As of 4 Aug 2014, 47% of total pts and 71% of ALK+ NSCLC pts remained on study. Median and maximum time on treatment were 5.5 mo and 29 mo (ongoing), respectively. Most common treatment-emergent adverse events, generally grade 1/2, included: nausea 45%; diarrhea 36%; fatigue 36%; cough 26%; headache 26%. Early-onset pulmonary events, observed ≤7 d after starting treatment, included dyspnea, hypoxia, or new pulmonary opacities on chest computed tomography suggestive of pneumonia or pneumonitis and occurred in 13/137 (9%) pts (6/44 [14%] pts started at 180 mg qd [once daily]; 2/50 [4%] pts started at 90 mg qd [pts treated with 90 mg qd or 90 mg qd for 7 d followed by 180 mg qd]). Of 72 evaluable ALK+ NSCLC pts, 52 (72%) responded: 45/65 (69%) with prior crizotinib and 7/7 crizotinib-naive pts. Median duration of response: 49 wks. Median progression-free survival (PFS): 56 wks; 47 wks with prior crizotinib. In a post hoc independent radiological review of pts with baseline intracranial central nervous system metastases, 6/12 pts with lesions ≥10 mm had a brain response (≥30% decrease in sum of longest diameters of target lesions) and 8/26 pts with only nonmeasurable lesions had disappearance of all lesions. Median intracranial PFS for these pts: 97 wks. **Conclusions:** Brigatinib has promising antitumor activity in ALK+ NSCLC pts with and without prior crizotinib, including pts with brain metastases. Early-onset pulmonary events were observed less frequently with the 90-mg starting dose compared with higher doses. A randomized ph 2 trial of brigatinib 90 mg qd vs 90 mg qd for 7 d followed by 180 mg qd in crizotinib-resistant ALK+ NSCLC (ALTA) is underway. Clinical trial information: NCT01449461.

8063 Poster Session (Board #386), Mon, 8:00 AM-11:30 AM

Phase (Ph) 1/2a study of TSR-011, a potent inhibitor of ALK and TRK, in advanced solid tumors including crizotinib-resistant ALK positive non-small cell lung cancer. *First Author: Hendrik-Tobias Arkenau, Sarah Cannon Research Institute, London, United Kingdom*

Background: Both intrinsic and acquired resistance mechanisms to ALK inhibitors have been observed in ALK rearranged (ALK+) non-small cell lung cancer (NSCLC). TSR-011 inhibits ALK (IC50 = 0.7nM), tropomyosin receptor kinase (TRK) A, B, and C (IC50 < 3nM), and tumor growth in vivo. **Methods:** A Ph 1/2a study is underway to evaluate safety, pharmacokinetics (PK), and preliminary efficacy of TSR-011. The ongoing Ph 1 is evaluating patients (pts) with ALK+ tumors, including those progressing on, or naïve to ALK inhibitor therapy (ALKi). **Results:** Forty-six pts with advanced cancer, including 19 ALK+ and 11 TRK+ pts, have been treated at total daily doses of 30 to 480mg, administered 1, 2 or 3 times a day. Dose-limiting toxicities (dysesthesia, QTc prolongation) were observed above 120mg/day, not with the fractionated dosing up to 120mg/day. PK modeling showed that a fractionated schedule achieves sustained trough concentrations above the ALK IC50, and minimizes peak exposure associated with QTc prolongation. TSR-011 at the current dose level of 40mg q8h is well tolerated (Table). In evaluable ALK+ pts, 3/3 achieved a response at or above 120mg total daily dose, and 5/9 achieved disease stabilization for 7 months or longer at lower doses; investigation with the 40mg q8h cohort continues. Duration on TSR-011 exceeded that of previous ALKi in a majority of patients with clinical benefit, up to 20 months longer than prior ALKi for a pt still continuing on study. **Conclusions:** TSR-011 is a well-tolerated, promising second-generation ALKi. Overall safety and ECG findings support further development of TSR-011 in pts with ALK+ NSCLC at a fractionated schedule. Development of a controlled release formulation is planned. Clinical trial information: 02048488.

	All Grades		Grades > = 3	
Adverse Events	40mg q8h N = 7 n (%)	Total N = 46 n (%)	40mg q8h N = 7 n (%)	Total N = 46 n (%)
Fatigue	1 (14.3)	12 (26.1)	0	3 (6.5)
Diarrhea	0	10 (21.7)	0	0
QTc prolonged	0	10 (21.7)	0	3 (6.5)
Headache	0	8 (17.4)	0	1 (2.2)
Decreased appetite	0	7 (15.2)	0	0
Urinary tract infection	0	7 (15.2)	0	1 (2.2)
Vomiting	0	7 (15.2)	0	1 (2.2)
Anemia	0	6 (13.0)	0	2 (4.3)
Asthenia	0	6 (13.0)	0	2 (4.3)
Constipation	1 (14.3)	6 (13.0)	0	0
Dysgeusia	0	5 (10.9)	0	0

8064 Poster Session (Board #387), Mon, 8:00 AM-11:30 AM

A phase 1 study of crizotinib and ganetespib (STA-9090) in ALK positive lung cancers. *First Author: Gregory J. Riely, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients with ALK + non-small cell lung cancer (NSCLC) initially respond to crizotinib, but eventually develop resistance. Treatment of patients with ALK positive lung cancer with HSP90 inhibitors leads to clinical and radiographic response. We hypothesized that treatment of patients with ALK rearranged NSCLC with crizotinib and ganetespib, an HSP90 inhibitor, would be safe. **Methods:** All patients had ALK rearranged metastatic non-small cell lung cancer not previously treated with crizotinib. Prior chemotherapy was allowed. Patients were treated with crizotinib 250 mg bid continuously; ganetespib was administered intravenously on days 1 and 8 of a 21-day cycle. In a standard 3+ 3 design, ganetespib was explored at 3 different dose levels. The primary objective was to determine the maximum tolerated dose of the combination of crizotinib and ganetespib. Secondary objectives included establishing the safety profile (CTCAE v4) of the combination in patients with ALK+ lung cancer, exploring the efficacy (RR by RECIST 1.1, PFS, and OS). **Results:** 12 patients were treated with combined crizotinib and ganetespib: 100 mg/m^2(n=3), 150 mg/m^2(n=3), and 200 mg/m^2 (n=6). Women: 8/12, Median Age: 56 (range 41-70), Prior therapy: none (7 pts), 1 line (4 pts), or 2 lines (1 pt). Median duration of treatment: 100 mg/m^2=30 weeks, 150 mg/m^2=54 weeks, and 200 mg/m^2= 6 weeks. There were no first-cycle DLTs. The maximum tolerated dose was crizotinib 250 mg bid/ganetespib 200 mg/m^2. The most common toxicities were fatigue, diarrhea, nausea, vomiting, and dizziness. Grade 4 elevation in ALT (n=1) and Grade 3 elevations in lipase (n=2), AST (n=1), and amylase (n=1) were observed. 5 patients stopped therapy due to toxicity. 4 discontinued due to progressive disease. 3 patients continue on treatment. PR = 67% (8/12), SD= 16% (2/12), PD =8% (1/12), Not Evaluable =8% (1/12). Median OS has not been reached (median f/u = 15 months, with 10 patients still alive). **Conclusions:** In patients with ALK+ lung cancers, crizotinib and ganetespib can be combined, with an MTD of crizotinib 250 mg bid continuously and ganetespib 200 mg/m^2 on days 1 and 8 of a 21 day cycle. Further evaluation of this combination in patients not previously treated with crizotinib is warranted. Clinical trial information: (NCT01579994).

8065 Poster Session (Board #388), Mon, 8:00 AM-11:30 AM

Crizotinib in patients with advanced ROS1-rearranged non-small cell lung cancer (NSCLC). Preliminary results of the ACSé phase II trial. *First Author: Denis Moro-Sibilot, Thoracic Oncology Unit Teaching Hospital A Michallon, INSERM U823, Grenoble, France*

Background: Molecular alterations of crizotinib (crz) targets (ALK, MET, ROS1) are found in a wide range of malignancies. To avoid uncontrolled off-label use and allow for a nationwide safe access to crz for patients (pts) with an ALK, MET or ROS1 positive (+) tumor, the French National Cancer Institute (INCa) launched the AcSé program, funding both access to tumor molecular diagnosis and an exploratory multi-tumor 2-stage design phase II trial. We report the preliminary results of the ROS1+ NSCLC cohort. **Methods:** ROS1 status was determined in 28 regional INCa molecular genetic centers by break-apart FISH assays. Patients with ROS1 rearrangements, progressing after at least one standard treatment (including a platinum-based doublet, unless pts were considered as unfit for chemotherapy) were proposed to receive crz 250 mg BID. Responses were centrally assessed using RECIST v1.1. The objective response rate (ORR) and disease control rate (DCR) were assessed every 8 weeks. **Results:** From Aug. 5, 2013 to Dec. 12, 2014, 34 pts with ROS1+ NSCLC were enrolled out of 37 expected pts. 32 pts had received crz, including 3 recently enrolled pts, leading to 29 pts with clinical information. Median age: 62 years (range 33–81), 69% females, 93% non-squamous histology, and 93% metastatic disease at study entry. Median number of prior treatments: 2 (range 1 –12). Twenty one pts were still on treatment at the cut-off date, 8 have stopped crz (5 PD, 2 adverse events (AEs), 1 death). Among the 24 pts evaluable for response at 8 weeks, we observed 1 CR, 14 PR, 6 SD and 3 PD, leading to ORR = 63% [95% CI:41-81], and DCR = 88% [68-97]. DCR at 6 months was 53% and disease control was achieved in 8/15 evaluable pts. Crz was well tolerated with only 9 grade $\geq$ 3 AEs or SAE. Most common AEs, mainly grade 1, were visual disorders (62% of pts), peripheral edema (55%), diarrhea (51%), nausea (41%), and elevated transaminases (51%). **Conclusions:** Crz was well tolerated and achieved a robust treatment response rate in ROS1+ NSCLC. These results underline the interest of integrating ROS1 in biomarkers routine screening. Survival data and duration of response will be presented. Clinical trial information: NCT02034981.

8066 Poster Session (Board #389), Mon, 8:00 AM-11:30 AM

***ROS1* rearrangement in non-small cell lung cancer (NSCLC): Prognostic and predicitve impact and genetic variability.** *First Author: Matthias Scheffler, Lung Cancer Group Cologne, Department I of Internal Medicine and Center for Integrated Oncology Cologne Bonn, University Hospital Cologne, Cologne, Germany*

Background: Rearrangements of the *ROS1* oncogene occur in about 1-2% of non-small cell lung cancer (NSCLC) patients. While data suggest that the EML4-ALK/MET/ROS1 inhibitor crizotinib is highly effective in these patients, few data is available about the prognostic impact, the predictive value for different treatments, and the genetic heterogeneity of *ROS1*-positive patients. **Methods:** 1137 patients with adenocarcinoma of the lung were analyzed regarding their *ROS1* status. In positive cases, next-generation sequencing (NGS) was performed. Clinical characteristics, treatments and outcome were assessed. Overall survival (OS) was compared with genetically defined subgroups of *ROS1*-negative patients. **Results:** *ROS1* status was analyzed in 1035 (91.0%) patients, whereof 19 (1.8%) had *ROS1*-rearrangement. The median OS of the patients has not been reached yet. Stage IV patients with *ROS1*-rearrangement had the best OS of all analyzed subgroups (36.7 months, $p < 0.001$). 9 of 14 (64.2%) patients had at least one response under chemotherapy. Pemetrexed-containing regimens showed higher response rates than paclitaxel-containing ones (80% vs 17%). Estimated mean OS for patients receiving chemotherapy and crizotinib was 5.3 years (median not reached). Ten patients with *ROS1*-rearrangement (52.6%) harbored additional genetic aberrations in *BRAF*, *MET*, *EGFR*, *MAP2K1*, and *TP53*. **Conclusions:** *ROS1*-rearangement is not only a strong predictive marker for response to crizotinib, but also seems to be the best prognostic molecular marker in NSCLC reported so far. In stage IV *ROS1*-positive patients, response to chemotherapy was remarkable high and overall survival regardless of systemic therapy significantly better compared to other genetically defined subgroups including *EGFR*-mutated and *ALK*-fusion-positive NSCLC.

8067 Poster Session (Board #390), Mon, 8:00 AM-11:30 AM

Defining the spectrum and "overlap" of HER2 aberrations in lung cancers: Associations of HER2 protein overexpression, *HER2* amplification, and *HER2* mutation. *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human epidermal growth factor receptor 2 (HER2, *ERBB2*) aberrations have been identified as oncogenic drivers and potential therapeutic targets in lung cancers. The molecular associations of HER2 protein overexpression, *HER2* gene amplification and *HER2*mutation in lung cancers have not been distinctly defined. To explore these associations, Memorial Sloan Kettering and the University of Colorado combined their data on HER2 in lung cancers. **Methods:** Tumor specimens from 175 patients with lung adenocarcinomas with no prior targeted therapy were evaluated for the presence of HER2 overexpression, *HER2* amplification and mutation. Overexpression was assessed by immunohistochemistry (IHC) using the 4B5 Ventana antibody. Amplification was assessed by fluorescence in-situ hybridization (FISH) using FDA approved probe sets (PathVysion, Abbott and *HER2* IQFISH pharmDx, Dako) and defined as HER2/CEP17 ratio $\geq$ 2.0. Mutation was assessed by fragment analysis and mass spectrometry genotyping for indels and recurrent point mutations in exon 20, respectively. The frequencies of HER2 overexpression, *HER2* amplification and mutation were calculated and their concordance examined. **Results:** *HER2* amplification by FISH was detected in 5 of 175 (3%) cases, and 46 (26%) showed polysomy (HER2 copy $\geq$ 4 but HER2/CEP17 ratio $<$ 2). HER2 overexpression (2+, 3+) on IHC was not detected in the 25 specimens tested to date and negative IHC correlated with negative results on FISH. *HER2* mutation was detected in 4 of 145 (3%) specimens, including 3 identical 12bp insertions [(p.A775_G776insYVMA (c.2324_2325ins12)] and a 9bp insertion, all in exon 20. None of the *HER2* mutant cases were amplified and 3 had polysomy. **Conclusions:** *HER2* mutations are not associated with *HER2* amplification or HER2 protein overexpression suggesting a distinct entity and therapeutic target. "HER2-positive lung cancers" may not be an adequate term and patient cohorts for the study of HER2 targeted agents should be defined by the specific HER2 aberrations present. Funded in part by Boehringer-Ingelheim, NCI 1 RC2 CA148394-01, NCI P50CA058187, and NCI CCSG P30CA046934.

8068 Poster Session (Board #391), Mon, 8:00 AM-11:30 AM

Outcomes with chemotherapies and molecular characteristics of *HER2*-mutant lung cancers. *First Author: Juliana Eng, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human epidermal growth factor receptor 2 (*HER2, ERBB2*) mutations occur in 3% of lung adenocarcinomas and are increasingly being identified with the growing adoption of multiplex next-generation genotyping. *HER2*-mutant lung cancers impart a distinct natural history with a median overall survival from stage IV diagnosis of 1.6 years (Kris JAMA 2014). While case reports and series have shown activity of HER2-targeted agents in these patients, little is known about outcomes of systemic treatments. **Methods:** Patients with stage IV *HER2*-mutant lung cancers at Memorial Sloan Kettering were reviewed. Patient demographics, types of *HER2* mutations, survival, and duration of systemic treatments were documented. **Results:** 37 patients with *HER2*-mutant lung cancers were identified: median age 62; majority were women (n = 24), never smokers (n = 21), and had adenocarcinomas (n = 36, 1 adenosquamous). A 12bp in-frame insertion in exon 20 (p.A775_G776insYVMA c.2324_2325ins12) was present in 23 (62%, 95% CI 45-78%) patients. In addition, there were four 9bp insertions, one 6bp insertion, and five 3bp insertions in exon 20, and four single base pair substitutions (3 exon 20, 1 exon 8). The median overall survival from date of diagnosis of stage IV disease was 2.3 years (95% CI 1.2-2.7). The median duration of all chemotherapy was 8 months (range 0.8-43 months). Median duration of treatment was 6 months for pemetrexed ±platinum/bevacizumab, 3 months for taxane ±platinum/bevacizumab, 4 months for gemcitabine, 4 months for vinorelbine, 5 months for mitomycin vinblastine. The median duration of targeted therapy was 3 months for trastuzumab, 4 months for small molecule HER2 tyrosine kinase inhibitors, 3 months for erlotinib. No objective responses were noted with trastuzumab (n = 2) or lapatinib (n = 4) alone. **Conclusions:** Most *HER2*-mutant lung tumors demonstrate an identical 12bp in-frame insertion (YVMA) in exon 20. In our cohort, the median duration of treatment with chemotherapy was double that of HER2-targeted therapies. Pemetrexed-containing regimens had the longest duration of treatment. As we search for better targeted therapies for patients with *HER2*-mutant lung cancers, chemotherapy remains an important component of care.

8069 Poster Session (Board #392), Mon, 8:00 AM-11:30 AM

EGFR mutation pattern in African American population in a community-based academic center. *First Author: Haiying Cheng, Montefiore Medical Center, Eastchester, NY*

Background: The two most common EGFR mutations, L858R in exon 21 and deletions in exon19, represent around 90% of all EGFR mutations in NSCLC and convey sensitivity to EGFR TKIs. Little is known about the patterns of EGFR mutations in different racial groups. Montefiore Medical Center (MMC), a community based academic center, treats a large minority patient population. For example, 33% (693/2104) of patients with lung cancer were identified as African American from 01/2009 to 06/2014. We initiated reflex molecular testing on all non-squamous NSCLC patients in 01/2012 at MMC. **Methods:** We retrospectively reviewed our cancer registry database from 01/2009 to 06/2014 and analyzed all non-squamous NSCLC patients with pathology available in our system for rates and patterns of EGFR mutations. EGFR testing was performed by Integrated Oncology (Labcorp) by PCR-based technology. **Results:** 1032 patients with non-squamous NSCLC had their pathological diagnosis at MMC: 386 (37.4%) were African American, 475 (46%) white, 46 (4.5%) other (Asian and others), and 125 (12.1%) race unknown, respectively. EGFR mutation analysis was performed in 446 patients and 63 were positive for EGFR mutations. The EGFR mutation rate was 14.1% (63/446) for all races, 12.4% (22/178) for African Americans and 14% (27/193) for whites. Interestingly, 25.4% (16/63) of mutations were uncommon EGFR mutations on exon 18 or exon 20, which is higher than the rates reported in the literature (~10%). In particular, 31.8% (7/22) of African Americans with EGFR mutations had uncommon mutations. The mean age at diagnosis of these 7 patients was 66 years, 5 were female, 2 never-smokers, and 5 had stage 3 or 4 disease. The types of uncommon mutations included S768I, V769L, N771_H773dupNPH, H773L, V774M mutations in Exon 20, G719A mutation in Exon 18 or combinations. **Conclusions:** This is the first report of a high uncommon EGFR mutation rate in African American lung cancer patients. Most uncommon EGFR mutations are less sensitive to EGFR TKIs than L858R and del 19. These results justify confirmation studies in larger cohorts of patients.

8070 Poster Session (Board #393), Mon, 8:00 AM-11:30 AM

EGFR mutations in Latinos from the United States and Latin America. *First Author: Ariel Lopez-Chavez, Sylvester Comprehensive Cancer Center at Univ of Miami, Miami, FL*

Background: Activating mutations in the epidermal growth factor receptor gene (EGFR) confer hypersensitivity to EGFR tyrosine kinase inhibitors in patients with advanced non–small-cell lung cancer (NSCLC). Racial and ethnic differences in the frequency of such mutations have been previously described; however, there are limited and conflicting reports on its frequency in the Latino population. **Methods:** We collected samples from 642 patients with NSCLC from 7 institutions in the US and Latin-America. Activating EGFR mutation analysis of exons 18 through 21 was performed at 2 CLIA certified central laboratories. Statistical analyses were performed using Fisher's exact test or Mehta's modification to Fisher's exact test to determine relationships among parameters. All p-values are two-tailed and reported without adjustment for multiple comparisons. **Results:** EGFR mutation analysis was successfully performed in 480 of 642 patients (75%) of which 90 (19%) were Latinos, 318 (66%) non-Latino Whites, 35 (7%) non-Latino Asians, 30 (6%) non-Latino Blacks and 7 (2%) from other race/ethnicities. EGFR mutations were found in 21 of 90 (23%) Latino patients and its frequency varied according to country of origin. The highest frequency was observed in Latinos from Peru (37%) followed by US (23%), Mexico (18%), Venezuela (10%) and Bolivia (8%). In Latinos never smokers and Latinos with adenocarcinoma histology, the frequency of EGFR mutations was 38% and 30% respectively. There was a significant difference in the frequency of EGFR mutations among the different racial/ethnic subgroups analyzed ($p < 0.001$) with non-Latino Asians having the highest frequency (57%) followed by Latinos (23%), non-Latino Whites (19%) and non-Latino Blacks (10%). However, there was no difference between Latinos (23%) and non-Latinos (22%) ($p = 0.78$) and Latinos and non-Latino Whites ($p = 0.37$). While patients from Peru had an overall higher frequency of mutations (37%) than all other Latinos (17%), such difference was not statistically significant ($p = 0.06$) and diminished greatly when smoking and adenocarcinoma histology subgroups were analyzed independently. **Conclusions:** There was no significant difference between the frequency of EGFR mutations in NSCLC in Latinos and non-Latinos.

8071 Poster Session (Board #394), Mon, 8:00 AM-11:30 AM

Clinical predictors of 5-year survival in patients with EGFR-mutant metastatic NSCLC treated with EGFR-TKIs. *First Author: Jessica Jiyeong Lin, Brigham and Women's Hosp, Brighton, MA*

Background: Activating mutations of the epidermal growth factor receptor (EGFR) were discovered over 10 years ago. EGFR mutations predict increased response rates and progression-free survival (PFS) when treated with EGFR tyrosine kinase inhibitors (TKIs) compared to combination chemotherapy in advanced NSCLC. However, long-term outcomes including 5-year survival among patients (pts) with EGFR-mutant metastatic NSCLC treated with EGFR-TKIs remain heterogeneous. Herein, we define clinical factors associated with prolonged overall survival (OS) in this cohort. **Methods:** A retrospective analysis was performed of pts with metastatic NSCLC harboring a sensitizing EGFR mutation and treated with EGFR-TKIs at Dana-Farber Cancer Institute between Jan 1, 2002 and Sept 31, 2009. Pts alive at time of analysis must have had at least a 5-year survival. OS was compared based on clinical features using log-rank test. Cox's proportional hazards models were used to estimate hazard ratios. **Results:** Among 134 pts, median PFS and OS were 13.1 mos (95% CI, 10.8-14.6) and 30.9 mos (95% CI, 28.2-35.7), respectively. 19 pts (14.2%) were long-term survivors (OS $\geq$ 5 years), of whom 10 remained alive at the time of analysis with median follow-up of 89.8 mos (range, 60.1-91.6). Multivariate analysis adjusted for factors significant at the 0.10 level in univariate models revealed that sensitizing EGFR mutations in exons other than exon 19 ($n = 55$) (HR 1.53; 95% CI, 1.05-2.23; $p = 0.03$), extrathoracic mets ($n = 77$) (HR 1.58; 95% CI, 1.04-2.43; $p = 0.03$) or brain mets ($n = 29$) (HR 2.17; 95% CI, 1.34-3.51, $p = 0.002$) at the time of diagnosis, and current smoking status ($n = 5$) (HR 4.31; 95% CI, 1.64-11.32; $p = 0.003$) were independent predictors of shorter OS. Age, gender, disease stage at diagnosis, liver or adrenal mets at diagnosis, specific TKI (erlotinib vs gefitinib), or line of TKI treatment did not correlate with OS. **Conclusions:** Our data estimate 5-year OS among EGFR-mutant metastatic NSCLC pts treated with EGFR-TKIs at 14%--vs less than 5% in historic results for an unselected population with distant-stage NSCLC. Planned studies will elucidate the genetic alterations that may co-occur with EGFR mutations and influence treatment outcomes.

8072 Poster Session (Board #395), Mon, 8:00 AM-11:30 AM

The impact on overall survival (OS) of first-line gefitinib (G) and erlotinib (E) and of clinical factors in advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor mutations (EGFR mut) based on meta-analysis of 1,231 patients (pts) enrolled in 6 major randomized trials. *First Author: Chee Lee, NHMRC Clinical Trials Centre, Sydney, Australia*

Background: We performed an individual pts data meta-analysis using trials that compared G or E vs platinum doublet chemotherapy (CT) on OS outcome. **Methods:** Treatment-naïve pts with common EGFR mut (Del19 or L858R), stage IIIB/IV/post-operative recurrence were randomized to either G (IPASS, NEJ002, WJTOG3405) or E (ENSURE, EURTAC, OPTIMAL) vs CT. We performed Cox regression to obtain hazard ratios (HR) and 95% confidence intervals (CI) for the overall population and pre-specified subgroups. We calculated pooled treatment estimate using the inverse variance weighted method. **Results:** Amongst 1231 pts (Del19 = 682, L858R = 540, Del19 and L858R = 9), 632 received EGFR tyrosine kinase inhibitor (TKI) and 599 received CT. The median follow-up was 35.0 months, and 780 (63%) pts had died. Following progression, 74% (CT group) received EGFR-TKI and 66% (EGFR-TKI group) received CT. There was no difference in OS between EGFR-TKI and CT (median 25.8 vs 26.0 months, HR = 1.01 [CI 0.88-1.17; P = 0.84]). There was no significant difference between Del19 (HR = 0.96, CI 0.79-1.16, P = 0.64) and L858R (HR = 1.06, CI 0.86-1.32; P = 0.59) subgroups (P-interaction = 0.47). There was also no significant difference according to smoking status (P-interaction = 1.00), sex (P-interaction = 0.80), performance status (P-interaction = 0.88), age (P-interaction = 0.61), ethnicity (P-interaction = 0.63), histology (P-interaction = 0.84), and staging (P-interaction = 0.43). Performance status (0 vs 1 vs 2: median 34.0 vs 24.1 vs 15.7 months, P-logrank < 0.001) and staging (IV vs IIIB vs post-operative recurrence: median 23.9 vs 31.0 vs 42.7 months, P-logrank < 0.001) were prognostic for OS. **Conclusions:** Despite significant PFS benefit, there is no OS difference with first-line G or E when compared with CT in advanced NSCLC with common EGFR mut, probably due to high rate of cross-over at progression. There is no significant difference in EGFR-TKI treatment benefit in all subgroups. Poor performance status and stage IV cancer are associated with poorer OS.

8073 Poster Session (Board #397), Mon, 8:00 AM-11:30 AM

Influence of dose adjustment on afatinib safety and efficacy in patients (pts) with advanced *EGFR* mutation-positive (*EGFRm+*) non-small cell lung cancer (NSCLC). *First Author: James Chih-Hsin Yang, National Taiwan University Hospital and National Taiwan University, Taipei, Taiwan*

Background: Afatinib 40 mg/day (oral) is approved for the treatment of pts with advanced *EGFRm+* NSCLC. Dose adjustment is recommended according to pre-defined tolerability criteria. We performed post-hoc analyses on the influence of afatinib dose reduction on adverse events (AEs), pharmacokinetics (PK) and progression-free survival (PFS) in the Phase III LUX-Lung 3 (LL3) trial, and analyzed dose reduction data collected in clinical practice. **Methods:** All pts treated with afatinib in LL3 were included in the analyses (n = 229). Pts experiencing drug-related grade 3 or selected prolonged grade 2 AEs on the initial 40 mg dose could dose reduce by 10 mg decrements to 30 mg or a final dose of 20 mg. Frequency and severity of the most common AEs before and after dose reduction were analyzed. Final PK data collected as part of the standard visit schedule (Day 43) were used to compare plasma afatinib concentrations in pts who reduced to 30 mg vs those remaining at 40 mg. PFS was compared between pts who dose reduced within the first 6 months of treatment and those who did not. Real-world data were collected by practicing experts. **Results:** Dose reductions occurred in 53% (122/229) of pts; the majority (86%) within the first 6 months of treatment. In pts who dose reduced, decreases in the incidences of drug-related all grade (grade ≥ 3) AEs were 99.2% (20.5%) to 46.7% (4.1%) for diarrhea, 88.5% (26.2%) to 38.5% (3.3%) for rash/acne, 77.0% (12.3%) to 27.9% (0%) for stomatitis, and 44.3% (16.4%) to 36.9% (4.9%) for nail effects. Dose reduction was more likely in pts with higher plasma concentrations of afatinib. On Day 43, pts who dose reduced to 30 mg ≥ 4 days previously (n = 38) had geometric mean plasma afatinib concentrations of 24.4 ng/mL, vs 23.7 ng/mL in pts who remained on the 40 mg dose (n = 126). Median PFS was 11.3 months in pts who dose reduced during the first 6 months of treatment, vs 11.0 months in pts who did not (HR = 1.25 [95% CI, 0.91–1.72]). Dose reduction outcomes from daily clinical practice will also be presented. **Conclusions:** Tolerability-guided dose adjustment of afatinib is an effective measure to reduce treatment-related AEs without reducing therapeutic efficacy. Clinical trial information: NCT00949650.

8074 Poster Session (Board #398), Mon, 8:00 AM-11:30 AM

Reduced-dose versus full-dose erlotinib for advanced EGFR-mutant non-small cell lung carcinoma (NSCLC): A retrospective analysis. *First Author: Benjamin L. Lampson, Brigham and Women's Hospital, Boston, MA*

Background: Erlotinib is an EGFR tyrosine kinase inhibitor (TKI) which is FDA-approved at the maximum tolerated dose (MTD) of 150mg daily with dose limiting toxicities of diarrhea and rash. Preclinical data and small clinical series suggest that lower doses of erlotinib are biologically active against EGFR mutations. However, this has not been systematically studied. We aimed to study whether reduced-dose erlotinib is as effective as full-dose erlotinib for EGFR-mutant NSCLC. **Methods:** An institutional database was reviewed to identify patients (pts) who received erlotinib for advanced NSCLC carrying an EGFR exon 19 deletion or L858R mutation. Using a retrospective chart review, erlotinib dose was determined at treatment start and after 4 months of therapy. Progression free survival (PFS) was calculated from time of treatment start until date when the treating clinician documented clinical disease progression. **Results:** 206 eligible pts were identified: 118 exon 19 del, 88 L858R; 144 1st-line, 62 later-line. 34 pts (17%) initiated erlotinib at a reduced dose: 100mg (n = 29), 50 mg (n = 4), 25 mg (n = 1). Reduced-dose pts were older than full-dose pts (median age 70 vs. 64 yrs, $p < 0.01$), but otherwise clinically similar (Table). Reduced-dose pts had a median PFS of 8.8 months, not significantly different from those at full-dose (11.2 months, HR = 1.3, p= 0.14). Of 173 pts who had not progressed at 4 months, the 86 (50%) on reduced-dose erlotinib at that time had a significantly lower median PFS (11.7 vs. 14.0 months, HR = 1.5, $p< 0.05$). **Conclusions:** This is the largest series to date describing outcomes when initiating treatment for EGFR-mutant lung cancer with reduced-dose erlotinib. PFS was acceptable when treating at a reduced biologically active dose, though trends towards a lower PFS than with MTD dosing. A multivariate analysis controlling for baseline differences is underway.

	Full dose (n = 172)	Reduced dose (n = 34)	p
Median age (years)	64	70	0.004
PS: 0-1, 2+	113, 8	20, 3	0.383
Brain mets at start	57 (33%)	9 (26%)	0.548
Line: 1, 2+	120, 52	24, 10	1.000
Median PFS	11.2	8.8	0.14 (HR 1.3)

8075 Poster Session (Board #399), Mon, 8:00 AM-11:30 AM

Single institution experience with 75 mg dose of erlotinib in Latin American patients with mutated metastatic non-small cell lung cancer. *First Author: Osvaldo Rudy Aren, Centro Internacional de Estudios Clínicos, Santiago, Chile*

Background: The recommended dose for erlotinib of 150 mg was developed based on the maximum tolerated dose (MTD); meanwhile the suggested dose for gefitinib is only one third of its MTD. Studies suggest that the optimal biologic dose of erlotinib should be lower and dependent of the body mass index. Hereby we present results and toxicity with 75 mg/day dose in South American patients. **Methods:** We performed a retrospective review of patients with histologically proven (+) EGFR (+) mutation mNSCLC treated with 75mg/day erlotinib as starting dose at Centro Internacional de Estudios Clinicos. Clinical information, including toxicity grade 1-4, drug discontinuation, clinical evolution and radiological evaluation were revised. Overall survival from initiation of treatment was obtained from death certificate information. **Results:** Twenty-eight patients received 75mg/day of erlotinib as starting dose. Twenty-one (75%) patients were treated in first and seven (25%) in second line treatment. Mean age was 61years (range 36-89 years and nineteen (67%) patients were female. All patients had mutation positive EGFR, 22 (78 %) had Del19 and 6 (22%) exon 21 mutation. One patient had partial response and one had complete response. Progression free survival was 17 months and median overall survival 19 months. The main grade 1-2 toxicities were rash (33%) and diarrhea (25%). No grade 3-4 toxicity and no cases of drug discontinuation were reported. As of the writing of this abstract six patients are without progression and continue on treatment. **Conclusions:** In South American population with mutated mNSCLC, a dose of 75mg/day of erlotinib was well tolerated. This dose resulted in comparable benefits in PFS and OS when compared to those reported in the literature with the standard dose. Genetic polymorphism in metabolic enzymes and lower body mass index could explain the same efficacy at lower dose. More studies are needed to explore the use of adjusted doses of biological agents in different ethnic backgrounds.

8076 Poster Session (Board #400), Mon, 8:00 AM-11:30 AM

A phase II trial of erlotinib for *EGFR* mutant NSCLC to prospectively assess biopsy feasibility and acquired resistance at disease progression. *First Author: Amanda J. Redig, Dana-Farber Cancer Inst, Boston, MA*

Background: Erlotinib is a first-line therapy for patients (pts) with advanced *EGFR* mutant non-small cell lung carcinoma (NSCLC). However, tumors develop acquired resistance; choice of further therapy, including third-generation EGFR inhibitors in development, often depends on the mechanism driving resistance. We performed a prospective trial to assess biopsy feasibility and resistance mechanisms in *EGFR* mutant pts with acquired erlotinib resistance. **Methods:** Advanced, EGFR TKI naïve *EGFR* mutant NSCLC pts were enrolled in a phase II trial of erlotinib. At study entry, eligible pts consented to undergo re-biopsy at progression. The primary endpoint was feasibility of re-biopsy and evaluation of acquired resistance. Re-biopsies underwent pathology review and genomic analysis. Secondary objectives included evaluating biopsy features and reason(s) why re-biopsy could not be performed. **Results:** Between 02/10 and 1/15, 60 EGFR mutant pts (44 women, 34 never-smokers) were enrolled (L858R (17); exon 19 deletion (38); other (5)). 16 pts remain on study. Median age (range): 62.5 years (34-90). Median PFS: 11.0 months. 44 pts discontinued therapy (39 for progression, 5 for adverse events); 31 (70%) underwent re-biopsy. 8 pts did not undergo re-biopsy because of pt refusal (3); clinical contraindication (3); sudden death (1); or discovery of germline T790M (1). 31 re-biopsies identified: T790M mutation (17, 55%); SCLC transformation (3, 10%); no T790M or SCLC (6, 19%); inadequate tissue (3, 10%). Re-biopsy targeted enlarging lesions (26) and stable lesions (5), with T790M identified in 5/5 stable lesions and 12/26 enlarging lesions. Genotyping was done on effusions (3/4), lymph node (8/8), lung lesion (15/17), peritoneal deposit (1/1), and bone (1/1). **Conclusions:** Repeat biopsy at disease progression on first-line *EGFR*-directed therapy is feasible in 70% of pts and yields clinically meaningful results for subsequent therapy. It may be possible to identify resistance mechanisms from biopsy of focally stable yet easily accessible sites of disease. However, non-invasive means of detecting acquired resistance will be important, as re-biopsy is not always possible. Clinical trial information: NCT00997334.

8077 Poster Session (Board #401), Mon, 8:00 AM-11:30 AM

Clinical implications of repeat tumor biopsy (RTB) in patients (pts) with advanced lung cancer (LC): The Cleveland Clinic (CC) experience. *First Author: Eberechi Sandra Agwa, Cleveland Clinic Foundation, Taussig Cancer Institute, Cleveland, OH*

Background: RTB at disease progression (PD) is increasingly used to profile tumor biomarkers and identify drug resistance mechanisms. However, information on safety and clinical consensus on the use of RTB remain lacking. **Methods:** The aim of this study is to review RTB patterns and safety in LC pts at CC and impact on treatment (Rx) decisions. Pts who were diagnosed and underwent RTB for suspected LC PD between 2007 and 2013 were studied. Statistical analysis is primarily descriptive. **Results:** The study involved 184 (56% male) pts. Median age at diagnosis was 65Y (21-87). 100 (54%) were treated initially with single modality (Surgery = 41; Chemo = 33; Radiation = 17; targeted therapy = 9) and 83 (45%) with multimodality Rx (2-modality = 57, 3-modality = 26), 1 (1%) unknown. # Of RTB per patient: 1 in 66.3% (n = 122), 2 in 20.1% (n = 37), 3 in 11.4% (n = 21), and 4 in 2.2% (n = 4). The most common procedure at 1st RTB was bronchoscopy (44.6%, n = 82), followed by CT guided biopsy (bx) (20.7 %, n = 38), surgery (10.3%, n = 19), excision bx (8.2%, n = 15), fine needle aspiration of skin & lymph node (LN) (7.6%, n = 14), ultrasound guided bx (5.9%, n = 11) & others (2.7%, n = 5). Lung was the most commonly re-biopsied site (46%) followed by LN (15%). Complications occurred in 13 of 181 (7.2%) pts at 1st RTB (data missing in 3 pts), 3 of 61 (4.9%) at 2nd RTB, 1 of 25(4%) at 3rd RTB, and 0 of 4 (0%) at 4th RTB. The 17 (6.2%) complications are shown in the table below. Histologic change was seen in 13 cases, including adeno-to-squamous carcinoma (at erlotinib resistance) and vice-versa, and non-small cell to small cell histology. The T790M-EGFR mutation was noted in 6 cases, the PIK3CA mutation in 1, and a change in ALK status in 3. Medical decision making was impacted in 16% of cases. **Conclusions:** RTB can be safely performed using minimally invasive techniques and can benefit LC Rx decision making.

Complication	n
Bleeding without hemodynamic compromise	6
Bleeding requiring transfusion	1
Pneumothorax	5
Hemodynamic instability after premedication	1
Cerebral salt wasting	1
Tracheoesophageal fistula	1
Severe cough	1
Incomplete procedure	1
Deaths	0

8078 Poster Session (Board #402), Mon, 8:00 AM-11:30 AM

Dynamic serial monitoring of EGFR mutations in plasma DNA samples in EGFR mutant NSCLC patients treated with EGFR TKI. *First Author: Myung-Ju Ahn, Samsung Medical Center, Seoul, South Korea*

Background: Detection of epidermal growth factor receptor (EGFR) mutation in non-small cell lung cancer (NSCLC) patients is mainly based on tissue biopsy, which is invasive and time consuming. Furthermore, there is still a need for serial monitoring of EGFR mutations and detection of EGFR tyrosine kinase inhibitors (TKIs) resistance. We hypothesized that plasma-based EGFR mutation analysis may be feasible for monitoring response to EGFR TKIs and could be used to predict the resistance. **Methods:** From February 2012 through April 2014, 200 EGFR mutant NSCLC patients were enrolled and treated with EGFR TKIs (141 patients for gefitinib, 46 patients for erlotinib, and 13 patients for afatinib). Plasma samples were prospectively obtained every 2 months from baseline until disease progression. The longitudinally collected plasma samples (n = 277) from 61 patients who progressed were analyzed using droplet digital PCR (ddPCR). We identified an association between serial EGFR mutant titers in plasma cell-free DNA (cfDNA) samples and the patient's clinical response to EGFR TKIs. **Results:** Of a total 60 baseline cfDNA samples available for ddPCR, 40 (67%) samples demonstrated same mutation in the matched tumors (i.e. sensitivity: 65% (13/20) for L858R vs 68% (27/40) for exon 19 deletions). The concordance rate of plasma with tissue results of EGFR mutation was 88% for L858R and 78% for exon 19 deletion, respectively. All the samples showing EGFR mutations in plasma showed a dramatic decrease of mutant copies (greater than 50%) in blood in the first 2 months after treatment. We also found the secondary mutation (T790M) emerged in 15 patients around 3~13 months after treatment and can be detected before disease progression as determined by CT scan. Correlation between the tumor volume and the level of cfDNA EGFR mutations will be updated. **Conclusions:** These results suggest that ddPCR is an appropriate method for determining plasma-based EGFR mutation status and may aid in monitoring response to EGFR TKIs and early detection of EGFR TKIs resistance.

Concordance between EGFR mutation status assessed by ddPCR and clinical tissue result.

	ddPCR			
prior treatment N=60	L858R +	L858R-	E19 +	E19 -
Tissue +	13	7	27	13
Tissue -	0	40	0	20

8079 Poster Session (Board #403), Mon, 8:00 AM-11:30 AM

Early prediction of response to tyrosine kinase inhibitors by quantification of EGFR mutations in plasma of non-small cell lung cancer patients. *First Author: Antonio Marchetti, Center of Predictive Molecular Medicine, SS. Annunziata Hospital, University G. D'Annunzio, Chieti, Italy*

Background: Several studies have investigated the feasibility of detecting EGFR mutations in liquid biopsies of Non-Small Cell Lung Cancer (NSCLC) patients. However, the potential to accurately quantify EGFR mutations in plasma for clinical purposes is largely unexplored. **Methods:** Plasma samples were obtained from 79 subjects: (a) 42 NSCLC patients with EGFR mutations in primary tumors tissue, from a prospective trial, where blood samples were collected at baseline prior to first-line erlotinib therapy and immediately after progression; (b) 15 previously untreated stage IIIB-IV NSCLC patients, with EGFR mutation positive tumor specimens, where plasma samples were collected at baseline and serially at 4-60 days during TKI therapy; (c) 22 negative control cases. EGFR mutation analysis in plasma was conducted by the cobas EGFR Mutation Test (EGFR test, under development, RMS, Pleasanton, CA) and ultra-deep next generation sequencing (UDNGS) by Roche 454-GS Junior and Illumina MiSeq. A semi-quantitative index (SQI) was derived from a dilution series of known mutation copy numbers. Clinical response, expressed as percent tumor shrinkage (PTS), was evaluated according to RECIST criteria. **Results:** The sensitivity and specificity of the EGFR test and UDNGS assay in plasma versus tissue was 72% and 100%, and 74% and 100%, respectively. Quantitative indices by the EGFR test and UDNGS showed a significant positive correlation ($p < 0.0001$). Serial testing of EGFR mutations revealed a progressive decrease in the EGFR semi-quantitative index (SQI) during therapy in all of the patients, starting from the 4thday of treatment in 90% of cases. The rate of SQI decrease was more than 50% at 15 days in 73% of patients (rapid responders) and less than 50% at 15 days in 27% of patients (slow responders) and was correlated with PTS at 2 months. **Conclusions:** Quantification of EGFR mutations with the cobas test in plasma is feasible. The variation of EGFR SQI during therapy could be useful for early prediction of response and diagnosis of relapse, with further implications for patient management. A prospective trial has been planned to confirm these results. Clinical trial information: EudraCT Number: 2010-023892-24.

8080 Poster Session (Board #404), Mon, 8:00 AM-11:30 AM

Association of plasma EGFR T790M ctDNA status with clinical outcome in advanced NSCLC patients with acquired EGFR-TKI resistance. *First Author: Di Zheng, Shanghai Pulmonary Hosp, Shanghai, China*

Background: *EGFR* T790M mutation occurs in around half of non-small cell lung cancer (NSCLC) patients with acquired EGFR-TKI (TKI) resistance, based on tumor tissue re-biopsies using an invasive clinical procedure. Here, we evaluated the feasibility of detecting T790M mutation in circulating tumor DNA (ctDNA), using serial plasma samples from NSCLC patients receiving TKI to further investigate its association with clinical outcome. **Methods:** Patients with advanced or recurrent NSCLC receiving TKI were enrolled consecutively and blood samples were taken every 2 months, including post-TKI failure. Upon TKI failure, patients were given continued TKI alone or TKI plus chemotherapy at the discretion of the physician. *EGFR* ctDNA in plasma was measured using Droplet Digital PCR (ddPCR) assay. Overall survival (OS) of starting from initial TKI treatment was analyzed according to the T790M ctDNA status detected in plasma. **Results:** Among 318 patients, 117 who acquired TKI resistance (with 391 plasma samples) were eligible for the analysis. T790M ctDNA was detected in the plasma of 55/117 (47%) patients. Almost half of the T790M ctDNA positive patients were identified at a median time of 2.2 months prior to clinical progressive disease (PD). Furthermore, T790M ctDNA positive patients had significantly shorter OS compared to negative patients (median OS: 808 versus 1083 days, P = 0.0418). **Conclusions:** Our study demonstrates the feasibility of monitoring EGFR mutation dynamics in serial plasma samples from NSCLC patients receiving TKI therapy. T790M ctDNA can be detected in plasma before and after PD and represents a potential poor prognostic factor.

8081 Poster Session (Board #405), Mon, 8:00 AM-11:30 AM

Kinetic monitoring of EGFR T790M in urinary circulating tumor DNA to predict radiographic progression and response in patients with metastatic lung adenocarcinoma. *First Author: Hatim Husain, UC San Diego Moores Cancer Center, La Jolla, CA*

Background: Acquisition of the EGFR T790M resistance mutation is a hallmark of disease progression in patients with metastatic EGFR mutant lung adenocarcinoma treated with anti-EGFR inhibitors. Biopsies are challenging in relapsed patients and a non-invasive approach to detecting T790M is desired. We sought to monitor urinary circulating tumor (ct) DNA for the early acquisition of T790M and understand ctDNA kinetics in patients on anti-EGFR treatment. **Methods:** In a biomarker study of 100 patients with EGFR-mutated metastatic lung adenocarcinoma (39 patients enrolled), urine samples were obtained at different time points up to 8 months prior to radiographic progression on anti-EGFR tyrosine kinase inhibitors (TKIs) and at multiple time points post progression on next line therapy. Urinary ctDNA was extracted by a method that preferentially isolates short, fragmented ctDNA. Quantitative analysis of T790M was performed using PCR coupled with next generation sequencing (MiSeq), with standardized reporting of mutant allele copies per 10^5 genome equivalents. **Results:** Interim analysis was conducted in 22 patients. EGFR T790M mutation was detected in the urine of 15 out of 22 (68%) patients who received anti-EGFR treatment. Of 15 patients positive for T790M by urine, 10 patients had T790M mutation in tissue biopsy (CLIA test). Three patients, who were tissue T790M negative (n = 3) but had a very high clinical suspicion of T790M, had detectable T790M in both urine and plasma. EGFR T790M was detected in urine up to 3 months prior to the detection of radiographic progression on anti-EGFR TKIs. Examination of urine samples collected daily after initiation of anti-EGFR TKIs and second line therapy revealed early peaks in ctDNA one day after therapy which predicted CT radiographic response. **Conclusions:** We demonstrate for the first time that T790M can be successfully detected in urinary ctDNA months before progression on anti-EGFR TKIs. Urinary ctDNA testing identifies additional patients who are potentially eligible for anti-T790M treatment. Urine monitoring can enable dynamic assessment of response and progression from a completely non-invasive sample.

8082 Poster Session (Board #406), Mon, 8:00 AM-11:30 AM

EML4-ALK rearrangement in blood platelets and outcome to crizotinib in non-small-cell lung cancer patients. *First Author: Niki Karachaliou, Quirón Dexeus University Institute, Translational Research Unit, Barcelona, Spain*

Background: Non-small-cell lung cancer (NSCLC) with EML4-ALK rearrangements is sensitive to crizotinib. However, despite initial response most patients (p) will eventually relapse and monitoring EML4-ALK rearrangements over the course of treatment may help identify them. Challenges associated with serial tumor biopsies have highlighted the need for blood-based assays for monitoring biomarkers. Platelets can sequester RNA released by tumor cells and are an attractive source for non-invasive biomarker assessment. **Methods:** EML4-ALK rearrangements were analyzed by reverse transcription-polymerase chain reaction (RT-PCR) in platelets and plasma isolated from blood obtained from 77 NSCLC p, 38 of whom had EML4-ALK-rearranged tumors. In a subset of 29 p with EML4-ALK-rearranged tumors treated with crizotinib, EML4-ALK rearrangements in platelets were correlated with progression-free survival (PFS) and overall survival (OS). **Results:** The study was designed with three parallel objectives: firstly to determine the sensitivity and specificity of detecting EML4-ALK rearrangements in platelets with plasma serving as a control biosource; secondly, to examine the potential impact of EML4-ALK rearrangement in platelets on outcome to crizotinib; thirdly, to test the feasibility of monitoring a p throughout treatment with EML4-ALK rearrangement assessment in platelets**.** RT-PCR demonstrated 65% sensitivity and 100% specificity for detection of EML4-ALK rearrangements in platelets. In the subset of 29 p treated with crizotinib, PFS was 3.7 months for p with EML4-ALK+ platelets and 16 months for those with EML4-ALK− platelets (hazard ratio, 3.5; P = 0.02). Monitoring EML4-ALK rearrangements in platelets of one index p over a period of 30 months revealed crizotinib resistance two months prior to radiographic disease progression. **Conclusions:** Platelets may provide a useful source for non-invasive assessment of EML4-ALK rearrangements and may prove useful for predicting outcome to crizotinib. Serial analyses of EML4-ALK rearrangements in platelets may help improve clinical decisions based on radiographic imaging alone by detecting resistance to therapy sooner.

8083 Poster Session (Board #407), Mon, 8:00 AM-11:30 AM

Phase I dose escalation study of ASP8273, a mutant-selective irreversible EGFR inhibitor, in subjects with EGFR mutation positive NSCLC. *First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ASP8273 is a mutant selective, third generation irreversible inhibitor of EGFR activating mutations and the EGFR T790M resistance mutation, with less effect on wild type EGFR. **Methods:** In a phase I dose escalation study, subjects diagnosed with EGFR mutation positive NSCLC who were previously treated with an EGFR TKI were enrolled at multiple centers in the United States into dose escalation and expansion cohorts. ASP8273 was administered once daily at doses of 25 mg to 400 mg. Endpoints included safety and tolerability, PK and preliminary anti-tumor activity. Response expansion cohorts enrolled subjects with known EGFR T790M mutation and required submission of tissue samples for central confirmatory testing. **Results:** As of 08 January 2015, 35 subjects were enrolled; 24 subjects in 6 dose escalation cohorts (25-400 mg) and 11 subjects in 2 expansion cohorts (100-200 mg). The majority were female (71.4%), median age 65 (38-85), all (100%) received prior erlotinib, and the median number of prior therapies was 2. The most common treatment emergent AEs included nausea (9; 25.7%) & diarrhea (6; 17.1%); most were CTCAE Grade 1, manageable and none required dose reductions. Of 5 evaluable subjects enrolled at 400mg, 2 DLTs were observed requiring dose reduction including one event of G3 hyponatremia and one event of G3 anorexia. No ILD-like events, QTc prolongation or hyperglycemia have been reported. PK appeared to be dose proportional with mean t½ ~12 hours. Objective responses were observed at dose levels of ≥ 100mg. Among 25 subjects evaluable for response at the cutoff date, 7 (28%) subjects achieved PR and 15 (56%) achieved stable disease. Among 12 known T790M+ subjects, 3 PRs (25%) have been reported to date. **Conclusions:** ASP8273 appears well tolerated in doses ranging from 25-300 mg and has demonstrated anti-tumor activity at 100-400 mg dose levels. The most common toxicities include diarrhea and nausea which were G1 and manageable. Based on current Bayesian modeling, the MTD is anticipated to be 400 mg and the recommended phase 2 dose to be 300 mg. As the data for the T790M+ population is immature at the time of this abstract, updated data will be presented at the ASCO meeting. Clinical trial information: NCT02113813.

8084 Poster Session (Board #408), Mon, 8:00 AM-11:30 AM

Updated safety and efficacy results from phase I/II study of HM61713 in patients (pts) with EGFR mutation positive non-small cell lung cancer (NSCLC) who failed previous EGFR-tyrosine kinase inhibitor (TKI). *First Author: Keunchil Park, Division of Hematology & Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: HM61713 is an orally available EGFR mutation-specific inhibitor with sparing EGFR WT tumors that previously showed promising efficacy in T790M positive tumors at the dose of 300 mg (overall response rate; 29.2%). We report here on updated data from the ongoing phase I/II study of HM61713 in pts with advanced NSCLC who had failed previous EGFR-TKIs (NCT01588145). **Methods:** Advanced NSCLC pts with EGFR mutation positive tumor were enrolled in dose escalation cohort and received doses ranging from 75-1200 mg/day. After safety evaluation, separate expansion cohorts opened for pts who failed prior EGFR TKI pts at 800 mg QD dose, respectively to investigate efficacy and tolerability of HM61713 in pts with centrally confirmed T790M positive NSCLC. **Results:** As of 15 Dec 2014, 173 patients were enrolled, 55 and 118 in dose escalation and expansion parts, respectively. Maximum tolerated dose (MTD) was established as 800 mg once daily (QD). Dose limiting toxicities (DLTs) included abdominal pain, diarrhoea, idiosyncratic drug reaction, and elevation of aspartate aminotransferase, alanine aminotransferase, amylase and lipase. Treatment-related adverse events occurred in 87.3% of 165 pts; mainly diarrhea, rash, skin exfoliation, nausea, pruritus, decreased appetite and dry skin. In the 34 pts with centrally confirmed T790M who received HM61713 with a dose more than 650 mg, the overall response rate was 58.8%, (10 confirmed/10 unconfirmed partial responses) and 13 pts achieved disease stabilization (disease control rate; 97.1%). Updated data will be presented at the meeting. **Conclusions:** HM61713 showed an encouraging clinical anti-tumor activity with good tolerability in pts with T790M positive NSCLC. Clinical trial information: NCT01588145.

8085 Poster Session (Board #409), Mon, 8:00 AM-11:30 AM

A phase II, single-arm, efficacy and safety study of poziotinib (NOV120101) in Korean patients with advanced or metastatic lung adenocarcinoma who have acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors. *First Author: Ji-Youn Han, National Cancer Center, Goyang, South Korea*

Background: Poziotinib is an oral irreversible inhibitor of EGFR, HER2 and HER4, and has shown preclinical activity in lung cancer models with *EGFR* mutations including T790M. This phase II study was aimed to access the efficacy of poziotinib in patients with *EGFR*-mutant lung adenocarcinoma and acquired resistance to erlotinib or gefitinib. **Methods:** Eligible patients had documented activating *EGFR*mutations and developed acquired resistance after treatment with erlotinib or gefitinib based on Jackman criteria. Patients received poziotinib at a dose of 16 mg once daily in 28-day cycles. The primary endpoint was PFS. All tumor responses were evaluated by independent review and, in a supportive manner, by investigator. **Results:** A total of 39 patients were treated with poziotinib in this study (29 women, median age 62 years [range, 43-84]). Most patients received erlotinib or gefitinib as first-line (n = 27) or second-line therapy (n = 11). The median time on erlotinib or gefitinib was 13.1 months (range, 3.4-33.2). Genotyping using tumor biopsy acquired at study entry was determined in 37 patients; 19 patients had *EGFR* T790M mutation, 2 *PIK3CA* mutation and no *MET*-amplification. Partial response with poziotinib was confirmed in 3 patients (8%; 95% CI, 2-21). Twenty patients (51%; 95% CI, 35-68) had disease control of at least stable disease for ≥ 8 weeks. The median PFS and overall survival were 2.7 (95% CI, 1.8-3.7) and 15.0 months (95% CI, 9.5-not estimable), respectively. The most frequently reported AEs of grade 3 by preferred term were rash (59%), stomatitis (18%), and diarrhoea (10%). Two patients were discontinued due to treatment-related AEs (one grade 3 rash and one grade 3 myositis). **Conclusions:** Poziotinib showed modest efficacy in patients with *EGFR*-mutant lung adenocarcinoma who had progressed on erlotinib or gefitinib. Obvious clinical evidence suggesting that poziotinib may overcome acquired resistance secondary to *EGFR* T790M mutation was not captured in this study. Clinical trial information: NCT01718847.

8086 Poster Session (Board #410), Mon, 8:00 AM-11:30 AM

A phase Ib/II study of afatinib in combination with nimotuzumab in non-small cell lung cancer patients with acquired resistance to gefitinib or erlotinib. *First Author: Myung-Ju Ahn, Samsung Medical Center, Seoul, South Korea*

Background: Afatinib (A) is a potent irreversible ErbB family blocker and nimotuzumab (N) is a humanized anti-EGFR mAb. In this phase Ib/II study, we aimed to assess the safety and activity of A plus N in advanced NSCLC patients with acquired resistance to gefitinib or erlotinib. In our preclinical study, using a mouse xenograft model, Nimotuzumab enhanced the antitumor efficacy of Afatinib. **Methods:** Major inclusion criteria were advanced NSCLC with activating EGFR mutation or disease control for at least six months with previous gefitinib or erlotinib therapy. In phase Ib study using classic 3+3 dose escalation method, patients were treated with A either 40mg/d or 30mg/d in combination with N either 100mg/w or 200mg/w. One cycle was composed of 4 weeks of treatment. In phase II study, patients were treated with A plus N in the level of RP2D defined in phase Ib study. **Results:** Overall, fifty pts were enrolled and treated: 13 in phase Ib and 37 in phase II. The median age of the patients was 55 years and 62% were female. EGFR mutation types were as follows: del19 (N = 23, 46%), L858R (N = 15, 30%), and others. All patients had received prior gefitinib (N = 34, 68%) or erlotinib (N = 16, 32%). At the first cohort (A 40mg/d + N 100mg/w), 1 out of 6 pts experienced 1 DLT (G3 diarrhea), and 2 out of 6 pts experienced DLTs (G3 diarrhea and G3 neutropenia, respectively) during the 1st cycle in the next cohort (A 40mg/d + N 200mg/w). Thus, RP2D was accordingly determined as A 40mg/d + N 100mg/w per protocol. In phase II part, there was no treatment related death and 27% (10/37) of patients experienced any grade 3 adverse events (no one in grade 4 or 5), including diarrhea and skin rash. In phase II part, the response rate was 38% (14/37), disease control rate 81% (30/37), duration of response 4.0 months (range, 1.8-8.5 months) and the median PFS was 4.2 months (95% CI:2.44-5.96 months). **Conclusions:** Combination of A and N showed an acceptable safety profile and promising antitumor activity in advanced NSCLC patients with acquired resistance to gefitinib or erlotinib. Clinical trial information: 1200.189.

8087 Poster Session (Board #411), Mon, 8:00 AM-11:30 AM

Biomarker analysis of a phase II trial of cabozantinib and erlotinib in patients (pts) with EGFR-mutant NSCLC with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) resistance: A California Cancer Consortium Phase II Trial (NCI 9303). *First Author: Karen L. Reckamp, City of Hope, Department of Medical Oncology and Therapeutics Research, Duarte, CA*

Background: Modulation of the MET and VEGFR signaling pathways are associated with resistance to EGFR TKI therapy in addition to acquired T790M mutation (mt). Cabozantinib is a TKI that targets MET and VEGFR2, and RET, AXL, IT and TIE-2. Third generation EGFR inhibitors are effective in T790M mt-pos tumors, although treatment of T790M-neg disease remains an area of unmet need. Cabozantinib and erlotinib in *EGFR*mt-positive NSCLC following PD on EGFR TKI showed benefit, and we evaluated potential mechanisms of resistance to therapy. **Methods:** Pts with *EGFR* mt and PD on an EGFR TKI immediately prior to enrollment were eligible. Erlotinib 150 mg daily + cabozantinib 40 mg daily were given on a 28 day cycle and ORR was the primary objective. Pts were required to have archival tissue available, and a subset had biopsy samples post-progression on EGFR TKI. *MET* amplification was determined by FISH and *EGFR*mt, including T790M, was analyzed by next-generation sequencing. **Results:** 37 pts were enrolled and baseline *EGFR* mt was del19 in 68%, L858R in 30%, and 1 patient had an exon 18 mt. 57% received two or more prior therapies. Fifteen (41%) had post-EGFR TKI biopsies available, with 8 T790M-pos. *MET*gene amplification was not found in any of those with post-progression biopsies. ORR was 12.5% in pts with T790M-pos tumors, but DCR and PFS was increased in pts with T790M-neg tumors (see Table). OS was longer in pts with T790M-pos mt, which may reflect post-study therapy or biologic differences. **Conclusions:** Cabozantinib and erlotinib had clinical benefit in heavily treated patients with EGFR mt and EGFR TKI resistance. Further investigation in pts with T790M-neg tumors is warranted, and remains an unmet need. Additional biomarkers will be evaluated in plasma. Supported by NCI N01CM2011-00038 and U01CA062505. Clinical trial information: NCT01866410.

	All (n = 37)	T790M-neg (n = 7)	T790M-pos (n = 8)	T790M n/a (n = 22)
ORR (%)	8	0	12.5	9.1
DCR at 8 weeks (%)	68	86	50	64
PFS, mo (95% CI)	3.7 (2.4, 5.6)	3.6 (1.7, 5.8)	2.7 (1.6, 9.9)	3.8 (1.7, 7.2)
OS, mo (95% CI)	9.1 (6.0, NR)	7.7 (2.4, 13.3)	NR (2.8, NR)	12.2 (5.6, NR)

8088 Poster Session (Board #412), Mon, 8:00 AM-11:30 AM

Genetic variability and clinical presentation of patients with non-small cell lung cancer (NSCLC) harboring *MET*-amplifications. *First Author: Anna Eisert, Lung Cancer Group Cologne, Department I of Internal Medicine, University Hospital of Cologne, Center for Integrated Oncology (CIO) Köln Bonn, Cologne, Germany*

Background: Amplification of *cMET* has been described as mechanism underlying resistance to EGFR-targeted therapy in EGFR-mutated NSCLC. Nevertheless, few is known about *cMET* amplification beside the EGFR-resistance setting. This study was performed in order to characterize patients with low-level, intermediate-level and high-level cMET amplification focusing on frequency, co-occuring driver mutations and clinical outcome. **Methods:** Within a regional molecular screening network *cMET* amplification status was analyzed by fluorescence in-situ hybridization (FISH) in 588 patients with NSCLC regardless of histology. Next-generation parallel sequencing (NGS) using 102 amplicons and 14 genes was performed in all analyzed samples. Clinical parameters (age, sex, UICC tumor stage, smoking status and medical and therapeutical history) of all patients were assessed. **Results:** 171 patients (29.1%) with *cMET* amplification were identified, whereof 17 (9.9%) had high-level amplification. *cMET* amplifications co-occured in 98 patients (57.3%) with a large spectrum of other driver mutations (*EGFR*, *KRAS*, *HER2*, *STK11*, *NRAS*, *BRAF*) or amplifications (*FGFR1)* in both adenocarcinoma (60.2%) and squamous cell carcinoma (21.1%). 9 patients of the high-level-amplified patients did not have an additional driver mutation, while the remaining 8 patients had mutations within *EGFR*, *KRAS*, *PIK3CA*, *BRAF* and *STK11*. *cMET* amplification was associated with a history of smoking and detected in all UICC tumor stages. **Conclusions:** Our data suggest a high prevalence of *cMET* amplification in NSCLC patients with many oncogenic driver mutations. Most patients with an additional mutations had *KRAS* mutations. These data show that screening for *MET*-amplified patients in order to identify patients for MET-targeted treatment should not be performed on the basis of sequencing results.

8089 Poster Session (Board #413), Mon, 8:00 AM-11:30 AM

Response to tyrosine kinase inhibtors in non-small-cell lung cancer with concomitant c-MET overexpression and driver genes. *First Author: Na-na Lou, Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: The common driver genes in non-small-cell lung cancer (NSCLC) include *EGFR*, *ALK* and *KRAS*. We investigate the frequency of MET overexpression coexisting with oncogenic drivers and response to tyrosine kinase inhibitors (TKIs). **Methods:** We screened 806 consecutive NSCLC patients for the presence of MET overexpression by immunohistochemistry (IHC), in which ≥ 50% tumor cells with moderate to high intensity staining were defined as MET positive. *MET* amplification and *ALK* rearrangements were detected by fluorescence in situ hybridization (FISH), and FISH positive was defined as gene focal amplification or high polysomy (at least 15% cells with ≥ 5 copy numbers). Meanwhile, *KRAS* and *EGFR*mutations were tested by DNA sequencing or Scorpion amplification refractory mutation system (ARMS). **Results:** The frequency of MET overexpression was 31.9% (257/806) in NSCLC. Among c-MET positive patients, the frequency of *EGFR* mutation was 38.1% (98/257) and that of *ALK* rearrangement was 8.7% (22/257). Response rate (RR) of EGFR-TKIs was 22.2% (8/36) in advanced NSCLC patients with concomitant *EGFR* mutation and c-MET overexpression, and 56.8% (21/37) in those with only *EGFR* mutation, *P*= 0.033. However, there was no significant difference in RR between the patients with concomitant *ALK* rearrangement and c-MET overexpression and those with only *ALK* rearrangement, 61.5% (8/13) vs. 75.0% (6/8), *P*= 0.656. Among 2 cases with concomitant *MET* amplification and *EGFR* mutations, one responded to gefitinib, but the other had stable disease. Dramatic response was observed in one with concomitant *MET* amplification and *KRAS* mutations. **Conclusions:** Advanced NSCLC patients with concomitant *EGFR* mutation and MET overexpression have significantly low RR with EGFR-TKIs, indicating that MET overexpression potentially causes intrinsic resistance to EGFR-TKIs. Similar response was observed in *ALK* positive patients with or without c-MET overexpression treated with crizotinib.

8090 Poster Session (Board #414), Mon, 8:00 AM-11:30 AM

Crizotinib in advanced non-small-cell lung cancer with *de novo* c-Met overexpression. *First Author: An Na Li, Guangdong Lung Cancer Institute, Guangzhou, China*

Background: *c-Met* gene amplification has been identified as one of the acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and *de novo* activation in advanced non-small-cell lung cancer (NSCLC). However, it is not clear whether c-Met overexpression could be as the biomarker for *de novo*. **Methods:** Advanced NSCLC patients with *de novo* c-Met expression were detected by immunohistochemistry (IHC) .≥50% tumor cells with moderate to high intensity staining were defined as c-Met positive. Gene copy numbers have been detected by FISH (By Cappuzzo scoring system ≥5 copies were positive or MET/CEP7 ratio ≥1.8 was defined as c-MET amplification).The statuses of *EGFR*, *ALK*, *KRAS* and *ROS1*were also tested. **Results:** From January 2013 to December 2014, 24 eligible patients with c-Met IHC overexpression received crizotinib treatment (3 female, median age 59 years), with 19 evaluable for response.Eleven of them achieved partial response (PR), 3 were stable disease (SD) and 5 were progressive disease (PD).All responders had high c-Met IHC status, and 8 with FISH positive. (Table 1).Adverse events of grade 3 QT prolongation have been found in 1 patient. For one death with interstitial lung disease, causality to crizotinib was not ruled out. The other most frequent drug-related AEs were grade1-2, including nausea (14/19), anorexia (14/19), vomiting(10/19),visual impairment (6/19). *EGFR*, *ALK*, *KRAS* and *ROS1* were all negative . Accrual of advanced patients is ongoing. **Conclusions:** c-Met overexpression could be as a biomarker for *de novo c-Met* amplified NSCLC. c-Met inhibitor against *de novo*c-Met overexpressed NSCLC is a good strategy. IHC seems not worse than FISH in predicting efficacy for c-Met inhibitor.

Objective response to crizotinib treatment for advanced NSCLC patients with *de novo* c-Met overexpression.

Patient No.	IHC of c-Met	FISH of c-Met	Response
1	55%×2	N/A	PR
2	100%×3	focus	PR
3	60%*2	-	PR
4	70%×2	-	SD
5	100%×3	focus	PR
6	50%×3+30%×2	-	PD
7	100%*3	-	PR
8	65%*3+25%*2	-	PD
9	15%*3+45%*2	-	SD
10	100%*3	focus	PD
11	70%*3	-	PD
12	80%×3+20%×2	-	PD
13	100%×3	focus	PR
14	100%*3	focus	PR
15	100%*3	focus	PR
16	100%×3	focus	PR
17	90%×2	-	PD
18	80%*3	N/A	PR
19	80%*2	focus	PR

8091 Poster Session (Board #415), Mon, 8:00 AM-11:30 AM

Targeting c-Met overexpression for overcoming acquired resistance to EGFR TKIs in NSCLC. *First Author: Lanying Gou, Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: c-Met amplification and T790M are both recognized as the common molecular mechanisms of acquired resistance (AR) to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in advanced NSCLC. **Methods:** Advanced NSCLC patients with AR to EGFR TKIs were detected for c-Met overexpression by immunohistochemistry ≥ 50% tumor cells with moderate to high intensity staining were defined as c-Met positive. The statuses of *EGFR*, *ALK*, *KRAS* and *ROS1* were tested. c-Met, p-Met, EGFR, p-EGFR, ERBB3, p-ERBB3, AKT, p-AKT, MAPK, p-MAPK, which were important markers in MET and EGFR signal pathway ,were tested by IHC. **Results:** From January 2013 to January 2015, 126 advanced NSCLC patients with AR to gefitinib or erlotinib were enrolled prospectively. The frequency of c-Met overexpression was 28.6% (36/126), c-Met overexpression+T790M 13.5% (17/126), T790M 24.6% (31/126), SCLC or squamous cell transformation 1.6% (2/126), *KRAS* mutation 0.8% (1/126), *ROS1* fusion 0.8% (1/126) ,*ALK* fusion 0.8%(1/126) and unknown mechanism 29.3% (37/126), respectively. Eleven c-Met overexpressed patients received gefitinib plus c-Met inhibitors crizotinib. Response rate (RR) by RECEIST was 45.5% (5/11), Disease control rate (DCR) was 54.5% (6/11), Progression disease (PD) was 45.5% (5/11). For patients with c-Met overexpression and without T790M DCR was 100% (5/5). Among these patients 40% (2/5) cases were ongoing at data cut-off. The longest duration of response to date is > 6 months. For patients with both c-Met/T790M positive no RR was found. We detected the protein expression of c-Met, p-Met, EGFR, p-EGFR, ERBB3, p-RBB3, AKT, p-AKT, MAPK, p-MAPK in tumor of 9 cases with c-Met/T790M by IHC. The results showed that all of the markers were positive in ≥ 50% cases (each marker was positive in at least 5 cases, respectively). **Conclusions:** c-Met overexpression could be as a biomarker for AR. Combination of EGFR TKIs and c-Met inhibitor is a good strategy to overcome AR for c-Met overexpressed patients, but not effective in c-Met/T790M-coexisting cases. One of the possible mechanism of resistance could contribute to both MET and EGFR signal pathway active.

8092 Poster Session (Board #416), Mon, 8:00 AM-11:30 AM

Phase I/II study of rilotumumab (R) and erlotinib (E) in previously treated patients (pts) with metastatic NSCLC. *First Author: Ahmad A. Tarhini, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: MET is frequently overexpressed in NSCLC. Amplification of MET and its ligand (HGF), are mechanisms of resistance to EGFR inhibitors. R is an IgG2 human mAb that targets HGF. This phase I/II trial evaluated the safety and recommended phase 2 dose (RP2D) of R combined with E for pts with metastatic previously treated NSCLC (Phase I) and whether efficacy is high enough to warrant further interest (Phase II). **Methods:** Phase I adopted a dose de-escalation design with R starting at 15 mg/kg IV every 3 weeks and E 150 mg orally daily (dose level 0). If dose de-escalation was needed it would proceed according to Narayana k-in-a-row design where a selected dose was estimated by isotonic regression. RP2D was the maximum below the dose associated with a 25% DLT rate. Phase II intended to test whether disease control rate (stable disease or response, DCR) of 50% for E could be improved by adding R. A Simon 2 stage design was used to select the optimal sample size for type I and II error of .10. Twenty-seven of 45 pts were required to have disease control for evidence of a statistically significant improvement over E alone. Response was assessed by RECIST every 6 weeks. **Results:** In the absence of need for de-escalation among the first 8 pts, the RP2D was defined as dose level 0. Overall, 45 response-evaluable pts with stage IV were enrolled (13 squamous and 32 adenocarcinoma; 2 EGFR and 7 KRAS mutant). Median age was 65 years. A median of 4 cycles (range 1-18+) were administered. Four pts had partial response (one with EGFR and one KRAS mutation), 23 had SD, and 18 had progression, for a response rate of 8.9% (90% CI, 3.9 - 18.1) and DCR of 60% (90% CI, 47.1 - 71.3). Median PFS 2.6 months (90% CI 1.4- 2.7). At a median follow up of 15 months, median OS was 6.6 months (90% CI, 5.6 - 8.9). Probability of surviving one year was .33 (90% CI, .23 - .47). Among grade 3/4 AEs that were considered at least possibly related were rash (3), oral mucositis (1), elevated alkaline phosphatase (3) and bilirubin (1), thromboembolic event (3), diarrhea (5). **Conclusions:** The combination of R and E in this study was found to have an acceptable safety profile and the DCR rate met the study's pre-specified criteria for success. Further investigation of this regimen is warranted. Clinical trial information: NCT01233687.

8093 Poster Session (Board #417), Mon, 8:00 AM-11:30 AM

Nationwide genomic screening network for the development of novel targeted therapies in advanced non-small cell lung cancer (LC-SCRUM-Japan). *First Author: Shingo Matsumoto, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan*

Background: Various driver gene alterations have emerged as critical targets for molecular therapies in non-small cell lung cancer (NSCLC), but these alterations other than *EGFR* mutations occur in rare populations. A nationwide genomic screening network in Japan (LC-SCRUM-Japan) was established in February 2013 for the development of novel targeted therapies against advanced NSCLCs harboring these rare alterations. **Methods:** Advanced non-squamous NSCLCs without *EGFR* mutations were eligible for inclusion in LC-SCRUM-Japan. The tumors were analyzed for *ALK/RET/ROS1* fusions using RT-PCR, and detected fusions were confirmed by FISH. Between November 2013 and March 2014, fusion-negative tumors were further examined for other driver gene mutations using a next-generation sequencing (NGS) system (Ion PGM with Ion Torrent AmpliSeq Cancer Hotspot Panel, version 2), enabling the simultaneous analysis of 50 cancer-related genes. **Results:** As of December 26, 2014, a total of 188 institutions across Japan were participating and 1347 patients had been enrolled in LC-SCRUM-Japan. Among 1271 available samples, *ALK/RET/ROS1* fusions were detected in 24 (2%)/31 (3%)/55 (4%) cases, respectively. The NGS analysis was performed in 201 cases without the fusions, and 82 cases (41%) had driver mutations, including 45 *KRAS* mutations (22%), 10 *BRAF* mutations (5%), 9 *ERBB2* mutations (4%), 2 *PIK3CA* mutations (1%), and 1 *NRAS* mutation (0.5%). *MET* and *ERBB2* amplifications were also detected by the NGS in 4 (2%) and 2 (1%) cases, respectively. Among a total of 198 cases harboring targetable gene alterations, 16 with *RET* fusions, 26 with *ROS1* fusions, and 2 with *BRAF* mutations were enrolled in clinical trials for vandetanib (LURET study, Japan), crizotinib (OO12-01, East Asia), and dabrafenib (BRF113928), respectively. **Conclusions:** This nationwide and population enrichment screening system enabled various rare driver gene alterations to be efficiently detected in advanced NSCLC, thereby contributing to the rapid accrual of matched patients in clinical trials for targeted therapies.

8094 Poster Session (Board #418), Mon, 8:00 AM-11:30 AM

Migration to next-generation sequencing and the identification of *RET* and *ROS1* rearrangements plus PTEN and MET protein expression in tumor specimens from patients with lung adenocarcinomas: Lung Cancer Mutation Consortium (LCMC 2.0). *First Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: LCMC 1.0 demonstrated that multiplexed genomic platforms can assay 10 oncogenic drivers at diagnosis in tumor specimens from patients with lung adenocarcinomas and this information can guide care. (Kris JAMA 2014) The number of molecular lesions that can be targeted with drugs continues to grow and Next-Generation Sequencing permits more comprehensive testing of more aberrations with less tumor tissue. To translate these advances, we initiated LCMC 2.0 to test initial tumor specimens for 12 oncogenic drivers and to provide the results to clinicians for treatment decisions and research. **Methods:** The 16 site LCMC 2.0 is testing tumors from 1000 patients with lung adenocarcinomas in CLIA laboratories for *KRAS, EGFR, HER2, BRAF, PIK3CA, MAP2K1, AKT1*, and *NRAS* mutations, *MET* amplification, rearrangements in *ALK*, *RET*, and *ROS1*,and PTEN (MAb 138G4) and MET (MAb SP44) expression by immunohistochemistry. All patients were diagnosed with stage IIIB/IV after May 2012, had a performance status 0-2 and available tumor tissue. **Results:** Of 986 patients registered, data is now reported for 617. An oncogenic driver has been found in 52% (95% CI 49 to 56%). Drivers detected 13 *RET* (2%, 95% CI 1 to 3%) , 17 *ROS* (1%, 95% CI $<$ 1 to 2%), 135 *KRAS* (22%, 95% CI 19 to 25%), 77 *EGFR* (13%, 95% CI 13 to 15%), 20 *ALK* (3%, 95% CI 2 to 5%), 18 *BRAF* (3%, 95% CI 2 to 4%), 4 *PIK3CA* ($<$ 1%, 95% CI $<$ 1to 1%), 9 *HER2 (*2%, 95% CI $<$ 1 to 3%), 12 *MET* amplification (2%, 95% CI 1 to 3%), 3 *NRAS* ($<$ 1%, 95% CI $<$ 1 to 1%), 1 *MAP2K1* ($<$ 1%, 95% CI $<$ 1 to 1%), 0 *AKT1*, 26 had $\geq$ 2 findings (4%, 95% CI 3 to 6%). PTEN loss was detected in15% (95% CI 12 to 17%) and MET expression in 54% (95% CI 50 to 58%). Next-Generation platforms were used at 81% of LCMC 2.0 sites. Results were used to select a targeted therapy or trial in 16%. **Conclusions:** Next-Generation Sequencing is rapidly becoming routine practice at LCMC 2.0 centers with use going from 0 to 81% of sites since 2012. LCMC 2.0 identified additional targets (*RET* and *ROS1* rearrangements and PTEN loss) and detected an actionable oncogenic driver in the majority of initial lung adenocarcinoma specimens. Supported by Free to Breathe Clinical trial information: NCT01014286.

8095 Poster Session (Board #419), Mon, 8:00 AM-11:30 AM

Clinical implementation of anchored multiplex PCR with targeted next-generation sequencing for detection of ALK, ROS1, RET and NTRK1 fusions in non-small cell lung carcinoma. *First Author: Anna F. Farago, Massachusetts General Hospital, Boston, MA*

Background: Chromosomal rearrangements resulting in expression of oncogenic receptor tyrosine kinase fusions occur in a subset of epithelial malignancies and can underlie sensitivity to tyrosine kinase inhibitors. In non-small cell lung cancer (NSCLC), rearrangements involving anaplastic lymphoid kinase (ALK), ROS proto-oncogene 1 (ROS1), and RET proto-oncogene (RET) occur at frequencies of approximately 4%, 1% and 1%, respectively. Rearrangements involving neurotrophic tyrosine kinase receptor type 1 (NTRK1) have been described, though the frequency is not well characterized. **Methods:** We implemented a multiplex polymerase chain reaction (PCR) technology, Anchored Multiplex PCR (AMP), for detection of fusion transcripts using targeted next-generation sequencing of cDNA generated from clinical samples (Zheng et al., 2014). The sequencing library targets known fusion exons in ALK, ROS1, RET and NTRK1. We retrospectively reviewed the NSCLC cases assessed by this method. **Results:** Between July 2013 and January 2015, 663 clinical NSCLC cases from our institution were assessed, providing $>$ 99% power to detect at least one fusion event at an underlying frequency as low as 1%. 584 cases were adenocarcinoma histology. We detected fusions involving ALK, ROS1, RET and NTRK1 at frequencies of 2.6%, 0.9%, 2.0% and 0.0% (17, 6, 13 and 0 cases), respectively. All were mutually exclusive. The histologic subtype was adenocarcinoma in all fusion cases except one. The average age at diagnosis was 57.0, 55.9 and 58.3 years, and average pack years were 8.5, 5.8 and 7.7 for patients with ALK, ROS1 and RET fusions, respectively. The ALK fusion partner in all cases was EML4; ROS1 fusion partners were SDC4, CD74, and EZR; and RET fusion partners were KIF5B, CCDC6, RUFY2 and TRIM24. Although no NTRK1 fusion was detected in NSCLC, we detected a PPL-NTRK1 fusion in a thyroid carcinoma. **Conclusions:** With this method, we identified ALK, ROS1 and RET fusions at frequencies and with patient characteristics consistent with previous studies. NTRK1 fusions appear to be rare in NSCLC, though it is possible that this assay may not detect all fusions.

8096 Poster Session (Board #420), Mon, 8:00 AM-11:30 AM

Feasibility of next-generation sequencing (NGS) for squamous non-small cell lung cancer (NSCLC): Implications for the NCI LungMAP study. *First Author: Adrian G. Sacher, Dana-Farber Cancer Inst, Cambridge, MA*

Background: While potentially targetable genomic alterations have been identified in squamous NSCLC, none have yet been translated into effective therapy. The NCI LungMAP study was designed to match patients (pts) with advanced squamous NSCLC to genotype selected treatment using targeted NGS. We studied a large cohort of consecutive pts with squamous NSCLC to gauge the feasibility of NGS for clinical trial arm allocation. **Methods:** All patients presenting to the Dana-Farber Cancer Institute are offered targeted NGS of existing biopsy samples under an institutional protocol (#11-104). This internally developed NGS assay sequences over 300 genomic targets of interest with a mean overall target coverage of 200x. All squamous NSCLC pts seen at our institution during the study period were identified from an institutional database. The rate of test utilization, assay failure, and detected genomic alterations were studied. **Results:** 174 pts with squamous NSCLC presented to our institution from 7/1/2013-11/18/2014. Of these, 100 consented to targeted NGS. Median age was 65, 89% and 11% were heavy versus light/never smokers, 66% were stage IIIB/IV. The majority of patients underwent core biopsy (52 core, 30 resection, 14 FNA, 3 cytology) Targeted NGS was successful in 74 patients, pending in 12 patients and failed in 13 patients due to insufficient tissue (5 FNA/cytology, 8 core). The mutational rates for each target of the LungMAP study were as follows: PIK3CA mutation 12% (9), CCND1-2 amplification 16% (12), CDK4 amplification 3% (2), FGFR1-4 amplification 24% (18), FGFR1-4 mutation 7% (5) and MET amplification 3% (2). Of these, 12% (9) pts had multiple targets detected. 18% (6/33) of these amplification events were high level (ploidy estimate $>$ 5 copies). **Conclusions:** NGS in a real-world squamous NSCLC cohort is feasible and yields a high rate (51% pts) of potentially targetable genetic alterations. The majority of amplification events are low-level (2-5 copies) which may be challenging to therapeutically target. Our findings support the use of targeted NGS as a tool to facilitate trial enrollment in studies such as the NCI LungMap and Match studies.

8097 Poster Session (Board #422), Mon, 8:00 AM-11:30 AM

***KEAP1*-mutations in patients with non-small cell lung cancer (NSCLC).** *First Author: Rieke Frank, Lung Cancer Group Cologne, Department I of Internal Medicine, University Hospital of Cologne, Center for Integrated Oncology (CIO) Köln Bonn, Cologne, Germany*

Background: Mutations in genes of the KEAP1-NFE2L2 pathway of patients with NSCLC are associated with an increased tumor growth, resistence towards cytostatic drugs and reduced survival rates. KEAP1 suppresses NFE2L2 under physiological conditions. Oxidative stress or electrophiles cause NFE2L2 to stabilize and translocate to the nucleus, resulting in the transcription of various cytoprotective genes. Mutations in *KEAP1* are described for diverse tumor entities with a relatively high frequency causing an increased level of NFE2L2. This leads to resistance of cancer cells against anti-cancer drugs and irradation. This study was performed to characterize *KEAP1*-mutated NSCLC clinically and genetically. **Methods:** Tumor tissue collected from 446 patients within a regional screening network was analysed for *KEAP1* mutations using next-generation sequencing (NGS). Clinical, pathological and genetic characteristics of these patients are described and compared with a control group of patients without *KEAP1* mutation. **Results:** So far, we identified 33 patients with *KEAP1* mutations. Among these we found 34 different mutations, of which the majority was not previously described. *KEAP1* mutations were not restricted to a special exon. In 30 patients (90.9%), additional driver aberrations in *KRAS*, *EGFR, FGFR1*, *FGFR3*, *STK11*, *ALK, DDR2, HRAS, BRAF, PIK3CA, PTEN, NFE2L2, EP300, TSC1, CREBBP, NRAS, MET* and *Her2* could be detected, as well as mutations and polymorphisms in *TP53*. *KEAP1* mutations occurred in both genders (male/female ratio 3/1), in squamous-cell carcinoma (36.4%) and adenocarcinoma (60.6%) and were significantly associated with smoking. The prognostic and predictive impact of *KEAP1* mutations in a prospective cohort will be presented. **Conclusions:** Our data suggest a role of *KEAP1*-mutations as a cofactor in addition to classical driver mutations underlying the malignant phenotype of lung cancer cells. So far, this is the largest cohort of patients with *KEAP1*-mutations analysed and described. Further survival and treatment analyses will reveal the role of these mutations for the outcome of these patients.

8098 Poster Session (Board #423), Mon, 8:00 AM-11:30 AM

Clinical and molecular characteristics of non-small cell lung cancer in patients harboring *CTNNB1* mutations. *First Author: Leonie Gogl, Lung Cancer Group Cologne, Departement I of Internal Medicine, University Hospital of Cologne, Center for Integrated oncology (CIO) Köln Bonn, Cologne, Germany*

Background: Although somatic mutations of *CTNNB1* in lung cancer have been described, there is still lack of information about prevalence, genetic variability, occurrence of additional aberrations and influence on outcome. This study was performed to analyze *CTNNB1*mutations in NSCLC genetically and clinically. **Methods:** Tumor tissue collected from 3885 patients within a regional screening network was analyzed for *CTNNB1* mutations using next generation sequencing (NGS). Clinical, pathological and genetic characteristics of these patients are described and compared with a control group of patients without *CTNNB1* mutation. **Results:** We have identified 58 (1.5%) *CTNNB1*-mutated patients, whereof 51 have been analyzed so far. This cohort consisted of 32 female and 19 male patients. Adenocarcinoma histology was found in 42 patients (82.4%), but CTNNB1 mutations were also found in squamous cell and neuroendocrine carcinomas. 21 different *CTNNB1* mutations were detected on exon 3, of which most are miss-sense mutations (49) besides 2 deletions. The most frequent mutations were S37F and S37C substitutions which each occurred in nine patients. Exclusive *CTNNB1* mutations were only detected in five patients. In all remaining patients an additional driver mutation was found including mutations in *KRAS*, *EGFR*, *BRAF, AKT*, *PIK3CA* and *ERBB2* as well as *MET* amplification, *RET-KIF5b*-Inversion, *ROS1*-fusion and mutations and polymorphisms of *TP53*. **Conclusions:** *CTNNB1* mutations occur alone or in combination with other known oncogenic aberrations in NSCLC. Results of the ongoing clinical characterization of the patients as well as the prognostic and predictive impact of *CTNNB1* mutations will be presented.

8099 Poster Session (Board #424), Mon, 8:00 AM-11:30 AM

Maximum severity score (MSS) of baseline patient-reported Lung Cancer Symptom Scale (LCSS) as a prognostic and predictive factor for overall survival (OS) in the Phase III SQUIRE study. *First Author: Martin Reck, Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), Member of the German Center for Lung Research (DZL), Grosshansdorf, Germany*

Background: SQUIRE, a randomized, phase III study (N = 1093) demonstrated that the addition of necitumumab (N) to gemcitabine-cisplatin (GC) improved OS in patients with stage IV squamous NSCLC. We further analyzed the results by baseline MSS and other cofactors that preliminary models suggested were prognostic for OS in this study. **Methods:** This post-hoc analysis defined the MSS for each patient as the worst (highest) score of any individual LCSS item at baseline. MSS was evaluated as a prognostic and predictive factor for OS and progression-free survival (PFS) using Cox and Kaplan-Meier methods. Cox models included baseline ECOG performance status, sum of target lesions, number of metastatic sites, body mass index, platelets, hemoglobin, and leukocytes. **Results:** As a continuous variable, MSS was prognostic for OS ($p < 0.001$) with a statistically significant interaction ($p = 0.006$) with treatment effect. These results manifested as subgroup differences shown in the table below. Results for PFS and OS were consistent. **Conclusions:** Prognosis for survival worsened with increasing LCSS severity, as shown with the MSS. The addition of N to GC was increasingly effective as severity increased, providing the greatest survival benefit in patients with more severe symptoms or more severely reduced functional ability or quality of life. This observation suggests baseline LCSS can provide information supporting treatment choice. Clinical trial information: NCT00981058.

Subgroup	N+GC N = 545	N+GC N = 545	GC N = 548	GC N = 548	OS treatment effect hazard ratio, p-value (Low hazard ratio favors N+GC)	PFS treatment effect hazard ratio, p-value (Low hazard ratio favors N+GC)
MSS Cutoff value	N	Median OS, mo	N	Median OS, mo		
≥ 15	490	11.6	489	9.5	0.82, 0.005	0.82, 0.006
≥ 30	446	11.4	441	9.1	0.79, 0.002	0.79, 0.002
≥ 45	370	11.1	377	8.3	0.76, 0.001	0.76, 0.001
≥ 60	263	10.7	266	7.3	0.67, < 0.001	0.69, < 0.001
≥ 75	172	10.1	160	6.9	0.70, 0.004	0.71, 0.006
< 15	33	9.3	35	16.4	1.76, 0.045	1.77, 0.037
< 30	77	12.9	83	15.7	1.22, 0.282	1.38, 0.066
< 45	153	13.3	147	15.2	1.14, 0.346	1.17, 0.228
< 60	260	12.6	258	13.0	1.06, 0.547	1.07, 0.493
< 75	351	12.4	364	11.7	0.92, 0.329	0.94, 0.468

8100 Poster Session (Board #425), Mon, 8:00 AM-11:30 AM

Afatinib (A) vs erlotinib (E) as second-line treatment of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following first-line platinum-based chemotherapy: Patient-reported outcome (PRO) data from the LUX-Lung 8 Phase III global trial. *First Author: Shirish M. Gadgeel, Karmanos Cancer Center, Detroit, MI*

Background: A is an irreversible ErbB family blocker that has shown clinical activity in pts with SCC of the head/neck and lung. The LUX-Lung 8 Phase III global trial compared A and E in pts with SCC of the lung following failure of platinum-based chemotherapy. Between Mar 2012 and Jan 2014, 795 stage IIIB/IV SCC pts were randomized 1:1 to receive A (40 mg/day) or E (150 mg/day) until progression. The primary endpoint of PFS, assessed after 414 events, was significantly higher for A than E (median: 2.4 vs 1.9 months; HR [95% CI]: 0.82 [0.68–1.00]; p = 0.04). PRO analyses of the PFS dataset are presented here. Updated PRO analysis of the OS dataset (to be undertaken after 632 deaths) will be available at the meeting. **Methods:** PROs were collected every 28 days until progression using the EORTC QLQ-C30/LC13 questionnaires. Percentage of pts improved on therapy, time-to-deterioration (TTD) and changes over time were analyzed for the pre-specified SCC symptoms: cough, dyspnea, and pain. **Results:** Improvement in global health status (GHS)/QoL was significantly greater with A than E (36.4 vs 27.1% pts; p = 0.026). More pts had an improvement in cough with A vs E (43.6 vs 32.6%; p = 0.010). The proportion of pts with improvements in dyspnea and pain were 49.4 vs 44.8% and 37.5 vs 37.5% with A and E, respectively. There were no significant differences in TTD of symptoms between treatment groups. However, trends favoring A were reported for dyspnea (HR [95% CI]: 0.82 [0.66–1.01]), fatigue (HR [95% CI]: 0.89 [0.73–1.09]), physical (HR [95% CI]: 0.81 [0.64–1.02]), and role (HR [95% CI]: 0.83 [0.67–1.03]) functioning. Changes in mean scores over time significantly favored A vs E for cough (p = 0.007), dyspnea (p = 0.021), and pain (p = 0.024), including chest pain, as well as fatigue (p = 0.006) and role (p = 0.001)/physical (0.024) functioning. **Conclusions:** Compared to E, A improved SCC symptoms, SCC symptoms over time, and overall GHS/QoL. PRO analyses of LUX-Lung 8 complement the significant improvement observed in PFS with second-line A vs E in pts with SCC of the lung. Clinical trial information: NCT01523587.

8101 Poster Session (Board #426), Mon, 8:00 AM-11:30 AM

Impact of crizotinib on patient-reported general health status compared with chemotherapy in patients with no prior systemic treatment for advanced non-squamous *ALK*-positive non-small cell lung cancer (NSCLC). *First Author: Enriqueta Felip, Vall d'Hebron University, Barcelona, Spain*

Background: The present analysis compares patient-reported general health status between crizotinib and chemotherapy in patients who had received no prior systemic treatment for advanced non-squamous *ALK*-positive NSCLC. **Methods:** Patients in the phase III PROFILE 1014 study (Pfizer; NCT01154140) were randomized to crizotinib (250 mg PO BID n = 172) or chemotherapy (pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC 5–6; all IV q3w for ≤ 6 cycles; n = 171). Patient-reported outcomes were assessed at baseline, day 1 of each cycle and end of treatment using EQ-5D, a standardized measure of health status that includes a descriptive system comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression rated at 3 levels (no, some, or extreme problems) and a single index score for health status (range 0 [dead] to 1 [full health]) calculated using a standard algorithm. In addition, a visual analog scale (VAS) measured health status from '0' (worst imaginable) to '100' (best imaginable). Repeated measures mixed-effects analyses were performed to compare overall VAS and index scores between treatments, controlling for baseline. **Results:** The mean (SD) scores at baseline were comparable between crizotinib and chemotherapy for VAS (70.78 [19.65] vs (66.64 [21.89]) and EQ-5D index scores (0.72 [0.30]) vs (0.71 [0.26]).The proportion of patients reporting presence of a problem at baseline for crizotinib and chemotherapy respectively were: mobility (27% vs 34%), self-care (13% vs 13%), usual activities (44% vs 46%), pain (56% vs 68%), and anxiety/depression (41% vs 39%). The overall mean VAS scores on treatment were statistically significantly higher ($p < 0.05$) in the crizotinib arm compared with the chemotherapy arm. The overall mean EQ-5D index scores on treatment were significantly greater ($p < 0.001$) for crizotinib [0.81] compared with chemotherapy [0.72]. **Conclusions:** Treatment with crizotinib leads to significantly greater overall general health status scores compared to chemotherapy in in advanced non-squamous *ALK*-positive NSCLC patients. Clinical trial information: NCT01154140.

TPS8102 Poster Session (Board #427a), Mon, 8:00 AM-11:30 AM

A randomized, phase III study (FLAURA) of AZD9291, a novel EGFR-TKI, versus gefitinib or erlotinib in treatment-naïve patients with advanced non-small cell lung cancer and an EGFR-TKI-sensitizing mutation. *First Author: Suresh S. Ramalingam, The Winship Cancer Institute of Emory University, Atlanta, GA*

Background: EGFR-TKI is the recommended treatment for patients with advanced NSCLC who have an EGFR-TKI-sensitizing mutation (EGFRm). However, most patients develop resistance, and in ~60% of cases the EGFR T790M mutation is the cause. AZD9291 is an oral, potent, irreversible EGFR-TKI selective for EGFRm and T790M mutations. Preliminary data from a Phase I/II study demonstrated clinical activity and a manageable tolerability profile for AZD9291 as first-line treatment of patients with EGFRm advanced NSCLC. **Methods:** This Phase III, double-blind, randomized study (FLAURA, NCT02296125) is designed to assess the efficacy and safety of AZD9291 (80 mg qd, orally) versus standard of care (SoC) EGFR-TKI (gefitinib [250 mg qd, orally] or erlotinib [150 mg qd, orally]) in treatment-naïve patients with locally advanced or metastatic EGFRm NSCLC. Eligible patients must have pathologically confirmed adenocarcinoma harboring an EGFR Ex19del or L858R mutation, alone or in combination with another EGFRm, determined by local (accredited laboratory) or central testing. Patients ≥ 18 years of age (≥ 20 in Japan), WHO performance status 0–1, will be randomized 1:1 to receive either AZD9291 or SoC EGFR-TKI, stratified by mutation status (Ex19del or L858R) and race (Asian versus non-Asian), until RECIST v1.1 defined progression or a discontinuation criterion is met. Patients may continue randomized treatment beyond RECIST defined progression if they continue to show clinical benefit, as judged by the Investigator. The primary objective is to compare progression-free survival (PFS) for AZD9291 to SoC EGFR-TKI. PFS in patients with tumors harboring T790M is a key secondary objective. Additional secondary objectives include PFS by Ex19del or L858R detectable in circulating tumor DNA, objective response rate, duration of response, disease control rate, depth of response, overall survival, PK, health-related quality of life, patient satisfaction with treatment, and the safety and tolerability profile of AZD9291 compared with SoC EGFR-TKI. The study was opened to accrual in November 2014. Clinical trial information: NCT02296125.

TPS8103 Poster Session (Board #427b), Mon, 8:00 AM-11:30 AM

KEYNOTE-024: Phase III trial of pembrolizumab (MK-3475) vs platinum-based chemotherapy as first-line therapy for patients with metastatic non-small cell lung cancer (NSCLC) that expresses programmed cell death ligand 1 (PD-L1). *First Author: Julie R. Brahmer, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: The current standard-of-care first-line therapy for patients with advanced NSCLC who lack *EGFR* sensitizing mutations or an *ALK* translocation is platinum-based combination chemotherapy with or without maintenance therapy. Median OS with platinum-based chemotherapy ranges from 10-12 months. Pembrolizumab, a humanized monoclonal antibody against PD-1, has shown antitumor activity as first-line therapy for NSCLC, particularly in patients whose tumors strongly express PD-L1. **Methods:** In the international, open-label, phase III KEYNOTE-024 trial (NCT02142738), adults with previously untreated, advanced NSCLC without *EGFR* sensitizing mutations or *ALK* translocation that expresses PD-L1 in ≥ 50% of tumor cells are randomized 1:1 to receive a 200-mg fixed dose of pembrolizumab intravenously every 3 weeks or investigator's choice platinum-based combination chemotherapy (carboplatin or cisplatin with pemetrexed or gemcitabine or carboplatin with paclitaxel). Patients with nonsquamous NSCLC may receive pemetrexed maintenance therapy. PD-L1 expression is determined by immunohistochemistry at a central laboratory. Randomization is stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and region (Asia vs rest of world). Pembrolizumab will be given for up to 35 cycles or until disease progression, intolerable toxicity, consent withdrawal, or discontinuation for other reason. Pembrolizumab recipients who experience disease progression after completing 35 cycles or who stop treatment after achieving complete response may be eligible for 1 year of pembrolizumab retreatment. Patients assigned to chemotherapy who experience progression may cross over to receive pembrolizumab. Tumor response is assessed every 9 weeks by RECIST 1.1 per central review. AEs will be monitored throughout the study and graded according to NCI CTCAE v4.0. Primary end point is PFS per RECIST 1.1 by central review. Secondary end points are ORR, OS, and safety. Enrollment is ongoing and will continue until approximately 300 patients are enrolled. Clinical trial information: NCT02142738.

TPS8104 Poster Session (Board #428a), Mon, 8:00 AM-11:30 AM

A phase III study of MEDI4736 (M), an anti-PD-L1 antibody, in monotherapy or in combination with Tremelimumab (T), versus standard of care (SOC) in patients (pts) with advanced non-small cell lung cancer (NSCLC) who have received at least two prior systemic treatment regimens (ARCTIC). *First Author: David Planchard, Gustave Roussy, Villejuif, France*

Background: M is a human IgG1 mAb that blocks programmed cell death ligand-1 (PD-L1) binding to programmed cell death-1 and CD-80 with high affinity and selectivity, and T is a selective human IgG2 mAb inhibitor of cytotoxic T-lymphocyte antigen-4 (CTLA-4). Both PD-L1 and CTLA-4 are regulators, or checkpoints, of T cell activation. Preclinical data, including mouse models of transplantable solid tumors, suggest that targeting both pathways may have additive or synergistic antitumor activity. Furthermore the Phase Ib dose-escalation/expansion study of M+T in advanced NSCLC (NCT02000947) shows a manageable safety, and early signs of clinical activity. **Methods:** This randomised, open label, multi-centre, phase III study (NCT02352948) is designed to evaluate the efficacy and safety of M vs SOC (gemcitabine, vinorelbine or erlotinib) in NSCLC pts with PD-L1-positive tumours (based on archival tumour sample or recent tumour biopsy) (Sub-study A), and the combination of M+T vs M or T vs SOC in NSCLC pts with PD-L1-negative tumours (Sub-study B). Eligible pts include pts (PS of 0-1) with locally advanced or metastatic NSCLC, who have received at least 2 prior treatment regimens including 1 platinum-based chemotherapy. Pts with known EGFR mutations and ALK rearrangements are not eligible. Approximately 300 pts will be randomised 1:1 in sub-study A and 600 pts in sub-study B (randomised 1:1:1:1). The primary objective is to assess the efficacy of M (PD-L1-positive) and M+T (PD-L1-negative) compared with SOC in terms of OS and PFS (per RECIST 1.1 as assessed by the Blinded Independent Central Review). Secondary objectives include objective response rate, duration of response, safety, tolerability, pharmacokinetics, immunogenicity and health-related QoL. Tumour assessments will be performed every 8 weeks (first 48 weeks) then every 12 weeks. A confirmatory scan is required following the initial demonstration of PD. Recruitment in the study is ongoing since January 2015. Clinical trial information: NCT02352948.

TPS8105 Poster Session (Board #428b), Mon, 8:00 AM-11:30 AM

Phase 3 KEYNOTE-042 trial of pembrolizumab (MK-3475) versus platinum doublet chemotherapy in treatment-naive patients (pts) with PD-L1–positive advanced non-small cell lung cancer (NSCLC). *First Author: Tony Mok, Department of Clinical Oncology The Chinese University of Hong Kong, Hong Kong, Hong Kong*

Background: Tumors can evade an immune response by co-opting the PD-1 pathway. The anti–PD-1 monoclonal antibody pembrolizumab has demonstrated promising efficacy and acceptable safety across doses and schedules in pts with NSCLC enrolled in the phase 1 KEYNOTE-001 trial, with greater efficacy observed in pts with PD-L1$^+$ tumors. In 45 treatment-naive, PD-L1$^+$ pts (n = 42 evaluable by RECIST v1.1 per central review), pembrolizumab provided a 26% ORR and 64% DCR. All 11 responses were ongoing after a median follow-up of 36 wk. The randomized, open-label phase 3 KEYNOTE-042 trial (ClinicalTrials.gov, NCT02220894) will evaluate the efficacy and safety of pembrolizumab vs platinum doublet chemotherapy as first-line therapy for PD-L1$^+$ advanced NSCLC. **Methods:** Eligible pts with advanced PD-L1$^+$ NSCLC without *EGFR* sensitizing mutations or *ALK* translocation and ≥1 measurable lesion will be randomized 1:1 to pembrolizumab 200 mg every 3 wk or investigator's choice of carboplatin plus paclitaxel or carboplatin plus pemetrexed. Randomization will be stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), region (East Asia vs non-East Asia), and PD-L1 expression (strong vs weak [staining in ≥50% vs 1-49% of tumor cells assessed by immunohistochemistry with the 22C3 antibody]). Pembrolizumab will be continued for 35 cycles or until disease progression, intolerable toxicity, or investigator decision; discontinuation is allowed for pts with complete response. Chemotherapy will be given for a maximum of 6 cycles. Pemetrexed maintenance is optional for pts with nonsquamous NSCLC. In both treatment arms, eligible pts may be treated beyond initial radiographic progression. AEs will be collected during and for 30 d after treatment. Response will be assessed every 9 wk per RECIST 1.1 by central review. Survival follow-up will occur every 2 mo. Primary end point is OS in pts with PD-L1–strongly-positive tumors; secondary end points include PFS in strongly positive pts and PFS and OS in all pts. Enrollment began in Nov 2014 and will continue in 28 countries in Asia, Canada, Europe, and South America until the target of 1240 pts is achieved. Clinical trial information: NCT02220894.

TPS8106 Poster Session (Board #429a), Mon, 8:00 AM-11:30 AM

A phase 3 randomized trial of veliparib (ABT-888) plus carboplatin and paclitaxel versus investigator's choice of standard chemotherapy in previously untreated patients with metastatic/advanced non-squamous (NSq) non-small cell lung cancer (NSCLC). *First Author: Mark D. McKee, AbbVie Inc., North Chicago, IL*

Background: Standard chemotherapy for patients (pts) with metastatic NSq NSCLC consists of 4−6 cycles of platinum-based doublet therapy +/– subsequent maintenance monotherapy. Clinical outcomes are generally poor, with the majority of pts surviving ~1 year. Veliparib is a potent, orally bioavailable PARP1/2 inhibitor shown to enhance antitumor activity of platinum-based therapy in preclinical models. A recent phase 2 trial suggested that the addition of veliparib to carboplatin (C) and paclitaxel (T) may provide clinical benefit in pts with NSCLC (Ramalingam et al, *Ann Oncol* 2014;25(Suppl 4):1234P). Smoking status was a strong predictor of efficacy for veliparib-chemotherapy combination in advanced NSCLC. This study compares veliparib plus C and T with investigator's choice of chemotherapy in NSq NSCLC. **Methods:** This is a randomized, multicenter, open-label trial (NCT02264990). Current or former smokers (≥ 18 years) who have received no prior chemotherapy for advanced/metastatic NSq NSCLC are randomized 1:1 to veliparib (120 mg p.o. BID on Days −2 through 5 of each 21-day cycle) plus C (AUC 6 mg/mL/min i.v. on Day 1) and T (200 mg/m^2 i.v. on Day 1), or investigator's choice of chemotherapy (C + T, or C + pemetrexed [P], or cisplatin + P). Randomization is stratified by smoking status, investigator's preferred platinum therapy, gender, and ECOG PS. Treatment continues for a maximum of 6 cycles, or until disease progression or unacceptable toxicity. Pts in either arm may receive maintenance P (500 mg/m^2 i.v. q3 weeks). The trial tests if combination treatment with veliparib improves survival in current smokers (primary objective) and in the overall population (secondary objective) compared with investigator's choice of chemotherapy. PFS and objective response rate are also compared between the 2 treatment arms, both in current smokers and the overall population. Duration of overall response, safety, tolerability, ECOG PS, and quality of life are evaluated. Recruitment began in Oct 2014 and 525 pts are planned to be included. Clinical trial information: NCT02264990.

TPS8107 Poster Session (Board #429b), Mon, 8:00 AM-11:30 AM

Veliparib (ABT-888) or placebo combined with carboplatin and paclitaxel in patients with previously untreated advanced/metastatic squamous (Sq) non-small cell lung cancer (NSCLC): A randomized phase 3 trial. *First Author: Mark D. McKee, AbbVie Inc., North Chicago, IL*

Background: NSCLC is often diagnosed at an advanced stage, conferring a poor prognosis. The current standard of care for first-line treatment comprises platinum-based regimens. Veliparib is a potent, orally bioavailable PARP1/2 inhibitor that can delay DNA repair following damage induced by chemotherapeutic agents. In preclinical tumor models, veliparib has been shown to enhance antitumor activity of carboplatin, and phase 1 data show that it can be safely combined with carboplatin and paclitaxel. A phase 2 study indicated favorable efficacy for veliparib plus carboplatin and paclitaxel vs placebo plus carboplatin and paclitaxel in the subgroup of patients with Sq NSCLC (Ramalingam et al. *Ann Oncol* 2014;25(Suppl 4):1234P). Based on these results, this phase 3 pivotal trial has been initiated. **Methods:** This is a randomized, double blind, multicenter, phase 3 trial (NCT02106546). Patients (≥ 18 years) who have received no prior chemotherapy or chemoradiotherapy for advanced/metastatic Sq NSCLC are randomized 1:1 to oral veliparib (120 mg) or placebo, twice daily on Days −2 through 5 (7 consecutive days) of 21-day cycles. Randomization is stratified by tumor extent, smoking history, ECOG performance status, and geographic region. All patients receive carboplatin (AUC 6 mg/mL/min i.v.) and paclitaxel (200 mg/m^2 i.v.) on Day 1 of each 21-day cycle. Treatment continues for a maximum of 6 cycles, or until radiographic progression or unacceptable toxicity. The primary study objective is to determine if the addition of veliparib to carboplatin and paclitaxel improves overall survival, compared with placebo plus carboplatin and paclitaxel. Secondary objectives are to assess progression-free survival and objective response rate. Duration of overall response, safety, tolerability, ECOG performance status, and quality of life are also evaluated. Sites from 37 countries are planned for trial participation. Recruitment began in Apr 2014 and 900 patients are planned for enrollment. Clinical trial information: NCT02106546.

TPS8108 Poster Session (Board #430a), Mon, 8:00 AM-11:30 AM

TIGER 1: A randomized, open-label, phase 2/3 study of rociletinib (CO-1686) or erlotinib as first-line treatment for EGFR-mutant non-small cell lung cancer (NSCLC). *First Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

Background: Activating EGFR mutations including exon 21 L858R and exon 19 deletions (del19) are key drivers of NSCLC in 10%–15% of patients (pts) of European and 30%–35% of Asian descent.[1] Acquired resistance (AR) to first-generation EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib is driven by additional EGFR mutations, with exon 20 T790M accounting for 60%–70% of cases.[2] Rociletinib (CO-1686) was designed to inhibit T790M as well as L858R and del19 while sparing wild-type EGFR and has demonstrated response rates up to 67% and is well tolerated in pts with AR to EGFR-TKIs during dose-finding studies.[3]TIGER 1 will evaluate whether rociletinib can improve progression-free survival (PFS) in the first-line setting. Novel exploratory endpoints include tumor kinetics, treatment post-progression, circulating tumor DNA, and blood-based biomarkers. **Methods**: Pts with histologically or cytologically confirmed metastatic or unresectable locally advanced recurrent NSCLC (no prior EGFR TKI therapy and no CNS disease), with documentation of ≥ 1 activating EGFR mutation (excluding exon 20 insertions) will be enrolled in this phase 2, open-label study (NCT02186301). Pts will be randomized 1:1 to rociletinib (625 mg) twice daily or erlotinib (150 mg) once daily until disease progression according to RECIST 1.1. Pts will be stratified by sensitizing EGFR mutation (T790M, del19, L858R, or other) and race (Asian vs non-Asian). The primary endpoint is PFS; secondary endpoints include efficacy as determined by objective response rate, duration of response, disease control rate and overall survival, and PFS in pts with baseline T790M mutations detected using allele-specific PCR. PFS and OS will be summarized with Kaplan-Meier plots. The stratified log-rank and hazard ratio will compare PFS distributions for rociletinib- vs erlotinib-treated pts. Safety will be assessed via standard adverse event reporting. Planned enrollment is for phase 2 is 200 pts up to 1000 for phase 3. Enrollment is underway with multiple patients in screening. Herbst R et al. *N Engl J Med*. 2008 Yu H et al. *Clin Cancer Res*. 2013 Sequist LV *J Clin Oncol*. 2014 Clinical trial information: NCT02186301.

TPS8109 Poster Session (Board #430b), Mon, 8:00 AM-11:30 AM

TIGER-3: A phase 3, open-label, randomized study of rociletinib vs cytotoxic chemotherapy in patients (pts) with mutant EGFR non-small cell lung cancer (NSCLC) progressing on prior EGFR TKI therapy and doublet chemotherapy. *First Author: James Chih-Hsin Yang, Department of Oncology, National Taiwan University Hospital; Graduate Institute of Oncology & Cancer Research Center, National Taiwan University, Taipei, Taiwan*

Background: Rociletinib is a small molecule inhibitor that selectively targets mutant EGFR and has been shown in preclinical studies to inhibit L858R, del19 and T790M while sparing wild-type EGFR. TIGER-X, a phase 1/2 dose-ranging trial, has provided evidence that rociletinib is associated with durable response and is well tolerated in pts with NSCLC and positive T790M status following progression on a TKI.[1] TIGER-3 is designed to investigate single agent rociletinib vs chemotherapy in pts who have failed EGFR therapy and platinum-based doublet chemotherapy; a setting of acquired resistance and a high unmet need of targeted therapeutic options. TIGER-3 will evaluate pts with T790M positive and negative status based on blood and tumor tissues, and biomarkers of response or resistance. **Methods**: Pts with histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC, with radiological progression on the most recent therapy will be enrolled in a phase 3, randomized, open-label study (NCT02322281). Pts must have documented evidence of a tumor with $\geq$ 1 EGFR activating mutations excluding exon 20 insertion, and prior treatment with an EGFR TKI and platinum-containing doublet chemotherapy. Pts will be randomized 1:1 to receive rociletinib twice daily or single agent cytotoxic chemotherapy (investigator choice specified before randomization) until disease progression according to RECIST 1.1. Pts will be stratified by presence or absence of brain metastases, ECOG performance status (0 vs 1), and race (Asian vs non-Asian). The primary endpoint is progression-free survival (PFS). Secondary endpoints include objective response rate, duration of response, disease control rate, and overall survival. Kaplan-Meier methodology will assess time to event variables. The stratified log-rank and the hazard ratio (HR) will be used for comparing PFS distributions. Serial assessment of safety will be carried out based on standard adverse event reporting. Planned enrolment is 600 pts with study start planned by end of May 2015. Sequist LV *J Clin Oncol*. 2014 Clinical trial information: NCT02322281.

TPS8110 Poster Session (Board #431a), Mon, 8:00 AM-11:30 AM

IFCT-1003 LADIE trial: Randomized phase II trial evaluating treatment with EGFR-TKI versus EGFR-TKI associated with anti-estrogen in women with non-squamous advanced stage NSCLC. *First Author: Julien Mazières, Hôpital Larrey CHU Toulouse, Toulouse, France*

Background: The incidence of lung cancer is increasing dramatically in women and displays some specific epidemiological, radiological, clinical and pathological characteristics. Two main mechanisms emerged from recent findings in the field of lung carcinogenesis in women: the preferential involvement of the EGFR pathway and the potential impact of hormonal factors. The interaction of estrogen receptors with growth factor receptor signalling has also been shown. Preclinical data have shown that the combination of an EGFR-Tyrosine Kinase Inhibitor (TKI) with an anti-estrogen could overcome resistance to EGFR-TKI by postponing the reactivation of the PI3K-AKT pathway through the estrogen-mediated non-genomic pathway. **Methods:** We launched an open-label phase II randomized trial dedicated to women with advanced stage adenocarcinoma. Patients are treated by gefitinib (250 mg/d) vs. gefitinib + fulvestrant 500 mg MI / month (with a supplementary dose at day 15) in the EGFR mutated group (EGFR +) in first or second line setting and by erlotinib (150 mg/d, according to marketing authorization at trial initiation) vs. erlotinib + fulvestrant in the EGFR wild-type group (EGFR WT) in second or third line setting. Treatments are given until progression or unacceptable toxicity. Follow-up is performed in both arms every month to minimize the potential bias due to monthly fulvestrant injection. Primary objective is progression-free survival (PFS) at 3 and 9 months for EGFR WT and EGFR + patients, respectively. Secondary objectives are safety, overall survival and quality of life. Exploratory objective is biomarkers analysis. The main inclusion criteria are histologically-confirmed non-squamous NSCLC, available tumor tissue for EGFR mutation analysis, post-menopausal women, PS 0-2. The study has been approved by all ethical committees. First patients have been enrolled in May 2012. To date, 223 patients (89 EGFR+, 134 EGFR WT) have been enrolled and 394 (204 EGFR +, 190 EGFR WT) are expected. Clinical trial registry number NCT01556191. Clinical trial information: NCT01556191.

TPS8111 Poster Session (Board #431b), Mon, 8:00 AM-11:30 AM

Addition of apatorsen, an inhibitor of Hsp27, to first-line gemcitabine/carboplatin in advanced squamous cell lung cancer: Design of the Cedar study. *First Author: Peter Schmid, Queen Mary, University of London, London, United Kingdom*

Background: Outcomes remain poor in patients with non-small cell lung cancer (NSCLC) of squamous origin. There are few established therapeutic targets, and benefits of chemotherapy are frequently short-lived, with rapid development of treatment resistance. More effective therapies are urgently required. Substantial preclinical data demonstrates that heat shock protein 27 (Hsp27) affects numerous pathways implicated in cancer progression and treatment resistance. Approximately 70-98% of squamous-cell tumours express Hsp27. Apatorsen (OGX-427) is a second generation antisense oligonucleotide that effectively down-regulates Hsp27 in vitro and in vivo; clinical studies are evaluating apatorsen in lung, bladder, prostate, and pancreatic cancers. **Methods:** The phase 2, UK, investigator led, randomized, open-label trial Cedar trial was initiated in July 2014. Eligible patients have confirmed Stage IIIB/IV squamous cell lung cancer and no prior chemotherapy for advanced disease, with ECOG score of 0-2 and adequate bone marrow, renal, and liver function; patients with known EGFR mutation or ALK rearrangements are excluded. Planned enrollment is 140 patients; randomization (1:1) is stratified by stage and performance status. Patients receive 21-day cycles of gemcitabine (1250 mg/m^2) and carboplatin (AUC5) or gemcitabine/carboplatin plus apatorsen (600 mg IV/wk, preceded by 3 doses during a 9-day loading period) for up to 6 cycles. Tumor evaluation occurs q6 wks. Patients randomized to apatorsen may continue weekly single agent maintenance until progressive disease (PD), unacceptable toxicity, or withdrawal of consent. The primary efficacy measure is progression-free survival. Secondary efficacy measures include objective response (OR), change in tumour size at 12 wks, clinical benefit rate, duration of OR/clinical benefit, overall survival, and proportion without PD at 12 and 24 wks. Efficacy analyses are intent-to-treat. Adverse events and laboratory results are assessed, and interim safety analyses are planned. Pre-specified subset analyses will characterize the relevance of Hsp27 expression in tumour and blood samples. Clinical trial information: 16622.

8500 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Phase IIa study of single-agent MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL). *First Author: Wojciech Jurczak, Jagiellonian University, Krakow, Poland*

Background: MOR208 is an Fc-engineered humanized monoclonal antibody that targets the B-cell-specific antigen, CD19. There remains a high unmet medical need for new therapies for patients (pts) with relapsed or refractory (R-R) B-cell NHL. **Methods:** This is a non-randomized, open-label, multicenter, two-stage, phase IIa study of MOR208 in pts with R-R NHL previously treated with rituximab, who were not candidates for high-dose chemotherapy with stem cell support. Adult pts with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), or other indolent NHL (iNHL), were treated with single-agent MOR208, 12 mg/kg intravenously, weekly, over two 28-day cycles. Pts with at least stable disease by the 2007 International Response Criteria were to continue MOR208 treatment for another cycle. Pts with complete or partial response (CR or PR) could then receive maintenance MOR208 every 2 or 4 weeks, depending on investigator decision, until progression. Overall response rate (ORR) was the primary endpoint. **Results:** By 17 November 2014, all pts (n = 89) had been enrolled (DLBCL, n = 35; FL, n = 31; MCL, n = 12; iNHL, n = 11). Thirty-five (39%) pts were female, median age 67 (range 35–90), 78 (88%) had stage III-IV disease, and the median number of prior lines of therapy was 2 (1–4). The mean number of cycles completed was 2.2 (0–3). The investigator-assessed ORR across all NHL subtypes was 22% (20/89) with clinical activity seen in the DLBCL (26% [9/35]; 2 CR, 7 PR; preliminary median duration of response [mDoR] 7.7 months), FL (23% [7/31]; 1 CR, 6 PR; preliminary mDoR 2.6 months) and iNHL (36% [4/11]; 1 CR, 3 PR) cohorts (MCL, 0/12 responses). Grade ≥ 3 non-hematologic and hematologic treatment-emergent adverse events were recorded in 30/89 (34%) and 8/89 (9%) pts, respectively. Infusion-related reactions (8 pts) were all grade 1-2 (except for one case of dyspnea, grade 4). There were no treatment-related deaths. **Conclusions:** MOR208 demonstrated encouraging single-agent efficacy with CRs observed in pts with R-R DLBCL, FL, and iNHL. MOR208 is well tolerated without significant infusional toxicity. Protocols are being developed to investigate MOR208 in combination with other agents. Clinical trial information: NCT01685008.

8501 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Safety and activity of the chemotherapy-free triplet of ublituximab, TGR-1202, and ibrutinib in relapsed B-cell malignancies. *First Author: Nathan Hale Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Multiple novel targeted agents are emerging for B-cell malignancies, but few studies have successfully and safely combined these agents. Ublituximab (UTX) is a novel glycoengineered mAb targeting a unique epitope on the CD20 antigen. TGR-1202 is a next generation, once daily, PI3Kδ inhibitor, active in patients (pts) with rel/ref hematologic malignancies (Burris, 2014). This Ph 1 trial evaluates the safety of the first triplet combination of a novel anti-CD20 + PI3Kδ + BTK inhibitor in pts with B-cell malignancies. **Methods:** Eligible pts had rel/ref CLL (including Richter's) or B-cell NHL with an ECOG PS ≤ 2 w/o limit to number of prior therapies. Pts refractory to prior PI3Kδ or BTK were eligible. CLL & NHL cohorts were evaluated independently in a 3+3 dose escalation design to evaluate safety and dose limiting toxicities (DLT). UTX was dosed at 900mg on D 1, 8, 15 of Cyc 1 & 2 and D 1 on Cyc 4, 6, 9 & 12. TGR-1202 was dose escalated (400mg, 600mg, 800mg, 1200mg). Ibrutinib was dosed at 420mg (CLL) and 560mg (NHL). Preliminary efficacy was examined (CLL per Hallek 2008 / NHL per Cheson 2007). **Results:** As of Feb 2015, 10 pts were evaluable for safety: 4 follicular (FL), 3 CLL/SLL, 1 marginal zone (MZL), 1 mantle cell (MCL) and 1 Richter's DLBCL. Med age 61 yo (range 51-76); 8 M/2 F; median prior Tx = 3 (range 1-4). No DLTs have occurred up to the current dose (600 mg TGR-1202). AEs (all causality) included: diarrhea, constipation and fatigue (30% each, no G 3/4), Day 1 infusion related reactions at 20% (no G 3/4) and neutropenia at 20% with 1 event G 3/4. 7 pts were evaluable for efficacy. ORR was 86% with all pts except the Richter's responding (FL (2), CLL/SLL (2), MZL (1) and MCL (1)). All responses were observed by week 8 (1 CR / 5 PR's). Patients remain on study from 1 – 5+ months. **Conclusions:** To date, this is the first combination of an anti-CD20, a PI3Kδ and a BTK inhibitor. UTX + TGR-1202 + ibrutinb was well tolerated with significant early activity across heavily pre-treated and high-risk B-cell malignancies. Dose escalation continues with TGR-1202 at 800mg. Based upon the early activity of the triplet, Ph II studies are planned. Clinical trial information: NCT02006485.

LBA8502 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma. *First Author: Laurie Helen Sehn, BC Cancer Agency, Vancouver, BC, Canada*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

8503 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Two doses of polatuzumab vedotin (PoV, anti-CD79b antibody-drug conjugate) in patients (pts) with relapsed/refractory (RR) follicular lymphoma (FL): Durable responses at lower dose level. *First Author: Ranjana H. Advani, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Based on early evidence of cumulative toxicity of PoV at a dose of 2.4 mg/kg (Morschhauser ASH 2014 NCT01691898), a dose of 1.8 mg/kg was explored. We report updated results of the dose comparison. **Methods**: Pts with RR FL received PoV at 2.4 mg/kg or 1.8 mg/kg with R at 375mg/m^2 q21d until progression or unacceptable toxicity. 5 pts from PhI (Palanca-Wessels ASH 2013) treated at the 2.4 mg/kg dose were included. Data at completion of PoV treatment were compared with data after 8 cycles. **Results**: 25 pts received PoV+R at 2.4 mg/kg, and 20 at 1.8 mg/kg. Median follow up was 14 mos for 2.4 mg/kg and 8 mos for 1.8 mg/kg. Baseline characteristics were balanced, except for age (median 68 yrs 2.4 mg/kg, 62 yrs 1.8 mg/kg) and tumor volume (SPD 1824 mm^2 2.4 mg/kg, 2655 mm^{2}1.8 mg/kg). 40% (10/25, 2.4 mg/kg) and 50% (10/20, 1.8 mg/kg) of pts were refractory to their last treatment. Pts received a median of 10 cycles of PoV+R at 2.4 mg/kg vs. 9.5 at 1.8 mg/kg. Dose intensity through cycle 8 was 88% for 2.4 mg/kg and 99% for 1.8 mg/kg. Safety is shown in Table. An 84 yr old pt in the 2.4 mg/kg cohort died 2 months after cycle 12 due to pulmonary congestion. ORR was similar for both dose levels: 19/25 (76%) at 2.4 mg/kg, 15/20 (75%) at 1.8 mg/kg. CR: 11/25 (44%) at 2.4 mg/kg, 2/20 (10%) at 1.8 mg/kg. After 8 cycles, CR: 32% at 2.4 mg/kg and 10% at 1.8 mg/kg. Median PFS: 15 mo at 2.4 mg/kg, n.r. at 1.8 mg/kg. **Conclusions**: PoV+R in RR FL showed high ORR at both doses, with higher CR at 2.4 mg/kg. AEs and d/c rates were reduced at both doses if only the first 8 cycles are considered vs. those reported through study completion. The safety of PoV can be improved by shorter treatment and/or lower dose. Updated PFS will be presented. Clinical trial information: NCT01691898.

Safety of PoV+R.

PoV+R	1.8 mg/kg all cycles	2.4 mg/kg all cycles	1.8 mg/kg 8 cycles	2.4 mg/kg 8 cycles
n (%)	20	25	20	25
Any AE G3-4	10 (50)	13 (52)	10 (50)	13 (52)
Neutropenia	7 (35)	4 (16)	7 (35)	4 (16)
Febr neutropenia	2 (10)	1 (4)	2 (10)	1 (4)
SAE	6 (30)	8 (32)	6 (30)	6 (24)
Deaths	-	1 (4)	-	-
AE leading to d/c	6 (30)	14 (56)	5 (25)	7 (28)
G2-4 PN[1]	8 (40)	18 (72)	5 (25)	10 (40)
G3+ infection	1 (5)	3(12)	1 (5)	2 (8)

AE per CTCAE V4.03. AEs G3/4 ≥ 10% reported. [1]MedDRA SMQ peripheral neuropathy.

8504 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Evaluation of complete response rate at 30 months (CR30) as a surrogate for progression-free survival (PFS) in first-line follicular lymphoma (FL) studies: Results from the prospectively specified Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) analysis with individual patient data (IPD) of 3,837 patients (pts). *First Author: Daniel J. Sargent, Mayo Clinic, Rochester, MN*

Background: Although PFS is the standard endpoint for new drug approvals in first-line FL, advances in efficacy (median PFS >7 y) coupled with the indolent nature of FL necessitate extended patient follow-up in clinical trials. The FLASH group conducted a meta-analysis to evaluate whether treatment effects on CR30, an earlier endpoint, could accurately predict treatment effects on PFS. **Methods:** Correlation of CR30 odds ratio (OR) with PFS hazard ratio (HR) was evaluated using both linear regression (R^2_{WLS}) and copula bivariate (R^2_{Copula}) models. Prespecified criteria for CR30 surrogacy required either R^2_{WLS} or $R^2_{Copula} \geq 0.80$ with a lower bound of the 95% confidence interval (CI) > 0.60, with neither estimate $<$ 0.70. The minimum CR30 difference to predict significant PFS difference was calculated. **Results:** Data from 13 randomized first-line trials (8 induction, 5 maintenance trials) with IPD for 3837 pts were included. The prespecified threshold for surrogacy was met: R^2_{WLS} of 0.88 (95% CI, 0.77-0.96) and R^2_{Copula} of 0.86 (95% CI, 0.72-1.00, **Table**), supporting the hypothesis that treatment effects on CR30 predict effects on PFS in pts with previously untreated FL. Multiple sensitivity and IPD surrogacy analyses supported the robustness of the primary analysis. A minimum 10% absolute improvement in CR30 over a control CR30 of 50% predicted significant improvement in PFS. **Conclusions:** This large IPD meta-analysis of chemo/immunotherapy trials establishes CR30 as a surrogate endpoint for PFS in first-line FL trials and supports its use to expedite therapeutic development.

Trial type	Trials, N (pts)	R^2_{WLS} (95% CI)[a]	R^2_{Copula} (95% CI)[a]
Overall	13 (3837)	0.88 (0.77-0.96)	0.86 (0.72-1.00)
Rituximab included	9 (2851)	0.85 (0.62-0.97)	0.80 (0.56-1.00)
No rituximab	4 (986)	0.91 (0.05-1.00)	0.96 (0.90-1.00)
Induction	8 (2207)	0.89 (0.75-0.98)	0.89 (0.74-1.00)
Maintenance	5 (1630)	0.93 (0.84-1.00)	0.89 (0.71-1.00)

[a] R^2 values range from 0 (no association) to 1 (perfect prediction).

8505 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Brentuximab vedotin plus AVD for non-bulky limited stage Hodgkin lymphoma: A phase II trial. *First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: ABVD plus radiation is standard therapy for limited HL, but carries risks of bleomycin-lung injury and radiation toxicity. Brentuximab vedotin is highly active in relapsed HL. We evaluated brentuximab plus AVD (A-AVD) for non-bulky stage I-II HL. **Methods:** This is a multicenter phase 2 study. Patients received a lead in cycle of brentuximab monotherapy 1.2mg/kg on days 1 and 15, followed by a PET scan. Patients then received 4-6 cycles of A-AVD, based on interim PETCT. The primary endpoint is complete response rate (CRR). A sample size of 34 was required to detect a CRR of 93% with 91% power and alpha error of 0.10. **Results:** 34 patients were enrolled. Median age is 36 (20–75). Risk was early favorable in 62%, unfavorable in 38%. The best CRR was 100%. After the monotherapy lead in, 18/34 subjects (53%) were in CR. After 2 cycles of A-AVD, 33 were in CR (97%), and 1 was removed for toxicity. At end of treatment (EOT), 30 (88%) were in CR, 2 were interpreted as progressive disease (PD), and 2 were removed for toxicity. At EOT, 8 subjects had PET scans interpreted as positive on central review, 6 of which were felt to be reactive by investigators. All 6 subjects were in confirmed CR on brief follow-up scan with no intervening therapy, confirming false positive scans. Two cases were considered PD at EOT, 1 of whom received 2 further cycles of AVD alone and was back in CR, suggesting that scan may also have been a false positive. At a median follow-up of 14 months, the PFS and OS are 90% and 97%. The most common adverse events were peripheral neuropathy (74%), fatigue (71%), nausea (24%), neutropenia (68%), anemia (56%), constipation (56%), diarrhea (35%), abdominal pain (32%), ALT elevation (29%) and febrile neutropenia (29%). Grade 3-4 toxicity occurred in 26/34 patients: neutropenia (56%), febrile neutropenia (29%) and peripheral neuropathy (24%). One elderly patient died of neutropenic sepsis in the first A-AVD cycle. One patient was removed for grade 2 hypersensitivity despite premedication. Brentuximab reductions were required in 38%, most for peripheral neuropathy. **Conclusions:** A-AVD x 4 produced a high CRR but with more toxicity than expected from AVD alone. False positive PET scans were common on EOT imaging and warrants further attention. Clinical trial information: NCT01534078.

8506 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Updated results of a phase II trial of brentuximab vedotin combined with R-CHOP in frontline treatment of patients (pts) with high-intermediate/high-risk diffuse large B-cell lymphoma (DLBCL). *First Author: Nancy L. Bartlett, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO*

Background: Pts with high-intermediate/high-risk DLBCL have relatively poor outcomes with R-CHOP. Single-agent brentuximab vedotin has shown activity in pts with relapsed or refractory DLBCL (CD30+ pts, 17% CR; CD30– pts, 10% CR). **Methods:** In this study, pts were randomized to 6 cycles of BV+R-CHOP: 1.2 or 1.8 mg/kg BV q3 wks intravenous with standard R-CHOP. Key inclusion criteria were standard International Prognostic Index (IPI) scores of 3–5 or age-adjusted IPI (aaIPI) scores of 2–3 (high-intermediate/high risk). Disease response was per Cheson 2007 with PET/CT. **Results:** At the planned interim analysis, 53 pts were enrolled and 51 were treated. At baseline, 62% were high-intermediate risk (IPI 3, aaIPI 2) and 38% were high risk (IPI 4-5, aaIPI 3). 70% had stage IV disease and 28% had an Eastern Cooperative Oncology Group score of 2. Due to an increased rate of G3 neuropathy seen early in the 1.8 mg/kg BV+RCHOP arm (30% vs 8%), an SMC recommended treatment continue at 1.2 mg/kg BV+R-CHOP. At EOT, the overall response rate was 97% with 80% PET-negative CR (1.2 mg/kg BV+RCHOP, 86% CR; 1.8 mg/kg BV+R-CHOP, 75% CR) for 30/51 pts with an assessment. CD30+ pts (n=13) had a higher CR rate than CD30– pts (n = 16) (92% vs 69%); 4 CD30– and no CD30+ pts have progressed after a median follow-up of 5 months. CR rates were similar between ABC and GCB subtypes. Treatment-emergent adverse events (AEs) occurred in 96% of treated pts; the most frequent ($\geq$ 30%) were nausea, fatigue, peripheral sensory neuropathy, diarrhea, anemia, decreased appetite, febrile neutropenia, and vomiting. $\geq$ G3 events occurring in > 20% of pts were febrile neutropenia (27%), neutropenia (25%), and anemia (24%). AEs of neuropathy (mostly G1/2) occurred in 55% (38%, 1.2 mg/kg BV+R-CHOP; 77%, 1.8 mg/kg BV+RCHOP). AEs caused discontinuations in 10% of pts; 2 pts died due to AEs (sepsis, hypovolemic shock), and 3 pts died following progression. **Conclusions:** BV+R-CHOP has encouraging activity in frontline high-intermediate/high risk DLBCL; data suggest that the CR rate in CD30+ pts was higher than in CD30– pts. When combined with R-CHOP, BV is better tolerated at 1.2 mg/kg than 1.8 mg/kg due to reduced neuropathy. The protocol has been amended to assess the safety and activity of 1.8 mg/kg BV+R-CHOP in CD30+ high-intermediate/high risk DLBCL pts. Clinical trial information: NCT01925612.

8507 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Allogeneic or autologous transplantation as first-line therapy for younger patients with peripheral T-cell lymphoma: Results of the interim analysis of the AATT trial. *First Author: Norbert Schmitz, Asklepios Hospital St. Georg, Hamburg, Germany*

Background: AlloSCT gives encouraging results in pts with relapsed PTCL. We did the AATT (Autologous or Allogeneic Transplantation in T-Cell Lymphoma) study in newly diagnosed PTCL and present results of an interim analysis leading to termination of the trial. **Methods:** We compared alloSCT with autoSCT in younger pts with PTCL. Pts were randomized after enrolment. Treatment was four courses of CHOEP-14. Pts achieving CR/ PR/ SD proceeded to DHAP and stem cell collection in pts randomized to autoSCT or without suitable (HLA 10/10) donor. BEAM high-dose therapy and autoSCT or myeloablative conditioning and alloSCT followed within 4-6 weeks. **Results:** 58/104 pts were eligible: median age was 50 years, 64% of pts were male. 11/30 pts randomized to autoSCT did not proceed to transplantation because of progressive disease / no response (n=8), infection (n=1) or change of histology (n=2). 13/28 pts (46%) randomized to alloSCT received it. Fifteen pts were not allografted due to progressive disease (n=10) or lack of a fully matched donor (n=5). Twenty-one pts have died 68-705 days after randomization. Twelve pts died of lymphoma (7 in the auto and 5 in the allo arm), 2 pts died from salvage therapy (1 in each arm) and 1 pt from EBV-pos PTLD. Two allografted pts died early (d +21, +65) and 2 late from infections (d+549, +577). Two pts died from acute GvHD (d +24, d +85). One-year event-free survival was 41 % [95%CI 27%-54%], OS was 69% [95CI 57%-82%] on the intent-to-treat-population. **Conclusions:** This pre-planned interim analysis showed no significant survival differences for pts randomized to autoSCT or alloSCT. 38% of randomized pts did not proceed to transplantation mostly because of early lymphoma progression. A conditional power calculation showed a low probability that the primary endpoint (25% EFS improval by allo SCT) could still be met. The data safety monitoring board decided to prematurely stop patient accrual.

8508 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

ELOQUENT-2: A phase III, randomized, open-label study of lenalidomide (Len)/dexamethasone (dex) with/without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *First Author: Sagar Lonial, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA*

Background: Elo, a monoclonal antibody (mAb) targeting Signaling Lymphocytic Activation Molecule F7 (SLAMF7), kills myeloma cells with minimal effect on normal tissue. Elo showed encouraging activity with Len/dex (Ld) in a phase Ib/II study in pts with RRMM. This phase III study (NCT01239797) compared efficacy and safety of Elo/Len/dex (ELd) vs Ld. **Methods:** Pts with RRMM, 1–3 prior therapies (not Len-refractory), were randomized 1:1 to ELd or Ld in 28-day cycles to disease progression/unacceptable toxicity: Elo (10 mg/kg intravenously) weekly cycles 1+2 then biweekly; Len (25 mg) D1–21; dex weekly (40 mg or [Elo wks] 28 mg oral + 8 mg intravenous). Response/progression was assessed by independent review committee by EBMT criteria. Primary endpoints were progression-free survival (PFS) and overall response rate (ORR). Results of an interim analysis are reported. **Results:** Six hundred and forty-six pts were randomized (321 ELd, 325 Ld; median age 66; del(17p) 32%; t[4;14] 9%; refractory to last therapy 35%). Median (range) prior therapies: 2 (1–4), including bortezomib 70%, thalidomide 48%, Len 6%. At data cut-off (4 November 2014), 35% (ELd) and 21% (Ld) of pts remained on therapy; discontinuation was mainly for disease progression (42% ELd, 47% Ld). Median follow-up was 24 months; median (95% CI) PFS: ELd 19.4 (16.6, 22.2) months, Ld 14.9 (12.1, 17.2) months (HR [95% CI] 0.70 [0.57, 0.85]; p = 0.0004). 1-year PFS was 68% ELd, 57% Ld; 2-year PFS: 41% ELd, 27% Ld. PFS benefit with ELd was consistent across key subgroups. ORR (95% CI) was 79% (74, 83) ELd, 66% (60, 71) Ld (p = 0.0002). G3–4 adverse events ≥ 15% (ELd vs Ld) were neutropenia (25%, 33%); anemia (15%, 16%). Exposure-adjusted infection rate was the same in both arms (incidence rate/100 person-years of exposure, 197). Infusion reactions (IRs) occurred in 10% of pts with ELd (mostly G1–2). There were 210 deaths (94 ELd, 116 Ld). **Conclusions:** A clinically relevant 30% reduction in risk of progression or death was seen with ELd vs Ld. More pts remain on ELd vs Ld and follow-up for long-term outcomes, including survival, is ongoing. IRs were manageable. Elo, a mAb with a novel immunotherapeutic mechanism of action, showed improved PFS, with minimal added toxicity in combination with Ld vs Ld alone, in pts with multiple myeloma. Clinical trial information: NCT01239797.

8509 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed multiple myeloma (RMM): Results from the phase III study ENDEAVOR. *First Author: Meletios A. Dimopoulos, National and Kapodistrian University of Athens, Athens, Greece*

Background: ENDEAVOR (NCT01568866) is comparing Kd with Vd in pts with RMM. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), overall response rate (ORR), rate of peripheral neuropathy (PN), and safety. **Methods:** Adults with RMM and 1-3 prior treatments were eligible; planned enrollment was 888 pts. Pts were randomized 1:1 and stratified by prior K or V (yes vs no), prior lines of treatment (1 vs 2-3), ISS stage (1 vs 2-3), and intended route of V (IV vs SC). The Kd arm received K (30-min IV infusion) on days (D) 1, 2, 8, 9, 15, and 16 of a 28-day cycle (20 mg/m^2 on D1 and 2 [cycle 1]; 56 mg/m^2 thereafter) and dexamethasone (dex; 20 mg) on D1, 2, 8, 9, 15, 16, 22, and 23. The Vd arm received V (1.3 mg/m^2; IV or SC on D1, 4, 8, and 11 of a 21-day cycle) and dex (20 mg) on D1, 2, 4, 5, 8, 9, 11, and 12. Cycles were repeated until disease progression or unacceptable toxicity. **Results:** Data are presented for Kd then Vd. In total, 929 pts (Kd: 464; Vd: 465) from 27 countries were randomized. In the Vd arm, 83.6% of pts received SC V. At the preplanned interim analysis, median treatment exposure was 39.9 and 26.8 weeks. Kd showed a significant improvement in median PFS vs Vd (18.7 months [mo] vs 9.4 mo; hazard ratio = 0.53; P< .0001). OS data were immature (75 and 88 deaths) and continue to be followed. ORRs were 76.9% and 62.6% (P< .0001); 54.3% and 28.6% had a very good partial response or better, and 12.5% and 6.2% of pts had a complete response or better. Treatment discontinuation due to an adverse event (AE) occurred in 14.0% and 15.7% of pts. On-study death due to an AE occurred in 3.9% and 3.4% of pts. AEs of interest (grade ≥ 3) included hypertension (preferred term; 8.9% vs 2.6%), dyspnea (high-level term; 5.6% vs 2.2%), cardiac failure (grouped term; 4.8% vs 1.8%), and acute renal failure (grouped term; 4.1% vs 2.6%). Rates of grade ≥ 2 PN (grouped term) were 6.3% vs 32.0% (P< .0001). **Conclusion**: Kd demonstrated statistically significant and clinically meaningful superiority over Vd in RMM, with a two-fold improvement in median PFS. In addition, Kd had a favorable benefit-risk profile. These data suggest that K is a potential best-in-class agent for RMM. Clinical trial information: NCT01568866.

8510 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). *First Author: Todd M. Zimmerman, University of Chicago, Chicago, IL*

Background: In a phase I/II study of combination treatment with CFZ, LEN, and DEX (KRd) without ASCT, KRd provided a high rate of sCR (55%) in NDMM patients (pts) and 3-year progression-free survival and OS rates of 79% and 96% (Jakubowiak et al. Blood 2012;120:1801-9; Jasielec et al. Blood 2013;122: 3220). To further improve response and outcomes, we designed a phase II study to assess activity of extended treatment with KRd and ASCT. **Methods:** Pts received 28-day (d) cycles of CFZ 20/36 mg/m^{2}IV (d1, 2, 8, 9, 15, 16), LEN 25mg PO (d1–21), and DEX 40/20 mg PO wkly (cycles1–4 induction/5–8 consolidation) with ASCT after cycle 4. For cycles 8–18, KRd was given with a modified CFZ schedule (d1, 2, 15, 16) and then LEN alone after cycle 18. Response was assessed by IMWG plus nCR. The primary endpoint is the rate of stringent complete response (sCR) at the end of cycle 8, with statistical hypothesis that the improvement of sCR from 30% (KRd without ASCT) to >50% will represent added benefit of ASCT. **Results:** As of December 31, 2014 the study accrual goal of 53 pts has been met; median age 62 yr (range 40-76), ISS stage II/III 53%, high-risk cytogenetics 27%, as per IMWG. To date, 49 pts completed induction, 41 transplant, 23 consolidation, and 7 have completed 18 cycles of KRd. A median 9.79x10^6/kg CD34+ cells were collected (range 3.89-16.79). Response improved with each phase of treatment (Table). At the end of 8 cycles, 15/17 evaluable pts (88%) were MRD-negative. After a median follow-up of 9.7 months (range 1.6-23), all pts were alive and 52 of 53 progression free. KRd was well tolerated during induction with no new or unexpected events. After ASCT, KRd-related AEs were mostly Grade (G) 1/; the, most common G3/4 AEs were lymphopenia (50%), leukopenia (14%), and neutropenia (21%). **Conclusions:** KRd with ASCT for NDMM resulted in higher sCR rates than KRd without ASCT and high rate of MRD-negative disease, suggestive of benefit of adding ASCT to KRd treatment. The results to date compare favorably to any prior treatment of NDMM. Clinical trial information: NCT01816971.

	Post-Induction	Post-Transplant	Post-Consolidation	Post-KRd
≥ PR %	98	100	100	100
≥ VGPR %	78	97	100	100
≥ nCR %	14	44	91	100
sCR %	10	25	70	86

8511 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Results from two phase III studies of bortezomib (BTZ) consolidation vs observation (OBS) post-transplant in patients (pts) with newly diagnosed multiple myeloma (NDMM). *First Author: Christian Straka, Schön Klinik Starnberger See, Berg, Germany*

Background: Following ASCT, consolidation therapy including novel agents can improve outcomes in pts with MM. Here we report the combined outcomes of two large randomized phase III studies investigating BTZ consolidation or OBS in pts with NDMM. **Methods:** MMY3012 (NCT00416273; 222 pts aged ≤ 60 yrs) and MMY3013 (NCT00416208; 158 pts aged 61–75 yrs) recruited adults with NDMM who underwent induction therapy followed by ASCT. Pts were randomized 1:1 to receive BTZ consolidation (1.6 mg/m² days 1, 8, 15, 22; 4 x 35-day cycles) or OBS, 60–120 days after ASCT. Primary endpoint was progression-free survival (PFS) from start of induction; secondary endpoints included response rate, overall survival (OS), and safety. **Results:** In 371 pts, median age was 59 yrs (35–76); 62% were male, 14%/84% were Durie-Salmon stage II / III. 37% of the 278 pts assessed for cytogenetics were classified as high-risk. 50% of pts had received prior BTZ; the most common induction regimen was VCD (40%). Others included dexamethasone/idarubicin (14%), dexamethasone (13%), and VAD (9%). Outcomes are shown in the table (median follow-up 42 mos). **Conclusions:** A higher proportion of pts had a response of ≥ VGPR after BTZ consolidation than OBS. PFS was significantly improved by ~6 mos, but there was no improvement in OS, likely related to the use of effective salvage options. Subgroups that seemed to benefit from BTZ consolidation were pts with < VGPR and those with high-risk cytogenetics. The BTZ dosing regimen was generally well-tolerated. Clinical trial information: NCT00416208 and NCT00416273.

	BTZ (N = 186)	OBS (N = 185)	HR (95% CI)	P-value
Best response ≥ VGPR before consolidation, n (%)	102 (55)	109 (59)		
Best response ≥ VGPR after consolidation, n/N* (%)	109/177 (62)	86/180 (48)		
Median PFS, mos†	33.6	27.8	0.70 (0.55, 0.90)	0.0058
Pts with < VGPR‡	33.3	24.5	0.58 (0.39, 0.88)	0.0089
Pts with high-risk cytogenetics‡§	30.6	24.2	0.66 (0.41, 1.05)	0.074
Median OS, mos	NR	NR	0.94 (0.64, 1.39)	0.75
TEAE, %	95	94		
Diarrhea	43	8		
Nausea	33	5		
Vomiting	27	3		
Fatigue	24	9		
Discontinuations due to AE, %	15	0		
SAE, %	11	17		
Deaths, %	25	30		

*Response-evaluable pts; †Cox proportional hazards regression model; ‡Univariate Cox regression; §del13q, t(4;14), del17p.

LBA8512 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius). *First Author: Sagar Lonial, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

8513 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

A phase I/II study of the combination of panobinostat (PAN) and carfilzomib (CFZ) in patients (pts) with relapsed or relapsed/refractory multiple myeloma (MM). *First Author: Jesus G. Berdeja, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

Background: Histone deacetylase inhibitors (HDACi) and proteasome inhibitors (PI) act synergistically through inhibition of the proteasome and aggresome pathways. We have previously reported the combination of the HDACi, PAN and the PI, CFZ in pts with relapsed and relapsed/refractory MM with encouraging results (Blood 2013;122:1937). The maximum tolerated dose (MTD) of CFZ and PAN was never reached and we extended our original study to investigate higher dose levels. Here we present the preliminary results of this ongoing trial. **Methods:** Pts with MM who relapsed after ≥ 1 prior treatment were eligible. PAN was administered orally on D 1, 3, 5, 15, 17, 19 of each 28-day cycle. CFZ was administered IV over 30 min on D 1, 2, 8, 9, 15, and 16. The maximum planned dose (MPD) from the original study was 30 mg PAN plus 20/45 mg/m^2 CFZ, so we next escalated to 30 mg PAN plus 20/56 mg/m^2 CFZ. Due to numerous PAN dose reductions in the previous cohorts, we explored PAN at 20 mg and CFZ 20/56 mg/m^2. Treatment continued until PD or intolerable toxicity. The primary efficacy endpoint was the overall response rate (ORR) (≥ PR). AEs were assessed according to CTCAE v 4.0 and responses were assessed using IMWG criteria (plus MRs as per the EBMT criteria). **Results:** As of the data cutoff (12/2014), 26 pts (median age 62 (range 49-91), 39% poor risk FISH) were enrolled. Pts had a median of 3 (range 1-9) prior therapies including 69% with prior PI, 58% with prior IMiDs and 50% with prior stem cell transplants. 27% were refractory to either IMiDs or PIs, and 26% were refractory to their last treatment regimen. There were no DLTs, but based on PAN dose reductions observed in the previous cohorts, the 20 mg PAN plus 20/56 CFZ dose level was expanded and 23 of the 26 enrolled pts were treated at this dose level. 12 (57%) pts remain on active treatment. The most common related ≥ grade (G) 3 hematologic AEs was thrombocytopenia, (31%) and the most common ≥ G3 non hematologic AEs included, fatigue (4%)and diarrhea (4%). The ORR was 82% with 34% ≥ VGPR and 48% PR. The clinical benefit rate was 91%. **Conclusions:** The combination of PAN 20mg and CFZ 20/56 in this schedule is safe and effective in this relapsed/refractory MM population. Clinical trial information: NCT01496118.

8514 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Cardiac and renal biomarker responses in a phase 1/2 study of NEOD001 in patients with AL amyloidosis and persistent organ dysfunction. *First Author: Morie A. Gertz, Mayo Clinic, Rochester, MN*

Background: Light chain (AL) amyloidosis is caused by an accumulation of misfolded proteins that induce the dysfunction of vital organs (e.g., heart and kidneys). NEOD001, a monoclonal antibody that targets these misfolded proteins, is hypothesized to neutralize circulating soluble protein aggregates and to clear insoluble aggregates from organs. We report data from a phase I/II dose-escalation/expansion study of NEOD001 in patients (pts) with AL amyloidosis and persistent organ dysfunction (NCT01707264). **Methods:** Pts who completed ≥ 1 prior anti-plasma cell systemic therapy, had partial response or better, did not require additional chemotherapy, and had persistent organ dysfunction received NEOD001 intravenously every 28 days (q28d). Dose levels of 0.5, 1, 2, 4, 8, 16, and 24 mg/kg were evaluated (3+3 study design). Primary study objectives were to determine safety/tolerability and maximum tolerated dose/recommended phase II dose (RP2D). Secondary and exploratory objectives included pharmacokinetics (PK), immunogenicity, and hematologic and best organ responses based on consensus criteria. **Results:** As of September 30, 2014, 27 pts in seven cohorts received 209 infusions. No deaths, drug-related serious adverse events (AEs), discontinuations due to drug-related AEs, dose-limiting toxicities, or antidrug antibodies were reported. Most frequently reported AEs were fatigue, cough, and dyspnea. 24 mg/kg was selected as RP2D. PK data support intravenous dosing q28d. Of the 14 pts evaluable for cardiac biomarker assessment, 50% met criteria for cardiac response (NT-proBNP: 30% reduction), and 50% achieved disease stabilization. Of the 14 renal-evaluable pts, 43% met criteria for renal response (24-hour urine protein: 50% reduction) and 57% achieved disease stabilization. **Conclusions:** Monthly infusions of NEOD001 were safe and well tolerated. 24 mg/kg was RP2D. Cardiac response rate was 50% and renal response rate was 43%. These organ response rates compare favorably to those reported with traditional chemotherapy. The phase II expansion phase is ongoing. A phase III study has been initiated. Antibody therapy may represent a new therapeutic platform for management of AL amyloidosis. Clinical trial information: NCT01707264.

8515 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Phase I trial of 19-28z chimeric antigen receptor modified T cells (19-28z CAR-T) post-high dose therapy and autologous stem cell transplant (HDT-ASCT) for relapsed and refractory (rel/ref) aggressive B-cell non-Hodgkin lymphoma (B-NHL). *First Author: Craig Steven Sauter, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: HDT-ASCT is the standard of care for patients with rel/ref diffuse large B-cell lymphoma (DLBCL). Herein, we report safety data on the first 8 patients of our phase I clinical trial of 19-28z CAR-T post HDT-ASCT for poor-risk rel/ref aggressive B-NHL (NCT01840566). **Methods:** Eligibility for this study includes rel/ref aggressive B-NHL chemosensitive to salvage therapy with: 1) FDG-PET (+) following 2 cycles of salvage therapy or 2) bone marrow involvement of B-NHL. T cells were retroviral transduced with anti-CD19 scFV linked to CD28 and CD3ζ signaling domains. Patients underwent BEAM conditioned HDT-ASCT and 19-28z CAR-T were administered on days +2 and +3. **Results:** See table for patient characteristics and results. Seven patients were treated at dose level #1 (5 x10^6 19-28z CAR-T/kg) with one dose-limiting toxicity (DLT) of prolonged grade III-IV cytopenias and non-relapse mortality (NRM) of mucormycosis pneumonia. One patient treated at dose-level #2, 1 x10^7 CAR-T/kg, experienced a DLT related to severe cytokine-release syndrome (CRS) and fully recovered. Fifty percent of the patients experienced CRS effectively treated with tocilizumab +/- corticosteroids. All patients engrafted neutrophils post-HDT-ASCT. Five of eight remain alive and progression-free at the time of this analysis. **Conclusions:** This is the first study of 19-28z CAR-T cells following consolidative HDT-ASCT for poor-risk rel/ref aggressive B-NHL. The use of 19-28z CAR T cells is a promising approach in poor-risk PET+ B-NHL patients undergoing HDT-ASCT with manageable CRS. Clinical trial information: NCT01840566.

Patient	Age	Disease	Disease at HDT-ASCT	Dose Level	CRS	Peak CRP (mg/dL)	Status Post-HDT-ASCT
1	34	transformed follicular lymphoma (tFL)	PET(+)PR	1	Yes	27.3	CR/18 mo
2	68	DLBCL	PET(+) PR	1	No	16.5	CR/17 mo
3	56	transformed marginal zone lymphoma	PET(+) PR, bone marrow (BM) involved	1	No	17.6	CR/11 mo
4	59	tFL/double-hit (DHL)	PET(+) PR	2	Yes	43.1	CR/10 mo
5	66	DLBCL	PET(+) PR	1	No	5	CR/11mo
6	64	CD5+ DLBCL	PET(+) PR	1	No	7.9	POD/6 mo
7	65	Burkitt lymphoma	PET(+) PR BM involved	1	Yes	11.8	POD/2 mo
8	56	DLBCL/DHL	PET (+) PR	1	Yes	18.1	NRM/d38

8516 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Phase IIa trial of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas. *First Author: Stephen J. Schuster, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Autologous T cells expressing a chimeric antigen receptor with an external anti-CD19 single chain antibody domain and CD3ζ and 4-1BB signaling domains (CTL019 cells) mediate anti-tumor effects in patients (pts) with relapsed/refractory (r/r) CD19+ leukemias. We are conducting a phase IIa clinical trial of CTL019 cells in r/r CD19+ non-Hodgkin lymphomas. **Methods:** Eligible pts have CD19+ follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), or mantle cell lymphoma (MCL) with anticipated survival less than 2 years. After collection of peripheral blood leukocytes, pts receive lymphodepleting chemotherapy based on histology and past therapies. One to 4 days after chemotherapy, pts receive 5 x 10^8CTL019 cells intravenously. Blood and marrow samples are collected for correlative studies. Response assessment is 3 months (mo) after infusion. Enrollment began February 2014; data reported are through January 2015. **Results:** Twenty-nine pts (19 DLBCL; 8 FL; 2 MCL) have enrolled. Median age is 56 (range: 25-77), male:female ratio 17:12, median prior therapies 4 (range: 1-8), and pts with prior ASCT 9 (31%). At enrollment, stages were: IV, 16 pts (55%); III, 5 pts (17%); II, 6 pts (21%); IE, 2 pts (7%); LDH was increased in 20 pts (69%). Eight pts are not evaluable for response (DLBCL 7; FL 1): 3 pts removed from study before T cell infusion due to progressive disease; 1 pt withdrew consent; 3 pts had inadequate T cell expansion; 1 pt received < protocol-specified cell dose. Twenty pts received CTL019 per protocol dose (12 DLBCL; 7 FL; 1 MCL). Pre-infusion chemotherapy regimens were EPOCH (2); cyclophosphamide (9); radiation + cyclophosphamide (2); bendamustine (6); cyclophosphamide-fludarabine (1). Cytokine release syndrome occurred in 15 pts (13 grade 2; 2 grade 3); neurologic toxicity in 3 pts: transient delirium (1 grade 2, 1 grade 3) and 1 possibly related, grade 5 encephalopathy. For 18 pts evaluable for response at 3 mo (12 DLBCL; 6 FL), overall response rate is 67% (DLBCL 50%; FL 100%). At median follow up 6 mo, progression-free survival for evaluable pts is 59% (DLBCL 37%; FL 100%). **Conclusions:** CTL019 cells induce durable responses in pts with r/r DLBCL and FL with acceptable toxicity. Clinical trial information: NCT02030834.

8517 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Safety and efficacy of anti-CD19 chimeric antigen receptor (CAR)-modified autologous T cells (CTL019) in advanced multiple myeloma. *First Author: Alfred L. Garfall, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: CTL019, a 2nd-generation anti-CD19 CAR transduced via lentiviral vector, can induce regression of refractory B cell malignancies. Though multiple myeloma (MM) is reported to be CD19-negative, we hypothesized that CTL019 would exhibit efficacy in MM due to low-level CD19 expression on MM plasma cells (PC) or CD19 expression in drug-resistant, disease-propagating subsets of the MM clone. Here, we report initial results of an ongoing phase 1 study of CTL019 in patients with advanced MM. **Methods:** MM patients are eligible if they experienced disease progression within one year of a prior autologous stem cell transplantation (ASCT) and are medically fit to undergo second ASCT. Study therapy consists of 1-5x10^7CTL019 cells infused 12-14 days after high-dose melphalan + ASCT. **Results:** 4 subjects have been treated and have completed 30-220 days of follow-up. Median prior lines of therapy is 7.5 (range 3-10). 3/4 have unfavorable cytogenetics; 1/4 had PC leukemia. Adverse events have included hypogammaglobulinemia (4/4) and grade 1 cytokine release syndrome (1/4). 3 subjects are evaluable for response. In all 3 subjects, CTL019 engraftment was achieved (peak 0.1-0.6% of peripheral blood T cells at days 30-42), and B cells were not detectable by flow cytometry in blood or marrow at day 42. At day 100, subject #1 attained MRD-negative stringent complete response (CR), and Subject #2 attained MRD-negative unconfirmed (due to unevaluable bone marrow core) CR. Response duration in Subject #1 has surpassed the response duration after this subject's prior ASCT (i.e., remission inversion). 99.95% of Subject #1's MM PC were CD19-negative by flow cytometry and RTPCR, indicating that efficacy in this subject is not due to direct cytotoxicity of CTL019 against the dominant MM PC population. Subject #3 experienced disease progression at day 43. Updated results on the first 5 subjects will be presented. **Conclusions:** Preliminary data suggest that CTL019 can be manufactured from and safely administered to refractory MM patients. CTL019 can engraft and induce B cell aplasia after salvage ASCT. Ongoing, deep responses in 2 of 3 evaluable subjects are encouraging with respect to potential efficacy. Clinical trial information: NCT02135406.

8518 Poster Discussion Session; Displayed in Poster Session (Board #335), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Combination of everolimus with R-CHOP (ever R-CHOP) as an initial therapy for diffuse large B-cell lymphoma (DLBCL): A phase I and feasibility study (NCCTG N1085 [Alliance]). *First Author: Patrick B. Johnston, Mayo Clinic, Rochester, MN*

Background: Everolimus was demonstrated to have single agent activity in relapsed DLBCL (*Leukemia*. 2011; 25(2):341-7). However, the safety and efficacy of everolimus in combination with R-CHOP is unknown. **Methods:** A phase I study was designed to determine the maximum tolerated dose (MTD) of everolimus on days 1-10 or 1-14 in combination with R-CHOP given every 21 days, with a feasibility cohort to examine response in patients with newly diagnosed CD20+ DLBCL. MTD was defined as the highest safely tolerated dose where at most 1 out of 6 patients experienced DLT. Starting everolimus dose was 10 mg days 1-10 and the planned dose escalation was 10 mg days 1-14. DLT was defined as any grade 3 or higher non-hematologic toxicity or a hematologic toxicity within the first cycle resulting in a delay of the next cycle of chemotherapy. The response was evaluated using PET/CT by standard criteria. A fourteen-patient feasibility extension was planned. **Results:** In the phase I portion, 3 patients received 10 mg everolimus daily for days 1-10 and 6 patients received 10 mg everolimus daily for days 1-14. No DLT was seen and no MTD was achieved; therefore, the dose for everolimus was determined to be 10 mg daily x 14 for the extension phase. 15 additional patients were enrolled in the feasibility portion. For the 24 patients: median age 58.5 years, 58% male, 50% with stage IV disease. The most common grade 3 and 4 adverse events in patients were febrile neutropenia (21%), anemia (17%), thrombocytopenia (21%), and neutropenia (75%). Grade 3 hypertriglyceridemia occurred in 12.5% and grade 3 pneumonitis occurred in one patient. Overall response rate at completion of 6 cycles was 100% in the phase I cohort (8 CR, 1 PR). The patient achieving a PR became PET negative by 12 months without further therapy, thus achieving a CR. Feasibility cohort data will be available for the presentation. **Conclusions:** Everolimus when combined with R-CHOP combination immunochemotherapy is well tolerated at 10 mg daily on days 1-10 and 1-14 of a 21-day cycle. The initial response rates in the phase I portion appear promising. A larger trial will be necessary to confirm the benefits of this novel combination. Clinical trial information: NCT01334502.

8519 Poster Discussion Session; Displayed in Poster Session (Board #336), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Multivariate analysis of PFS from the AETHERA trial: A phase III study of brentuximab vedotin consolidation after autologous stem cell transplant for HL. *First Author: Jan Andrzej Walewski, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland*

Background: In the phase III, randomized, placebo-controlled AETHERA trial, PFS was significantly improved with brentuximab vedotin (BV) vs placebo (HR=0·57, P=0·001) in HL pts at risk of progression post-autologous stem cell transplant (ASCT). A multivariate analysis was performed to determine which factors significantly influence PFS by investigator assessment. **Methods:** After ASCT, 329 pts were randomized to receive BV 1.8 mg/kg q3wk (n=165) or placebo (n=164) for up to 16 cycles. The primary endpoint was PFS per independent review. Multivariate analysis using a Cox-proportional hazards model was developed on the following factors: treatment, age, sex, weight, geographical region, initial disease stage, time from diagnosis, no. of treatments pre-ASCT, chemosensitivity, response to frontline (FL) and salvage, type of FL therapy, prior radiotherapy, extranodal disease pre-ASCT, ASCT conditioning regimen, B symptoms at pre-ASCT relapse, no. of risk factors, baseline ECOG, baseline lesions, and pre-existing peripheral neuropathy. Significant factors ($p<0.05$) were determined after a stepwise addition and elimination of nonsignificant factors from the model. **Results:** Multivariate modeling indicated that factors significantly associated with PFS by investigator assessment included: treatment (BV vs. placebo), salvage response, gender, no. of treatments pre-ASCT, type of FL therapy, B symptoms pre-ASCT, and weight. **Conclusions:** After adjustment for significant clinical factors in a multivariate regression analysis, consolidation treatment with BV significantly reduced the risk of treatment failure compared to placebo with a HR of 0.44. These results support the primary analysis. Clinical trial information: NCT01100502.

Multivariate analyses of PFS by investigator assessment.

Effect	Hazard Ratio (95% CI)	P value
Treatment (BV vs Placebo)	0.44 (0.31, 0.62)	<0.001
Salvage response (CR vs PR/SD)	0.44 (0.30, 0.64)	<0.001
Gender (F vs M)	0.60 (0.43, 0.85)	0.004
No. treatments pre-ASCT (2 vs >2)	0.65 (0.47, 0.90)	0.010
FL therapy (ABVD vs BEACOPP/Other)	0.63 (0.44, 0.91)	0.013
B symptoms pre-ASCT (No vs Yes)	0.64 (0.45, 0.92)	0.015
Baseline weight (≤100 vs >100 kg)	0.58 (0.36, 0.94)	0.026

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8520 Poster Discussion Session; Displayed in Poster Session (Board #337), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Interim analysis of a phase I study of INCB040093, a PI3Kδ inhibitor, alone or in combination with INCB039110, a selective JAK1 inhibitor, in patients (pts) with relapsed or refractory (r/r) B-cell malignancies. *First Author: Tycel Jovelle Phillips, University of Michigan, Ann Arbor, MI*

Background: Inhibiting the PI3K or JAK-STAT pathways may be therapeutic in B-cell malignancies due to their contribution to tumor growth and survival and effects on the tumor microenvironment. Blocking both pathways may be synergistic due to JAK-STAT augmentation of BCR activation of the NFκB pathway. **Methods:** This ongoing dose escalation study with expansion cohorts enrolled adult pts with r/r B-cell malignancies. INCB040093 was given at doses between 100–300 mg QD or BID alone or 150–300 mg QD or BID with INCB039110 at 400–600 mg QD. Safety, efficacy, and pharmacodynamics were evaluated. **Results:** A total of 83 pts have been enrolled: FL n = 19; cHL n = 17; DLBCL n = 15; CLL/SLL n = 13; others n = 19. Median age was 61 years and 70% were men. The median number of prior regimens was 4 and 24% underwent HSCT. Median exposure was 185 days (range: 5 – 491+ [ongoing]) for INCB040093 alone and 99 days (range: 6 – 337+ [ongoing]) for INCB040093 + INCB039110. The most common AEs were fatigue (28%), headache (19%), pyrexia (19%) and the most common grade $\geq$ 3 AE was pneumonia (6%). The most common laboratory abnormalities were liver enzyme elevations and cytopenias. One pt had a DLT on INCB040093 100 mg BID (GI bleed secondary to gastric DLBCL regression). Doses of INCB040093 100 mg BID and INCB040093 100 mg BID + INCB039110 400 mg QD were selected for expansion cohorts based on the incidence of liver enzyme elevations with INCB040093 and cytopenias with INCB040093 + INCB039110 at higher doses. At the selected doses, pAKT was decreased by ~90% at trough on INCB040093 and IL6-induced pSTAT3 was decreased an average of 65% on INCB039110. Of 75 pts thus far evaluated for a response, 28 responses have been reported. Notably, ORR was 60% (3 CRs) for r/r cHL and both pts with the non-GCB subtype of DLBCL had CRs. **Conclusions:** Treatment with INCB040093 $\pm$ INCB039110 was tolerable and produced responses, including CRs, in pts with heavily pretreated r/r B-cell malignancies. Given this activity, the study was expanded to enroll additional cohorts of pts with r/r B-cell malignancies such as DLBCL and cHL, and a phase II study in pts with r/r cHL was initiated. Clinical trial information: NCT01905813.

8521 Poster Discussion Session; Displayed in Poster Session (Board #338), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma: Activity in T-cell lymphoma. *First Author: Neha Mehta-Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Epigenetic manipulation and immunomodulation are therapeutic strategies in hematologic malignancies. Romidepsin (romi), a histone deacetylase inhibitor, and lenalidomide (len), an immunomodulatory agent, both have efficacy and lack cumulative toxicity in relapsed/refractory (rel/ref) lymphoma and myeloma. **Methods:** The phase I part of the study was reported at ASCO 2014. The MTD defined in cycle 1 was romi 14 mg/m^2 IV on days 1, 8, and 15 and len 25 mg oral on days 1-21 of a 28-day cycle. Patients (pts) were treated to progression or intolerance. Disease-specific cohorts in T-cell lymphoma (TCL), B-cell lymphoma and multiple myeloma were enrolled at the MTD. We report the results of the TCL subjects. **Results:** 21 pts with TCL (10 CTCL, 11 PTCL) were enrolled with 15 treated at the MTD. Median age was 64 with 52% male (n = 11).19 pts were evaluable for efficacy with an ORR of 53% (10/19). Two pts were not evaluable for response (one due to toxicity in cycle 1 without progression, one on steroids for idiopathic thrombocytopenic purpura with PET normalization prior to dose 1). The ORR in PTCL was 50% (5/10, 5 PR). Responses were seen in PTCL-NOS (3), AITL (1), T-PLL (1). One with relapsed ATLL remains on therapy with SD ongoing at 24 weeks (w). The ORR in CTCL was 56% (5/9, 2 CR, 3 PR). CR was seen in transformed MF (1), and Sezary syndrome (1). The median time to response was 7.3 w (range: 2.8-16.9 w). Median OS was not reached. Median event free survival was 15.5 w (CTCL 30.0 w, PTCL 13.5 w). However 48% (10/21) pts remain on therapy (2 CR, 6 PR, 2 SD) at a median of 15.3 w (range: 9.0-106.6 w). 7 pts discontinued for progression, 3 for toxicity and 1 for transplant. The median number of cycles was 4 (range: 1-27). 71% of pts had AEs $\geq$ Grade 3, with the most common ($\geq$ 10%) being neutropenia (48%), thrombocytopenia (38%), anemia (33%), electrolyte abnormalities (K, Phos, glucose, Mg) (43%). **Conclusions:** The combination of romi and len appears to have significant activity in rel/ref TCL (ORR 53%) with acceptable safety profile. These results support further evaluation of romi and len in patients with TCL, including additional studies in both CTCL and PTCL. Clinical trial information: NCT01755975.

8522 Poster Discussion Session; Displayed in Poster Session (Board #339), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Prognostic index for chronic and smoldering types adult T-cell leukemia/lymphoma. *First Author: Hiroo Katsuya, Fukuoka University, Fukuoka, Japan*

Background: Adult T-cell leukemia/lymphoma (ATL) has been divided into 4 clinical subtypes: acute, lymphoma, chronic and smoldering. The prognosis in patients with chronic and smoldering type ATL is better than the others, but they have not been treated uniformly because of diverse clinical courses even in the same clinical type. The aim of this study is to develop a novel prognostic index (PI) for chronic and smoldering type ATL. **Methods:** We conducted a nationwide retrospective survey of ATL patients in Japan newly diagnosed between 2000 and 2009. Among chronic and smoldering types, fully eligible 248 individuals were used for this analysis; this is a largest study in chronic and smoldering ATL. We randomly selected subjects equally into training and validation samples, and developed a PI. **Results:** In univariate analysis, gender, performance status, log10[soluble interleukin-2 receptor (sIL-2R)] as well as the number of neutrophil and lymphadenopathy showed P values less than .05 in the training sample. A multivariate analysis was performed in factors above, and log10(sIL-2R) was only identified as an independent prognostic factor in the training sample. Using a regression coefficient of this variable, a prognostic model was formulated to identify different levels of risk: Indolent ATL-PI (iATL-PI) = 1.51 x log10[sIL-2R(U/ml)]. The values calculated by iATL-PI were divided into 3 groups using a quartile point. In the validation sample, median survival times (MSTs) were 1.6, 5.5 years and not reached for patients at high, intermediate, and low risk, respectively ($P<$ .0001). To make the scoring system simpler and clinically practicable, we then simplified the original iATL-PI according to trichotomizing sIL-2R at 1,000 and 6,000 U/mL using a quartile point. Patients of more than 6,000 of sIL-2R were categorized into high risk group, less than and equal to 1,000 into low risk group, and the others into intermediate risk group. MSTs were 1.6, 5.5 years and not reached at high, intermediate, and low risk, respectively ($P<$ .0001). **Conclusions:** The iATL-PI makes it possible to discriminate patients with chronic and smoldering type ATL into three distinct risk groups, and it will be a novel promising tool for risk adopted therapeutic approach.

8523 Poster Discussion Session; Displayed in Poster Session (Board #340), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Updated analysis of CALGB/ECOG/BMT CTN 100104: Lenalidomide (Len) vs. placebo (PBO) maintenance therapy after single autologous stem cell transplant (ASCT) for multiple myeloma (MM). *First Author: Sarah A. Holstein, Roswell Park Cancer Institute, Buffalo, NY*

Background: CALGB 100104 studied Len vs. PBO maintenance following ASCT for newly diagnosed MM patients (pts), demonstrating improved time to progression (TTP), overall survival (OS) and increase in second primary malignancies (SPM) for Len at 34 months (mos) median follow-up. This is an updated intent-to-treat analysis of TTP, OS, and SPM at 65 mos median follow-up for OS. **Methods:** 460 pts age $<$ 70 years with stable disease or better 100 days post ASCT were randomly assigned to Len (n = 231) vs. PBO (n = 229). Starting dose was 10 mg daily and was escalated to 15 mg daily after 3 mos. Primary endpoint was TTP (time of progressive disease (PD) or death from any cause). After several interim analyses, the study was unblinded at 18 mos median follow-up and 86/128 PBO pts without PD chose to cross over to Len. **Results:** SPMs diagnosed after randomization but before PD included 14 hematologic and 11 solid tumor SPMs in the Len arm vs. 3 hematologic and 7 solid tumor SPMs in the PBO arm (Table 1). Estimated median TTP is 53 mos for Len and 27 mos for PBO (hazard ratio (HR):0.54 ($p < 0.001$)). Median OS has not been reached for the Len arm and is 76 mos for PBO (HR: 0.60, $p = 0.001$). Cumulative incidence risk (CIR) of developing a SPM is higher for Len compared with PBO ($p = 0.005$) and the CIR of PD ($p < 0.001$) or death ($p < 0.001$) is higher for PBO. There was no difference in OS after PD between the Len or PBO arms. The TTP and OS benefit with Len was observed regardless of whether pts were in a complete response or not at randomization and for thalidomide vs. Len induction therapy. **Conclusions:** There is an increased incidence of SPMs for Len compared to PBO. Post ASCT Len maintenance continues to demonstrate significantly improved TTP and OS. Clinical trial information: NCT00114101.

	SPM Type	
Treatment Arm	Hematologic (n)	Solid tumor (n)
Len	MDS/AML (10) B-cell ALL (3) Hodgkin lymphoma (1)	Breast (3) Prostate (2) Colon (1) Endometrial (1) Glioblastoma multiforme (1) Melanoma (1) Papillary thyroid (1) Salivary gland carcinoma (1)
PBO		
Cross over to Len	B-cell ALL(2) MDS (1)	Endometrial (1) Melanoma (1) Renal cell (1) Invasive SCC (1)
No cross over		Melanoma (1) Ovarian/endometrial (1) Lung carcinoid (1)

8524 Poster Discussion Session; Displayed in Poster Session (Board #341), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

FIRST study: Updated overall survival (OS) in stem cell transplant (SCT)-ineligible newly diagnosed multiple myeloma (NDMM) patients (pts) treated with continuous lenalidomide plus low-dose dexamethasone (Rd) vs melphalan, prednisone, and thalidomide (MPT). *First Author: Thierry Facon, Service des Maladies du Sang Place de Verdun, Lille, France*

Background: MPT is considered a standard treatment (Tx) option in many countries for SCT-ineligible pts with NDMM. The FIRST trial showed that continuous Rd improved progression-free survival (PFS) and was associated with an OS advantage vs MPT (Benboubker, *NEJM*2014). This abstract presents an updated OS and safety analysis, not initially planned, but requested by regulatory authorities. **Methods:** SCT-ineligible NDMM pts were randomized 1:1:1 to Tx with continuous Rd (28-day cycles), Rd for 18 cycles (Rd18), or MPT for 12 cycles (42-day cycles). The primary endpoint was comparison of PFS (Rd vs MPT) based on IRAC review. Secondary endpoints included OS, overall response rate, and safety. Time from randomization to second progression or death (PFS2) was an additional analysis. **Results:** 1623 pts were randomized; 535 pts received continuous Rd, 541 received Rd18, and 547 received MPT. As of March 3, 2014, 91 pts remained on Tx with Rd. 697 pts (42.9%) have died (38.9% Tx with Rd, 42.1% with Rd18, and 47.7% with MPT). With a median follow-up of 45.5 mos, median OS was 58.9 vs 56.7 vs 48.5 mos for pts treated with continuous Rd, Rd18, and MPT, respectively (for continuous Rd vs MPT, HR = 0.75 [95% CI, 0.62-0.90]). The majority of 2nd-line Tx were bortezomib-based (55.7% of pts who began 2nd line Tx). 58% of pts had a PFS2 event; median PFS2 was extended with continuous Rd vs Rd18, and MPT (42.9, 40.0, and 35 mos, respectively; HR for continuous Rd vs MPT = 0.74 [95% CI, 0.63-0.86]). Average Tx duration for continuous Rd, Rd18, and MPT was 97.8, 54.8 and 51.9 wks, respectively. Discontinuation of lenalidomide vs thalidomide due to AEs was 22.6 vs 27.0%. **Conclusions:** In this updated analysis from the FIRST trial, OS benefit was maintained with continuous Rd and it was better tolerated vs MPT in SCT-ineligible NDMM pts. PFS2 improvements suggest benefit of continuous Rd is retained through 2nd-line therapy and does not induce resistance. Safety profile remained consistent with the interim analysis. These findings reinforce continuous Rd as a new standard of care for the studied population. Clinical trial information: NCT00689936.

8525 Poster Discussion Session; Displayed in Poster Session (Board #342), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Effect of carfilzomib, lenalidomide, and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients with relapsed multiple myeloma (RMM) by line of therapy: Secondary analysis from an interim analysis of the phase III study ASPIRE (NCT01080391). *First Author: Meletios A. Dimopoulos, National and Kapodistrian University of Athens, Athens, Greece*

Background: Previously reported results from ASPIRE (N = 792 patients) showed that KRd significantly improved progression-free survival (PFS) vs Rd in RMM with a favorable benefit-risk profile (Stewart et al. *N Engl J Med*2015;372:142–52). A secondary analysis of efficacy and safety results from patients treated with KRd or Rd after first relapse (1 prior line of therapy) vs ≥ 2 prior lines of therapy are presented. **Methods:** Adults with RMM who received 1–3 prior lines were eligible. Patients were randomized (1:1) to KRd or Rd. All patients received lenalidomide (25 mg) on days 1–21 and dexamethasone (40 mg) on days 1, 8, 15, and 22 of a 28-day cycle. Patients in the KRd arm received carfilzomib as a 10-min infusion on days 1, 2, 8, 9, 15, and 16 during cycles 1–12 (20 mg/m^2 [days 1 and 2 of cycle 1]; 27 mg/m^{2}thereafter). Carfilzomib was omitted on days 8 and 9 during cycles 13–18 and was not administered beyond 18 cycles. **Results:** Median PFS for patients receiving 1 prior line (n = 341) was 29.6 months (95% confidence interval [CI]: 23.2–33.5) for KRd vs 17.6 months (95% CI: 15.0–22.2) for Rd (hazard ratio [HR]: 0.694; *P*= .0083). Median PFS for patients receiving ≥ 2 prior lines (n = 451) was 25.8 months (95% CI: 22.2–31.0) for KRd vs 16.7 months (95% CI: 13.9–22.0) for Rd (HR: 0.688; *P*= .0017). No grade ≥ 3 adverse events (AEs) occurred ≥ 5.0% more frequently with KRd vs Rd in patients who received 1 prior line of therapy; hypokalemia was the only grade ≥ 3 AE that occurred ≥ 5.0% more frequently with KRd (11.0%) vs Rd (3.4%) in patients who received ≥ 2 prior lines. For patients on KRd, neutropenia was the only grade ≥ 3 AE that occurred ≥ 5.0% more frequently after ≥ 2 prior lines (32.4%) vs 1 prior line of therapy (26.4%). **Conclusions:** The use ofKRd after first relapse led to a 1-year improvement in median PFS vs Rd compared with a 9-month improvement in median PFS vs Rd in pts with ≥ 2 prior lines of therapy, with similar HRs. KRd had a favorable benefit–risk profile after 1 and ≥ 2 prior lines of therapy in patients with RMM. Clinical trial information: NCT01080391.

8526 Poster Discussion Session; Displayed in Poster Session (Board #343), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who received prior bortezomib and IMiDs: A predefined subgroup analysis of PANORAMA 1. *First Author: Jesus F. San Miguel, Clinica Universidad de Navarra, Pamplona, Spain*

Background: Panobinostat (PAN) is a potent pan-deacetylase inhibitor (pan-DACi) that targets key biological aberrations in multiple myeloma (MM), including epigenetics and protein metabolism. PAN + bortezomib (BTZ) and dexamethasone (Dex; PAN-BTZ-Dex) led to a clinically relevant and statistically significant increase in progression-free survival (PFS) of ≈4 months compared with placebo + BTZ and Dex (Pbo-BTZ-Dex) in patients (pts) with relapsed or relapsed and refractory MM in the PANORAMA 1 phase 3 clinical trial. **Methods:** The study design was described previously (San-Miguel. *Lancet Oncol.* 2014;15:1195-206). For this subanalysis, pts who received prior BTZ and IMiDs (lenalidomide or thalidomide) were analyzed for outcomes and safety. **Results:** A total of 193 pts (25%) received prior BTZ and IMiDs (PAN-BTZ-Dex [n = 94] or Pbo-BTZ-Dex [n = 99]). Median PFS as determined by investigator assessment for the PAN arm was 10.6 mo (95% CI, 7.6-13.8) vs 5.8 mo (95% CI, 4.4-7.1) for the Pbo arm (HR 0.56 [95% CI, 0.39-0.80]; *P* = .0011). Most (76%) received ≥ 2 prior lines and the difference in median PFS increased in these pts: PAN arm (n = 73): 12.5 mo (95% CI, 7.3-14.0); Pbo arm (n = 74): 4.7 mo (95% CI, 3.7-6.1; HR 0.47 [95% CI, 0.32-0.72]; *P* = .0003). For all pts who received prior BTZ and IMiDs, overall response rate was 58.5% (95% CI, 47.9%-68.6%) vs 41.4% (95% CI, 31.6%-51.8%; *P* = .0179) and ≥ near complete response rate was 22.3% (95% CI, 14.4%-32.1%) vs 9.1% (95% CI, 4.2%-16.6%) in the PAN and Pbo arms, respectively. Common grade 3/4 adverse events and laboratory abnormalities in each arm included thrombocytopenia (68.5% vs 48.0%), lymphopenia (50.0% vs 46.5%), neutropenia (35.9% vs 17.2%), diarrhea (30.4 vs 13.1%), and asthenia/fatigue (25.0% vs 12.1%). The percentage of on-treatment deaths in each arm was similar (6.4% vs 5.1%). **Conclusions:** PAN-BTZ-Dex demonstrated efficacy, with an increased median PFS of 4.8 months among MM pts who received prior BTZ and IMiDs, a population with a clear unmet need. The safety profile is consistent with that in the overall PANORAMA 1 population, although on-treatment deaths were similar. Clinical trial information: NCT01023308.

8527 Poster Discussion Session; Displayed in Poster Session (Board #344), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

Updated results from CHAMPION-1, a phase I/II study investigating weekly carfilzomib with dexamethasone for patients (Pts) with relapsed or refractory multiple myeloma (RRMM). *First Author: James R. Berenson, Institute for Myeloma & Bone Cancer Research, Los Angeles, CA*

Background: Carfilzomib (K) is a selective proteasome inhibitor that is approved for the treatment of relapsed and refractory multiple myeloma in the US. CHAMPION-1 (NCT01677858) is a multicenter, single-arm, phase 1/2 study evaluating the safety and efficacy of weekly K with dexamethasone (dex; Kd) in pts with RRMM. **Methods:** Pts who received 1−3 prior regimens were eligible. In the phase 1 portion, pts received K as a 30-min IV infusion on days 1, 8, and 15 of a 28-day cycle using a 3+3 dose-escalation scheme. Pts received K at 20 mg/m^2 on day 1 of cycle 1; subsequent doses started at 45 mg/m^2 and were escalated to 56, 70, or 88 mg/m^2 until the maximum tolerated dose (MTD) was reached for use in the phase 2 portion. Pts received dex 40 mg (IV or oral) on days 1, 8, 15, and 22 of cycles 1–8; dex was omitted on day 22 in cycles ≥ 9. Kd was administered until disease progression or unacceptable toxicity. **Results:** The MTD was reported previously (70 mg/m^2). As of January 7, 2015, 104 pts were enrolled at the MTD (phase 1, n = 15; phase 2, n = 89). Median pt age was 68.5 y (range, 41–88). Pts received a median of 1 prior regimen (range, 1–3); 82% of pts had received prior bortezomib (BTZ). A total of 48% of pts were BTZ-refractory, 28% were lenalidomide (LEN) refractory, and 16% were refractory to BTZ and LEN. Preliminary median K treatment duration in the ongoing study was 5.3 mo (range, 0.03–18.8). The overall response rate (≥ partial response) was 72% (95% confidence interval [CI]: 63%–81%); the clinical benefit rate (≥ minimal response) was 80% (95% CI: 71%–87%). Median PFS was 10.6 mo (95% CI: 7.2–not estimable). Seven pts (7%) discontinued treatment due to an adverse event (AE). The most common grade ≥ 3 AEs were fatigue (9%), thrombocytopenia (6%), dyspnea (6%), back pain (6%), anemia (5%), and acute renal failure (5%). Four pts died on study: 1 pt had sepsis, respiratory distress, pneumonia, and acute renal failure; and 1 pt each had acute renal failure, cardiopulmonary arrest, and disease progression. **Conclusions:** At the MTD (70 mg/m^2), weekly Kd had acceptable safety and tolerability with promising efficacy in pts with RRMM. Updated results will be presented at the meeting. Clinical trial information: NCT01677858.

8528 Poster Discussion Session; Displayed in Poster Session (Board #345), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM

A phase II study of panobinostat with lenalidomide and weekly dexamethasone in myeloma. *First Author: Ajai Chari, Mount Sinai, New York, NY*

Background: Preclinical data support deacetylation of oncogenic proteins/histones with the pan histone deacetylase inhibitor (HDACi) panobinostat (pan), which renders MM cells more susceptible to other anti-MM agents. Clinically, pan added to btz & dex in the PANORMA 1 phase III study resulted in both improved CR & PFS by 3.9 months. However, grade 3/4 diarrhea also increased from 8 to 25%. Though the MTD of pan-len-dex was attained in a phase 1b study of Rel Ref MM (Mateos et al, ASCO '10), 4 day pulses of dex *3 per cycle was toxic. We modified that regimen; pan 20 mg D1, 3, 5, 15, 17, 19 + len 25 mg qd D1-21 + dex 40 mg D1, 8, 15 in 28 day cycle. **Methods:** Pts with RRMM with PD, measurable disease, & adequate PS/heme/organ function were eligible. Use of QTc prolonging agents & prior HDACIs were prohibited. Evaluation of the ORR was the primary objective & safety, DOR, OS, & PFS were secondary objectives. **Results:** 20 evaluable pts median 64 yo (45% > 65 yo) with 3 median lines of Rx over 4 years were enrolled. 13 (65%) were high molecular risk, 16(75%) were len- refr, & 35, 45, 30% were refr to each: pom, btz, & cfz. Responses include 1 CR, 3 VGPRs, 5 PRs, 8 MRs, & 2 SD, for an ORR of 45%, CBR of 85 % and a median PFS of 7.5 mos. In the 16 len-refr pts, there were 3 VGPRs, 3 PRs, 7 MRs, with a median PFS of 6.5 mos. Grade 3/4 toxicities (regardless of drug attribution) were primarily heme, with neutropenia (55%), thrombocytopenia (40%) and anemia (5%) respectively. Grade 3/4 nonheme AEs included infections in 4 (1 while neutropenic), 3 diarrhea (transient) & 2 PEs and 1 pt each with: neck pain, QTc prolongation, fatigue, & weight loss. Pts requiring dose reductions of len/pan respectively were 4/2 for ANC, 2/1 for plts, & 1 len for fatigue, & 1 pan for asymptomatic T wave inversions. No doses were held or reduced for GI toxicities. **Conclusions:** In RRMM, the completely oral pan len dex demonstrates durable responses, even in high risk len-refr pts, indicating the essential role of pan in attaining responses. In notable contrast to PANORMA 1 there were no significant GI toxicities & primarily expected heme toxicities. Updated results of planned 27 pts, including correlatives, will be presented at the annual meeting. Clinical trial information: NCT01651039.

8529 Poster Session (Board #346), Sun, 8:00 AM-11:30 AM

Idelalisib efficacy and safety in follicular lymphoma patients from a phase 2 study. *First Author: Gilles A. Salles, Hospices Civils de Lyon, Université Claude Bernard, Pierre Bénite, France*

Background: There is an unmet need for new treatment options in FL, particularly for heavily pretreated, high-risk patients refractory to anti-CD20 and chemotherapy. Idelalisib, a PI3Kδ inhibitor, showed antitumor activity and acceptable tolerability as monotherapy in a pivotal phase 2, open-label study in indolent non-Hodgkin lymphoma (iNHL) refractory to rituximab (R) and an alkylating agent (NCT01282424). This post hoc analysis evaluated efficacy and safety in the FL patient subset. **Methods:** Double refractory patients with histologically confirmed iNHL received oral idelalisib 150 mg BID until disease progression (PD) or unacceptable tolerability; patients with FL (grade 1, 2, or 3a; n = 72) were included in this analysis. Responses were evaluated by an independent review committee using standardized criteria. The primary endpoint was the overall response rate (ORR). **Results:** At study entry, patients' median age was 62 y, 54% had a high-risk FLIPI score, 22% had bulky disease, and 17% had FL grade 3a. Median (range) number of prior treatments was 4 (2–12); 86% were refractory to their last therapy (32/50 to bendamustine). At data cutoff, median (range) treatment duration was 6.5 (0.6–31.0) mo, with 65 (90%) patients off treatment (PD, 38; adverse events [AEs], 15; investigator decision, 7; death, 5). Lymph node size decreased during treatment by ≥ 50% SPD in 57%. The ORR (95% CI) was 56% (43–67; $P < 0.001$), including 10 complete responses (CR) and 30 partial responses. Kaplan-Meier (KM)—estimated median (range) time to response was 2.6 (1.6–11.0) mo, median response duration was 11 mo (27 mo in patients with CR), and progression-free survival was 11 mo, substantially longer vs the last regimen. Median overall survival (OS) was not reached; KM-estimated OS at 1, 1.5, and 2 y was 87%, 74%, and 68%.The most common AEs (any/grade ≥ 3, %) were diarrhea (51/14), cough (32/0), pyrexia (29/4), fatigue (28/0), and nausea (28/3). Rates of grade ≥ 3 transaminase elevation, pneumonitis, neutropenia, anemia, and thrombocytopenia were 14%, 4%, 22%, 3%, and 6%. **Conclusions:** Idelalisib demonstrated rapid, durable responses and acceptable safety in highly refractory, relapsed FL patients with limited treatment options. Clinical trial information: NCT01282424.

8530 Poster Session (Board #347), Sun, 8:00 AM-11:30 AM

Lenalidomide and low-dose dexamethasone (Ld) is equivalent to Ld plus autologous stem cell transplant (ASCT) in newly diagnosed multiple myeloma (NDMM): Results of a randomized, phase III trial. *First Author: Suzanne Lentzsch, Columbia University Medical Center, New York, NY*

Background: Upfront ASCT is the current standard of care for transplant-eligible NDMM. However, its use has come into question with the emergence of novel agents such as lenalidomide. This randomized phase III study evaluated the role of upfront ASCT in NDMM, with Ld administered as induction therapy. **Methods:** Patients aged 18–75 years with transplant-eligible, previously untreated, NDMM were randomized to four 28-day cycles of lenalidomide (25 mg days 1–21) plus low-dose dexamethasone (40mg days 1, 8, 15, 22) followed by stem-cell mobilization and: ASCT conditioned with 200 mg/m^{2}melphalan (Arm A; Ld+ASCT); or Ld for 4 additional cycles (Arm B; Ld). Patients subsequently received maintenance lenalidomide (10–15 mg) for ≤ 2 years or until disease progression. Patients with stable disease prior to stem-cell collection, or with progressive disease at any time, went off study. The primary objective was to compare best response in Arm A versus Arm B. Secondary objectives were comparisons of the duration of response, progression-free survival (PFS), and overall survival (OS). **Results:** Sixty patients were randomized between February 2009 and August 2014: 31 into Arm A, and 29 into Arm B. Baseline characteristics were similar in the two arms. The mean age was 62 years (range 48–75), and 43.3% of patients had International Staging System stage 1 disease. In an intention-to-treat analysis, neither the overall response (≥ partial response) rate (83.9% vs. 72.4%; p = 0.28) nor the complete response rate (21.9 vs. 19.3%; p = 0.28) differed significantly between Arm A and Arm B. The median follow-up time for the entire study population was 53.5 months (95% confidence interval [CI]: 49.5–58.3). OS and PFS at 4 years were estimated at 79.0% (95% CI: 56.2–90.8) vs. 86.5% (95% CI: 63.7–95.4) (p = 0.31) and 69.3% (95% CI: 47.6–83.4) vs. 56.8% (95% CI: 34.3–74.2) (p = 0.30) in Arm A vs. Arm B, respectively. **Conclusions:** Ld without upfront ASCT appears to provide similar treatment response, OS, and PFS benefits to Ld plus ASCT in NDMM. Clinical trial information: NCT01731886.

8531 Poster Session (Board #348), Sun, 8:00 AM-11:30 AM

Phase 1 open-label dose escalation study of the dual SYK/JAK inhibitor cerdulatinib (PRT062070) in patients with relapsed/refractory B-cell malignancies: Safety profile and clinical activity. *First Author: Ian Flinn, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: Inhibition of SYK and JAK independently has demonstrated clinical activity in patients with B cell malignancies. We present here an update on the first-in-human study of a dual SYK and JAK inhibitor, cerdulatinib, in patients with relapsed/refractory B cell malignancies. **Methods:** This was a 3+3 dose escalation study with 28-day cycles beginning at 15 mg once daily oral dose. PK, PD, and safety were monitored. Response was assessed by standard criteria. **Results:** No dose-limiting toxicities have been reported to date. As of January 15th, 2015, a total of 25 patients with CLL/SLL or B cell NHL were dosed. Median age was 72 years (23-85) and median prior therapies was 4 (1-6). Treatment emergent AEs of ≥ grade 3 regardless of causality were: grade 3 hyperkalemia (n = 1) and anemia (n = 1) and grade 5 Pneumocystis pneumonia (PCP; n = 1) at 30 mg total daily dose; grade 3 fatigue (n = 1) and AST increase (n = 1) were observed at the 45mg dose. The patient with grade 3 AST had tumor progression to the liver. PK is suitable for once daily dosing with a half-life of 12-16 hours and a 2:1 peak-trough ratio. Saturating inhibition of SYK and JAK in circulating lymphocytes (80-90% inhibition) and serum inflammation markers (e.g., β2M, CRP, CCL4; 50-90% inhibition) occurs at plasma concentrations of ~ 0.6-1μM, achieved at Cmin of the 40mg dose. At 30mg once daily, one partial response was observed in a CLL patient with a 17 p deletion who relapsed on six prior regimens and was intolerant of a PI3K inhibitor. At the 45mg dose, two partial responses were observed at completion of the second cycle of therapy: the first in a follicular lymphoma patient with 3 prior regimens and the second in a CLL patient with 4 prior regimens. Dose escalation continues to identify the maximum tolerated dose. **Conclusions:** Cerdulatinib continues to demonstrate a favorable PK profile and good tolerability at high levels of SYK and JAK inhibition. The clinical responses seen at the 45mg dose level support further development. A phase II expansion study at this dose is planned to begin in the first quarter of 2015. Clinical trial information: NCT01994382.

8532 Poster Session (Board #349), Sun, 8:00 AM-11:30 AM

Idelalisib monotherapy and durable responses in patients with relapsed or refractory Waldenstroms Macroglobulinemia (WM). *First Author: Steven Coutre, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA*

Background: Idelalisib (Zydelig), a selective oral inhibitor of PI3Kδ, demonstrated considerable anti-tumor activity in patients with relapsed/refractory iNHL in phase 1 (p1; Flinn, 2014), and refractory iNHL in phase 2 trials (p2; Gopal, 2014). This analysis evaluates the outcomes in the subset with WM. **Methods:** Eligible WM patients (pts) included those with relapsed/refractory disease (p1), or those with disease refractory to both rituximab and an alkylating agent (p2). Idelalisib dosages were 150 mg QD, and 50 mg-200 mg BID (p1), and 150 mg PO BID (p2) and were administered continuously until disease progression. WM response was assessed by IgM levels and CT-imaging (Owen, 2013). **Results:** Enrolled pts, (p1 N = 9; p2 N=10), had a median age of 63 and 60 years [range 42-83] and 78% and 80% were male, respectively. Patients had received a median of 4 prior regimens in both groups. Overall response rate (ORR) was 5/9 (56%), and 8/10 (80%; Table 1). Median time to minor or first response was 2 months, and most responses continued to improve over 6 months or longer. Median DOR was 32.8 months (p1), and not yet reached (p2). 67% have continued response at 2 years (p2). Median PFS is 33.3 months, and 22.1 months, respectively. Interestingly, > 3 gram/dL improvements in hemoglobin were noted in 5/9 and 7/10 subjects respectively over 3-6 month timeframe. Grade ≥ 3 adverse events included increased ALT/AST 5/9, and 1/10, and diarrhea/colitis 1/9, and 3/10. One G3 ALT elevation and 1 G3 diarrhea resulted in study discontinuation. **Conclusions:** These combined data suggest single agent idelalisib monotherapy is active in Waldenstroms macroglobulinemia. Durable responses were seen in the majority of subjects. Marked improvements in hemoglobin level are also associated with response. The safety profile was acceptable and manageable, with no apparent disease specific safety signals. Phase 3 clinical trials of idelalisib with combination therapy are in progress for iNHL subjects, including WM subjects.Clinical trials: (p1) NCT00710528. (p2) NCT01282424. Clinical trial information: NCT01282424.

	02 (n=9)	09 (n=10)
ORR, n (%) [95% CI]	5 (56%) [21-86]	8 (80%) [44-98]
CR	0	0
PR	1 (11%)	7 (70%)
MR	4 (44%)	1 (10%)
SD	2 (22%)	1 (10%)
PD	1 (11%)	1 (10%)
NE	1 (11%)	0

8533 Poster Session (Board #350), Sun, 8:00 AM-11:30 AM

A phase I study combining bendamustine with rituximab, etoposide and carboplatin (TREC) in patients with aggressive relapsed or refractory lymphoma. *First Author: L. Elizabeth Budde, City of Hope National Medical Center, Duarte, CA*

Background: Traditional multi-agent salvage strategies for lymphoma are less effective after failed modern front line therapies. Bendamustine (Treanda, T) has considerable anti-lymphoma activity and a favorable toxicity profile. We hypothesized that bendamustine could replace ifosfamide within the (R)ICE regimen yielding a feasible and effective salvage strategy (TREC). **Methods:** This multicenter phase I study used a two stage design followed by 2 expansion cohorts for patients with diffuse large B cell lymphoma (DLBCL) and Hodgkin lymphoma (HL). Eligibility included measurable relapsed/refractory lymphoma, ECOG performance status ≤ 2, adequate blood counts and organ function. The primary objective was to define a maximally tolerated dose (MTD) of bendamustine associated with a dose limiting toxicity (DLT) rate of ≤ 25%. Therapy consisted of bendamustine ranging from 60 mg/m2 to 120 mg/m2 daily on days 1 and 2 with standard doses of carboplatin, etoposide, and rituximab (CD20+ disease only) used in the RICE regimen every 21 days for 2 cycles. **Results:** A total of 46 treated patients with median age of 58 years and median of 1 prior therapy, were enrolled with 3 at the dose escalation cohorts and 43 at the recommended phase 2 dose (RP2D). MTD was not reached. Primary refractory disease or early relapse was seen in 13 (65%) patients with HL (n = 20) and 14 (74%) patients with DLBCL (n = 19). All cycles were successfully given in the outpatient setting. Fourteen patients suffered ≥ grade 3 non-hematologic adverse events but without DLTs. The most common ones were febrile neutropenia (n = 4, 9%) and rash (n = 3, 4%). Per Cheson 2007 criteria overall response rates were 67% with 84% (14 CR, 2 PR) in HL, and 63% (8 CR, 4 PR) in DLBCL. Mobilization of peripheral blood stem cells (PBSC) was successful in all attempts immediately following the treatment with a median collection of 5.9 x 10^6CD34/kg. To date, 16 of 22 (77%) CR patients underwent transplant. **Conclusions:** The outpatient administration, manageable toxicity profile, and high response rate in HL and DLBCL of the TREC regimen are encouraging. These data support future evaluation of TREC. Clinical trial information: NCT01165112.

8534 Poster Session (Board #351), Sun, 8:00 AM-11:30 AM

A phase I study of gemcitabine and bendamustine in relapsed/refractory Hodgkin's lymphoma. *First Author: Jonathon Brett Cohen, Emory University - Winship Cancer Institute, Atlanta, GA*

Background: Salvage regimens for Hodgkin lymphoma (HL) can be challenging due to either need for inpatient admission or frequent dosing. Based on previously reported single agent activity of bendamustine (benda) and gemcitabine (gem), we conducted a phase I study of benda and gem in patients (pts) with relapsed/refractory classical HL who failed at least 1 prior therapy to determine the maximum tolerated dose. **Methods:** Utilizing a cohorts of 3 design, pts received gem dosed at 1000mg/m^2 on day 1 and benda doses of 60mg/m^2 to 120mg/m^2on days 1 and 2 of each cycle for up to 6 cycles, with cycle lengths of 28 (dose levels [DL] 1-3) and 21 (DL 4-5) days. Dose limiting toxicity (DLT) was determined during cycle 1. **Results:** Fourteen pts (8 males) with a median age of 38.5 years (range: 23-60) and a median of 4 (range: 1-7) prior lines of therapy have completed a median of 4 cycles at DL 1 (n = 3), 2 (n = 3), 3 (n = 3), 4 (n = 4), and 5 (n = 1). Seven pts had a prior autologous transplant (ASCT), and 1 pt had a prior ASCT and allogeneic transplant. One pt only received day 1 of therapy in cycle 1 at DL 4 and was thus not considered in dose escalation determination. The benda dose was 60mg/m^2 for 3 pts, 90mg/m^2 for 6 pts, and 120mg/m^2 for 4 pts. No DLTs have been observed. Four pts have required hospitalization, including 2 heavily pretreated pts with pulmonary symptoms after cycle 2. One underwent a biopsy that was consistent with a drug-induced pneumonitis likely gem-related, while the other had grade 5 respiratory failure that was deemed secondary to infection although a relationship with gem could not be ruled out. Additional grade 3-4 toxicities include: lymphopenia (n = 10) thrombocytopenia (n = 2), atrial fibrillation (n = 1), fever (n = 1), renal failure (n = 1), hypotension (n = 1), pneumonia (n = 1), hypoalbuminemia (n = 1), hypokalemia (n = 1), and rash (n = 1). In 13 evaluable pts, the response rate was 77% (CR, n = 3; PR, n = 7; SD, n = 2; PD, n = 1). Two pts have had an ASCT with collection of 5.1 x 10^6 CD34+ cells over 2 days and 4.94 x 10^6CD34+ cells over 3 days. **Conclusions:** The combination of benda 120mg/m^2 with gem 1000mg/m^2 is tolerable and appears efficacious. We continue to monitor closely for additional pulmonary toxicity as we complete accrual to our final dose level using a 21-day cycle. Clinical trial information: NCT01535924.

8535 Poster Session (Board #352), Sun, 8:00 AM-11:30 AM

Interim results from a dose-escalation study of the BCL-2 inhibitor venetoclax (ABT-199/GDC-0199) plus bendamustine (B) and rituximab (R) in patients (pts) with relapsed/refractory (R/R) Non-Hodgkin's Lymphoma (NHL). *First Author: Sven De Vos, Department of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Venetoclax (VEN) is a selective, potent, orally bioavailable BCL-2 inhibitor that has shown single agent activity in R/R NHL. The current study evaluates VEN with BR, an active regimen widely used for NHL. **Methods:** Objectives were safety, PK, preliminary efficacy, MTD, and recommended Phase 2 dose. Dose escalation (DE) used a 3+3 design on a 28 day (d) cycle (C) with 3 VEN (50–400 mg) schedules: 3, 7, and 28 d/C. The BR regimen was 6 C: B (2 d/C, 90mg/m^2) and R (1 d/C, 375mg/m^2). DLTs for DE were assessed during C1. Responses were first assessed on C3 d1. Pts who completed VEN + BR with continued tolerability and without disease progression could continue VEN monotherapy up to 2 yrs. **Results:** As of 1/9/15, 33 were treated: 20 (61%) FL, 10 (30%) DLBCL, and 3 (9%) MZL. Median age was 62 (29-90) yrs. All had prior R or R-combination, of which 32 (97%) had R-based chemotherapy and 8 (24%) had prior B or BR. 16 (48%) pts are active; 17 discontinued (12 PD, 2 AE, 1 each withdrew consent, non-compliance, pt decision). Median time on study was 90 d (1–876); 15 (45%) completed 6 C of the combination. The most common AEs (in >25%) were nausea (58%), anemia, neutropenia (each 42%), thrombocytopenia, diarrhea (each 39%), hyperglycemia (36%), and vomiting, hypokalemia, fatigue (each 27%). The most common gr 3/4 AEs (in >10%) were neutropenia (30%), leukopenia, thrombocytopenia, lymphopenia (each 21%), and anemia (18%). The most frequent SAE was febrile neutropenia (9%). There were no drug-related AEs that led to death. Co-administration of BR did not significantly impact VEN PK. 29 pts had ≥1 assessment: 6 (21%) CR and 13 (45%) PR. The ORR was 66% in all pts and 74% in pts with FL. **Conclusions:** Preliminary data demonstrate a tolerable safety profile of VEN + BR. Early responses were seen across all cohorts. Cohort 9 is enrolling at 600 mg 28 d/C. Clinical trial information: NCT01594229.

Cohort	1	2	3	4	5	6	7[a]	8[a]
Pts, n	4	4	4	3	3	4	5	6
VEN, mg	50	100	100	100	200	200	400	400
Schedule, d/C	3	3	7	28	28	7	7	28
DLTs, n								
Thrombocytopenia					1			
Febrile neutropenia					1			
Stevens-Johnson Syndrome[b]								1

[a]Post-amendment to G-CSF prophylaxis and DLT criteria; [b]Primary reasonable possibility due to allopurinol; pt discontinued.

8536 Poster Session (Board #353), Sun, 8:00 AM-11:30 AM

Development of the molecular diagnostic (MDx) DLBCL Lymphoma Subtyping Test (LST) on the nCounter Analysis System. *First Author: Brett Wallden, NanoString Technologies, Inc., Seattle, WA*

Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin's lymphoma with two distinct molecular cell-of-origin (COO) subtypes known as germinal center B-cell (GCB) or activated B-cell (ABC). DLBCL subtypes have been reported to be prognostic and potentially predictive of treatment benefit, underscoring the need for a precise and accurate MDx test. NanoString's LST is based on the Lymph2Cx gene expression profile (GEP). These studies describe the development of the LST and analytical robustness and clinical accuracy of the Linear Predictor Score (LPS) and DLBCL subtypes (ABC and GCB). **Methods:** 51 banked formalin fixed, paraffin embedded (FFPE) DLBCL specimens were used to recalibrate the algorithm using a clinical grade assay. The subtype accuracy of the final locked algorithm was verified by testing 68 independent specimens with gold standard (GS) GEP results. Analytical precision was measured across 2 operators and 3 reagent lots by testing 10 FFPE DLBCL RNA samples. Reproducibility was measured across 2 operators and pathologists by testing replicate tissue sections from 64 FFPE DLBCL blocks following independent pathology review of H&E slides. Following guided macrodissection of pathologist identified tumor tissue, isolated RNA was tested on the NanoString nCounter system. The assay was evaluated across the assay RNA input range (62.5-1000 ng) and with the inclusion of adjacent non-tumor tissue. **Results:** The estimated misclassification rate compared to the GS result was 5.9% (95% CI: 4.6%-7.1%). The total standard deviation in LPS was $<$ 2% of the score range, including all sources of assay variation, with no significant differences between operators or reagent lots. Average LST subtype concordance with independent pathology review was $>$ 95% with no GCB to ABC misclassifications (or vice versa). The assay was robust across the specified range and against the inclusion of tissue interferents. **Conclusions:** The NanoString LST is a highly precise and accurate method for determining the COO from FFPE DLBCL tissue. The assay is well suited to clinical applications and is being used to select ABC patients for a Phase III study investigating lenalidomide (REVLIMID) in DLBCL.

8537 Poster Session (Board #354), Sun, 8:00 AM-11:30 AM

Phase 1 first-in-human trial of oral CUDC-907, a dual inhibitor of PI3K and HDAC, in patients with refractory/relapsed lymphoma or multiple myeloma. *First Author: Jesus G. Berdeja, Sarah Cannon Research Institute, Nashville, TN*

Background: CUDC-907 is an oral inhibitor of class I PI3K as well as class I and II HDAC enzymes. Anti-tumor effects of CUDC-907 have been demonstrated in B-cell lymphoma and multiple myeloma xenografts via inhibition of PI3K, MAPK, and STAT pathways. **Methods:** In a 3+3 dose escalation and expansion trial, CUDC-907 was administered on 3 dosing schedules: once daily (QD), intermittent (ie, twice [BIW] or thrice [TIW] weekly), or five days on/two days off (5/2) in 21 day cycles. Re-staging was performed every 2 cycles. **Results:** 45 subjects received CUDC-907 at doses up to 60 mg on the QD or 5/2 schedules, and up to 150 mg on the BIW or TIW schedules. Dose limiting toxicities occurred in 3 subjects: 1 at 60 mg QD (hyperglycemia and diarrhea); 1 at 150 mg BIW (hyperglycemia); and 1 at 150 mg TIW (diarrhea). No DLT occurred on the 5/2 schedule. The most common treatment-related adverse events (AEs) included diarrhea (44%), fatigue (29%), nausea (16%) and thrombocytopenia (11%). 38 subjects are evaluable for response. 4/8 subjects with DLBCL or t-FL/DLBCL (median of 4 prior therapies) achieved objective responses including 1 CR (DLBCL) and 3 PRs (1 with DLBCL; 2 with t-FL/DLBCL); with 3/8 achieving stable disease (SD). SD lasting a median of 101 days (40 – 717) has been observed in 21/38 (55%) subjects including: HL (8/10) and MM (3/4). PK plasma levels have revealed a dose-dependent increase in CUDC-907 exposure on the BIW and TIW schedules. Accumulation of active metabolite was only observed on the QD schedule. **Conclusions:** The safety profile of CUDC-907 for gastrointestinal, hematologic, and hyperglycemic AEs was predictable based on experience with other HDAC and PI3K inhibitors. AEs have been reversible and managed with standard interventions or dose interruption, and fatigue and thrombocytopenia have not been dose limiting. CUDC-907 has achieved objective responses and long-term SD across multiple tumor types and dosing schedules, with objective response achieved in a heavily pretreated DLBCL patient population. Though MTD was not reached in the intermittent or 5/2 schedules, expansion is being studied at 120 mg TIW and 60 mg 5/2 dose levels based upon their efficacy and toxicity profiles. Clinical trial information: NCT01742988.

8538 Poster Session (Board #355), Sun, 8:00 AM-11:30 AM

Phase II study of Hyper-CVAD with pegylated liposomal doxorubicin alternating with methotrexate and cytarabine (HCVIDD/MA) in patients with newly diagnosed T- and NK-cell lymphoma (T/NKCL). *First Author: Dai Chihara, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Prognosis of T/NKCL is poor after standard CHOP therapy. To prospectively evaluate the role of dose intensified chemotherapy, we conducted a phase II trial of HCVIDD/MA in patients with newly diagnosed T/NKCL. **Methods:** Eligible patients were adults with newly diagnosed untreated T/NKCL excluding ALK positive ALCL. Patients received HCVIDD/MA every 21 days for up to eight cycles. In this trial, pegylated liposomal doxorubicin at 25mg/m^{2}was used instead of conventional doxorubicin. **Results:** Fifty-three patients were enrolled (PTCL-NOS: 24, AITL: 7, Systemic ALK negative ALCL: 7, HSTL: 7, extranodal NKCL: 5, Others: 3). The median age of patients was 54 (range 20-72). Eighty-five percent of the patients were in advanced stage, 32% had bone marrow involvement and 43% had IPI score $>$ 2. The median cycle number of treatment given was five. Only 5 of 53 patients (9%) received seven or more cycles primarily due to prolonged cytopenias. Of 47 patients who were eligible for response evaluation, the overall response rate was 66% with complete response rate of 57%. Six patients (11%) underwent consolidative autologous stem cell transplant at treating physician's discretion. Median progression free survival (PFS) of all patients was 8.1 months. With the median follow-up time of 83 months, five-year PFS and overall survival (OS) rates were 22% and 49%, respectively. The patients with extranodal NKCL had shorter PFS (all 5 progressed $<$ 13 months) than other types. Patients with HSTL had slightly longer PFS (median 49 months) than other types. There was no significant difference in PFS or OS by treatment cycles beyond five and by consolidative ASCT. Grade3/4 anemia, neutropenia and thrombocytopenia were observed in 66%, 74% and 79%, respectively. Of note, 11 patients (21%) were taken off study due to thrombocytopenia with median of 5 cycles. **Conclusions:** HCVIDD/MA for the first line treatment of T/NKCL showed response rate and survival outcome similar to previously reported those with conventional CHOP, and was associated with higher hematologic toxicities. (clinicaltrials.gov identifier: NCT00290433) Clinical trial information: NCT00290433.

8539 Poster Session (Board #356), Sun, 8:00 AM-11:30 AM

Pre-treatment circulating tumor DNA as a biomarker for disease burden in diffuse large B cell lymphoma (DLBCL). *First Author: Florian Scherer, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Patients with DLBCL reveal striking heterogeneity in clinical outcomes. Plasma cell-free DNA (cfDNA) levels have been shown to be adversely prognostic. Both circulating tumor DNA (ctDNA) as a minor fraction of cfDNA and circulating tumor cells (CTCs) can be used for DLBCL monitoring with ctDNA reported to be superior (Kurtz et al 2014 ASCO). However, the relationship between ctDNA and CTC levels with DLBCL clinical indices remains poorly defined. **Methods:** We profiled 43 DLBCL patients treated with R-CHOP based therapy and quantified their pre-treatment cfDNA, ctDNA and CTC levels. Pre-treatment ctDNA levels were determined by high-throughput sequencing of tumor specific immunoglobulin genes (Ig-HTS) of plasma cfDNA, and CTCs were enumerated by Ig-HTS of blood leukocytes. Metabolic tumor volume (MTV) was measured from pre-treatment ^{18}FDG PET/CT scans using MetaVol. Parametric vs. non-parametric tests supported identical conclusions. **Results:** Blood cfDNA levels varied widely (2.8-1,713.5 ng/mL, median: 12.6), as did ctDNA levels (0-129,928 molecules/mL, median 87.5) and CTCs (0-454,400 CTCs/million cells, median 6.6). Total cfDNA levels and the amount of ctDNA were strongly associated ($r = 0.73$, $P < 0.0001$). Both cfDNA and ctDNA levels were significantly correlated with LDH ($r = 0.79$ and 0.74, $P < 0.0001$) and MTV ($r = 0.62$ and 0.53, $P < 0.0001$ and $P = 0.002$). CtDNA was detectable in 14 of 19 patients (74%) with normal LDH levels. Higher cfDNA and ctDNA levels were associated with adverse prognostic parameters including advanced stage ($P < 0.0001$ and $P = 0.04$), IPI 3-5 ($P < 0.0001$ and $P = 0.04$), marrow involvement ($P = 0.04$ and $P = 0.009$) and presence of B-symptoms ($P = 0.0003$ and $P = 0.0001$). CTCs levels were not associated with any of these prognostic parameters, despite showing a correlation with LDH ($r = 0.43$, $P = 0.02$). **Conclusions:** Our study demonstrates that, in contrast to CTCs, ctDNA levels better capture disease burden in DLBCL, including tumor volume and metabolic properties. The prognostic value of cfDNA levels appears directly related to ctDNA levels, and not to CTCs. Therefore, ctDNA is a specific biomarker of tumor burden in DLBCL and, compared to cfDNA, less prone to physiological perturbations.

8540 Poster Session (Board #357), Sun, 8:00 AM-11:30 AM

Bendamustine and rituximab and lenalidomide (BRR) in the treatment of relapsed and refractory low grade non-Hodgkin lymphoma (NHL): Final results of phase 1 study NCCTG N1088/ALLIANCE. *First Author: Grzegorz S. Nowakowski, Mayo Clinic, Rochester, MN*

Background: The combination of bendamustine and rituximab is effective in the treatment of low grade NHL. Lenalidomide shows significant synergy when combined with rituximab and rituximab-containing chemotherapy. The primary aim of this phase 1 study was to establish a maximum tolerated dose (MTD) of bendamustine, rituximab and lenalidomide. Secondary endpoints included toxicity, overall response and progression-free survival. **Methods:** Eligible patients (pts) had relapsed or refractory low grade NHL, treated with at least 1 prior regimen. A 3+3 phase was used. Dose levels are shown in the Table. Bendamustine was given on day 1 and 2, rituximab on day 1 and lenalidomide orally, daily, days 1-10 of 28-day cycle for up to 6 cycles. Pegfilgrastin was given on day 3 of the cycle. **Results:** 15 patients were enrolled. The median age was 58 years (47-71), 5/15 patients were female, 12/15 patients had stage 4 disease. The histological subtypes were: follicular lymphoma grade 1 and 2 (6/15 pts), marginal zone lymphoma (5/15 pts) and lymphoplasmacytic lymphoma (4/15 pts). No dose-limiting toxicity was seen. Dose escalation beyond 25 mg daily of lenalidomide was not performed, since 25 mg is considered a biologically effective dose. The most common toxicity was hematological, with 2/15 pts experiencing grade 3 neutropenia. The overall response was 100% (Table). Only 1/15 pts experienced grade 3 or more non-hematological toxicity (grade 3 urticaria). All patients remain alive with median follow up of 17 months (6-28) and only 1 pt disease progression at 12 months. **Conclusions:** Lenalidomide at 25 mg/day, days 1-10 of a 28-day cycle can be safely combined with the standard dose bendamustine rituximab regimen and is well tolerated. The encouraging response rates in a relapsed setting warrant further evaluation of this combination in larger trials. Support: U10CA180821, U10CA180882, CA025224 Clinical trial information: NCT01429025.

Dose escalation and response summary.

Dose level	Lenalidomide Days 1-10	Bendamustine Day 1-2	Rituximab Day 1	DLTs	Response
1	15 mg	70 mg/m2	375 mg/m2	0/3	3 PR
2	20 mg	70 mg/m2	375 mg/m2	0/3	1 CR, 2 PR
3	20 mg	90 mg/m2	375 mg/m2	0/3	2 CR, 1 PR
4	25 mg	90 mg/m2	375 mg/m2	0/6	3 CR, 3 PR

8541 Poster Session (Board #358), Sun, 8:00 AM-11:30 AM

Telomere profile of Reed-Sternberg and Hodgkin cells in diagnostic biopsy in Hodgkin lymphoma as a predictor of clinical response. *First Author: Jeffrey B Tompkins, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada*

Background: Markers that predict poor response to primary therapy in Hodgkin's lymphoma (HL) are currently lacking. Much of the difficulty stems from the rarity of the malignant mononuclear Hodgkin's (H) cells and multinuclear Reed-Sternberg (RS) cells in the tumor. We have developed a 3D quantitative fluorescent in situ hybridization (3D qFISH) telomere profile, with telomere fluorescent intensity, number, distribution and aggregation, as markers of genomic instability. Telomere profiles differ between H and RS cells; increased genomic instability accompanies the switch from H to RS phenotype. Cases of relapsed/refractory HL have greater H cell genomic instability compared to those entering stable remission. Telomere profiles of H and RS cells at time of diagnosis may predict aggressive disease behavior, as indicated by relapse or refractoriness to therapy. **Methods:** Incident cases of classical HL from 2002-2010 were retrospectively identified from the provincial cancer registry in Manitoba, Canada. Patients with only palliative treatment or who had insufficient biopsy material for analysis were excluded. Primary outcome was treatment failure (primary refractory, relapse or death from HL). H and RS cell telomeres in the initial diagnostic biopsies were subject to 3D qFISH with telomere specific probes. Resultant images were analyzed with TeloView software. Subhazard ratios (SHR) were computed using competing risk models. **Results:** 295 patients were diagnosed with HL, of which 145 met the eligibility criteria, and 28 had treatment failure. Median follow up was 4.0 years. H cell mean telomere intensity (SHR 0.77; 95% CI 0.59-1.00; $p = 0.048$), total telomere intensity (SHR 0.90; 95% CI 0.83-0.98; $p = 0.013$) and the ratio of RS/H cell total intensity (SHR 1.94; 95% CI 1.43-3.52; $p < 0.001$), were predictive of treatment failure. RS/H cell total intensity was predictive of outcome while controlling for disease stage (SHR 1.95; 95% CI 1.24-3.05; $p = 0.004$). **Conclusions:** Genomic instability of the H and RS cells measured by telomere 3D qFISH is predictive of primary refractory or relapsing HL independent of disease stage and is a potential biomarker of disease behavior at time of diagnosis.

8542 Poster Session (Board #359), Sun, 8:00 AM-11:30 AM

Lenalidome in combination with rituximab for relapsed or refractory mantel cell lymphoma: Updated analysis of a phase 2 trial. *First Author: Yucai Wang, Rutgers New Jersey Medical School, Newark, NJ*

Background: We previously reported favorable safety and efficacy of lenalidomide plus rituximab in relapsed or refractory (R/R) mantle cell lymphoma (MCL) in a phase 1/2 trial (Wang *et al*, Lancet Oncol 2012). We performed an updated analysis of the phase 2 data after an extended follow up. We also investigated whether Ki-67 level affected response and survival in this study, as we recently reported that lower Ki-67 was associated with extremely high response rate to ibrutinib plus rituximab in R/R MCL (Wang *et al*, ASH 2014). **Methods:** Patients with R/R MCL were enrolled in this single arm phase 1/2 trial. In phase 2, lenalidomide was administered orally at 20 mg daily dose on days 1-21 of each 28-day cycle, and 375 mg/m^2 rituximab was administered intravenously weekly during the first cycle only. Treatment was continued until disease progression, stem-cell transplantation, or severe toxicity. The primary endpoint was overall response, and the secondary endpoint was survival. Analysis was by intention to treat. **Results:** 46 patients were enrolled, of which 42 were male. The median age was 66.5 (range 46-85). Median number of prior lines of therapy was 2 (range 1-4). At a median follow up of 24.7 months (range 1.2-96.1), 16 (34.8%) and 10 (21.7%) patients achieved CR and PR, respectively, with an ORR of 56.5%. An additional 10 (21.7%) patients achieved MR or SD. ORR was independent of age, gender, number of prior lines of therapy and Ki-67 at registration. Median time to response was 1.8 months (range 1.6-7.7). Median duration of response was 20.9 months (95% CI 10.9-NR). The median PFS was 14.1 months (95% CI 8.2-26.7), and median OS was 24.6 months (95% CI 16.8-33.7). The 12- and 24-month PFS rates were 53.1% and 39.9%, respectively. The 1-, 2- and 5-year OS rates were 82.6%, 52.2% and 26.1%, respectively. Lower Ki-67 at registration ($< 50\%$) and fewer prior lines of therapy (< 2) were predictive of better PFS (HR = 0.242, 95% CI 0.070-0.715, P = 0.012; and HR = 0.245, 95% CI = 0.071-0.841, P = 0.025) and OS (HR = 0.267, 95% CI 0.110-0.648, P = 0.003; and HR = 0.363, 95% CI = 0.147-0.896, P = 0.028). **Conclusions:** Lenalidomide plus rituximab is efficacious in treating R/R MCL. Lower Ki-67 is associated with better survival outcomes. Clinical trial information: NCT00294632.

8543 Poster Session (Board #360), Sun, 8:00 AM-11:30 AM

Analysis of "double-hit" lymphoma cases by genetic subtype. *First Author: Daniel Jeffrey Landsburg, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: "Double-hit" lymphoma (DHL), defined as a B cell non-Hodgkin lymphoma harboring rearrangements in *c-MYC* as well as *BCL2* and/or *BCL6*, carries a poor prognosis. Here we report characteristics and outcomes of DHL patients (pts) by genetic subtype. **Methods:** From our previously-described database of DHL pts (*Blood* 2014 124:2354-61), we identified cases which underwent cytogenetic testing for *c-MYC* as well as both *BCL2* and *BCL6* rearrangements. Cohorts were defined by the presence (+) or absence (-) of rearrangements: *c-MYC*+/*BCL2*+/*BCL6*- (BCL2-DHL), *c-MYC*+/*BCL2*-/*BCL6*+ (BCL6-DHL) and *c-MYC*+/*BCL2*+/*BCL6*+ (THL). Therapy was given at the discretion of the treating physician. **Results:** Data from 117 cases were included. Pts with BCL6-DHL were more likely to have extranodal disease as compared to BCL2-DHL ($p=0.04$) and THL ($p=0.04$) pts. Treatment received and outcomes are described in Table. Univariate analysis revealed that elevated LDH, stage ≥ 3 disease, IPI ≥ 4 and bone marrow involvement in BCL2-DHL pts and IPI ≥ 4 and bone marrow involvement in THL pts predicted for inferior overall survival (OS). **Conclusions:** Analysis of the largest reported series of BCL2-DHL, BCL6-DHL and THL pts by genetic subtype did not reveal significant differences in outcome, potentially due to small cohort sizes. Nevertheless, high rates of primary refractory disease and relapse seen across all subtypes provides a rationale for offering novel therapeutic approaches to these pts in the front-line setting.

Treatment received and outcomes.

	DHL subtype			p value		
	BCL2-DHL (n=76)	BCL6-DHL (n=16)	THL (n=25)	BCL2-DHL vs. BCL6-DHL	BCL2-DHL vs. THL	BCL6-DHL vs. THL
Receipt of DE[1]	55%	44%	65%	0.42	0.35	0.19
Complete response (CR1)	54%	75%	46%	0.17	0.49	0.10
If receiving DE[1]	55%	86%	63%	0.22	0.77	0.37
Stem cell transplant (SCT) in CR1	36%	22%	55%	0.47	0.31	0.18
Primary refractory disease	32%	13%	33%	0.14	1.0	0.25
If receiving DE[1]	25%	14%	14%	1.0	0.71	1.0
Relapse (if responding)	42%	50%	23%	0.75	0.33	0.23
If receiving DE[1]	36%	33%	25%	0.67	0.29	1.0
Median OS (months)[2]	34.8	14.5	17.2	0.89	0.69	0.90
If receiving DE[1]	37.5	12.1	NYR[3]	0.67	0.91	0.84

[1]DE=dose-escalated front-line chemotherapy (EPOCH, hyperCVAD, CODOX-M/IVAC). [2]Median length of follow-up 12.0 months (range 0.1-85.6). [3]Not yet reached.

8544 Poster Session (Board #361), Sun, 8:00 AM-11:30 AM

Phase 1 trial of brentuximab vedotin in combination with gemcitabine for pediatric and young adult patients with relapsed or refractory Hodgkin lymphoma, a Children's Oncology Group report. *First Author: Peter D. Cole, The Children's Hospital at Montefiore, Bronx, NY*

Background: Salvage therapy followed by autologous stem cell transplantation improves outcomes for patients with primary refractory Hodgkin lymphoma (HL) or early relapse. Brentuximab vedotin (Bv) and gemcitabine each produce high overall response rates in this context. Compared to alternate retrieval regimens, this combination offers the advantage of avoiding agents that are associated with late treatment sequelae, such as anthracyclines, alkylators, or epipodophyllotoxins. This phase 1 trial was conducted to describe the toxicity of the combination and to define a recommended phase 2 dose (RP2D) for Bv when given with gemcitabine. **Methods**: Patients ≤ 30 years old with primary refractory HL or early relapse were eligible. Bv was given on day 1 of each 21-day cycle, at two dose levels (DL): DL1, 1.4 mg/kg and DL2, 1.8 mg/kg. Gemcitabine 1000mg/m^2 was given on day 1 and 8. Dose limiting toxicity (DLT) was assessed during cycle 1 to define the RP2D, and response after every 2 cycles. **Results**: Fifteen patients have enrolled (14 evaluable for hematologic toxicity), with median age of 17 years (range 5-28). No DLTs were seen among 3 patients treated at DL1. Two of six patients experienced non-hematologic DLT at DL2: one with grade 3 hypotension and one with asymptomatic Grade 3 elevation of liver enzymes. Both had resolution of all toxicity and continued on study treatment with dose reduction of Bv to 1.2 mg/kg. An expansion cohort of six patients was enrolled at DL2; none experienced DLT. Grade 3-4 neutropenia was common (13 of 14 patients during cycle 1) but self-limited. No grade 4 non-hematologic toxicity occurred. No cases of interstitial pneumonitis or pulmonary toxicity attributable to study therapy were observed. **Conclusions**: Bv can be safely given in combination with gemcitabine. The RP2D of Bv is 1.8 mg/kg. The ongoing Phase 2 trial will describe the complete response rate observed within four cycles of Bv with gemcitabine. Clinical trial information: NCT01780662. Clinical trial information: NCT01780662.

8545 Poster Session (Board #362), Sun, 8:00 AM-11:30 AM

Survival of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and peripheral T-cell lymphoma (PTCL): A propensity matched analysis of the Surveillance, Epidemiology and End Results (SEER) database. *First Author: Samyak Manandhar, UPMC Mercy, Pittsburgh, PA*

Background: SPTCL is a rare entity with no prior population-based study. Using the SEER database, we compared the characteristics and survival of SPTCL and PTCL. **Methods**: We used the SEER 18 database to identify adult patients with SPTCL and PTCL diagnosed between 1973 and 2011. Prior to 2008, T-cell receptor gamma/delta phenotype of SPTCL was not recognized as a separate entity, hence could not be excluded from this study. Actuarial, relative and cause specific survivals of SPTCL were computed. The actuarial survival of SPTCL was compared to a propensity matched cohort of PTCL. Kaplan Meier survival curves were plotted. Multivariate analysis was conducted using weighted Cox proportional hazard regression model. **Results:** Patients with SPTCL (n = 118), compared to PTCL (n = 3296), were more likely to be younger (median age of 47 vs. 62 years, $p < 0.01$), women (67 % vs 40%, $p < 0.01$) and diagnosed with stage I/II disease (46% vs. 36%, $p = 0.01$). The five year actuarial, relative and cause specific survival for SPTCL was 40%, 57% and 64% respectively. After propensity matching, the 5-year overall survival (OS) of SPTCL was better than that of PTCL (57% vs. 40%. $p < 0.01$). In a multivariate analysis, mortality was significantly lower among SPTCL vs. PTCL (hazard ratio, HR 0.54; 95% CI 0.39-0.75; $p < 0.01$) after adjusting for age, gender, race and stage of the disease. Among patients with SPTCL, advanced age ($p < 0.01$) and diagnosis before the year 2008 (p 0.02) were predictors of worse OS in a multivariate analysis. **Conclusions**: Our study provides characteristics and OS of a large cohort of this rare entity, which can be used for patient education and may provide background information for future research. As compared to PTCL, SPTCL patients were more likely to be younger, females and diagnosed at an early stage. Even though T-cell receptor gamma/delta phenotype, which has an unfavorable outcome, could not be excluded, the OS of SPTCL was found to be better than PTCL. Advanced age and year of diagnosis were the predictors of OS among patients with SPTCL.

8546 Poster Session (Board #363), Sun, 8:00 AM-11:30 AM

Treatment of refractory/relapse vitreoretinal lymphoma: Result of a multicenter retrospective study from the LOC network on temozolomide in monotherapy. *First Author: Sylvain Choquet, APHP-CHU Pitié-Salpêtrière, Paris, France*

Background: Vitreoretinal lymphoma (VRL) is a rare subset of non Hodgkin lymphoma. Its overall survival (OS) is from 35% to 68% at 5 years (Riemens et al Jama ophtalmol 2014) in first line, but relapse/refractory (R/R) VRL survival is usually of few months. Temozolomide (Tz) has been described effective in some cases of CNS lymphoma. **Methods:** VRL not eligible for IV chemotherapy or local treatment were proposed to be treated by Tz at 150mg/m^2/j 5 days/month. Diagnosis of VRL was made by vitrectomy with a cytological, phenotypical and molecular analysis, dosages of IL10 and IL6 were also made. Extra-ocular localizations were searched by brain RMI, lombar puncture and CT-scan or PET-scan. **Results:** 16 patients were included, mean age was 75 years [35-90]. 12 previously received systemic chemotherapy with high dose methotrexate or cytarabin, 8 were in second line, 3 in third, 2 in forth, and 1 in fith who relapsed after autologous stem-cell transplantation (ASCT). The 2 patients treated in first line where more than 80 years old. All but one had an isolated VRL, one an association with a cerebral localization. Median duration of treatment was 5 months. The median follow-up (fu) is 16 months. Overall response rate is 75%, with 10 CR (63%) and 2 PR (13%). At the last fu, 6 patients are still in CR. The median disease free survival is 12,3 months. The patient treated after ASCT relapse is still in CR at 77 months. The two old patients treated in first line are in CR at last fu. One patient with cerebral localization had a persistent ocular and cerebral CR. Three patients were treated a second time by Tz after relapse, obtaining 2 new CR, one of 4 months and one persistent at 12 months, and one new persistent PR. Median OS is not reached. Only 2 patients experienced hematological grade 3/4 toxicity. There was no treatment related deaths. **Conclusions:** This work represents the biggest study with an homogeneous treatment in R/R VRL. Temozolomide appears as a safe and efficient treatment of R/R VRL and first line VRL in patients in bad condition, even after high dose chemotherapy and/or in elderly patients. Longer follow-up, prospective and larger studies are necessary to confirm these data.

8547 Poster Session (Board #364), Sun, 8:00 AM-11:30 AM

Subgroup analysis of the phase II randomized MCL-002 (SPRINT) study of lenalidomide vs investigator's choice in relapsed/refractory mantle cell lymphoma. *First Author: Marek Trneny, Charles University Hospital, Dept. of Hematology, Prague, Czech Republic*

Background: Lenalidomide, an immunomodulator with antineoplastic and antiproliferative effects, showed clinically significant improved activity over investigator choice (IC) in relapsed/refractory (R/R) MCL. This preplanned MCL-002 analysis evaluated efficacy across patient subgroups receiving lenalidomide vs IC. **Methods**: Patients received lenalidomide (25 mg/day PO on days 1-21/28 days) or single-agent IC therapy (chlorambucil, cytarabine, fludarabine, gemcitabine, or rituximab). The primary endpoint was progression-free survival (PFS); prespecified exploratory analyses of PFS by subgroups were conducted. **Results**: 254 patients with R/R MCL (median 2 prior therapies) were randomized 2:1 to lenalidomide (n = 170) or IC (n = 84). Patients receiving lenalidomide showed a significant improvement in median PFS vs IC (8.7 vs 5.2 months; HR = 0.61, P= 0.004). Subgroup analysis of PFS by central review demonstrated statistically significant reductions in the risk of progression or death in favor of lenalidomide vs IC across most baseline demographic and disease characteristics including: age ≥ 65 years, females, any stage at diagnosis, ECOG PS 0-1, both high or low tumor burden, Ki-67 < 10%, normal/elevated LDH , WBC counts < 10x10^9/L, no bulky disease, high MIPI score, negative bone marrow, and normal renal function. The only subgroups without risk reduction were WBC ≥ 15x10^9/L and positive bone marrow (both statistically insignificant), partly explained by low patient numbers in the IC arm. Risk reduction in the remaining categories was insignificant. Overall, factors associated with significantly better PFS by univariate Cox regression analysis, beside treatment group (HR = 0.619; P= 0.004), were non-elevated LDH, WBC < 10x10^9/L, low+intermediate MIPI, low tumor burden, and Ki-67 ≤ 30%. Highly significant in the multivariate analysis were treatment group (HR = 0.384) and Ki-67 ≤ 30% (HR = 0.344). **Conclusions**: Multivariate and subgroup analyses of the primary study endpoint PFS favored lenalidomide over IC therapy in providing consistent clinical benefit in patients with R/R MCL irrespective of baseline demographics or disease characteristics. Clinical trial information: NCT00875667.

8548 Poster Session (Board #366), Sun, 8:00 AM-11:30 AM

Ublituximab plus TGR-1202 activity and safety profile in relapsed/refractory B-cell NHL and high-risk CLL. *First Author: Matthew Alexander Lunning, University of Nebraska Medical Center, Omaha, NE*

Background: Ublituximab (UTX) is a novel glycoengineered anti-CD20 mAb. TGR-1202 is a novel once daily oral PI3Kδ inhibitor. UTX + TGR-1202 has shown strong synergistic activity *in-vitro* (Lugano 2013). This phase I trial evaluates the safety and efficacy of the combination of UTX + TGR-1202 in patients (pts) with heavily pre-treated rel/ref NHL and CLL. **Methods**: A 3 + 3 design is utilized with rel/ref NHL or CLL pts accruing independently. No limits on prior therapies (Tx). Pts refractory to prior PI3K or BTK inhibitors are eligible. UTX administered D 1, 8, 15 of Cyc 1 & 2, followed by D 1 of Cyc 4, 6, 9 & 12. TGR-1202 is daily, with an improved micronized formulation introduced in later cohorts. Primary endpoints: Safety and dose limiting toxicities (DLT). Secondary endpoints: Efficacy (ORR, CR rate). **Results**: 32 pts enrolled and evaluable for safety: 12 CLL/SLL, 10 FL, 8 DLBCL, 1 MZL and 1 Richter's. Med age 64 yo (range 35-82); 20 M/12 F; Median prior Tx = 3 (range 1-9). AE's (all causality) include: Day 1 infusion reactions at 44%, neutropenia 41% (31% Gr 3/4), diarrhea 34%, (0% Gr 3/4), and nausea 28% (0% Gr 3/4). To date, TGR-1202 related hepatotoxicity has not been reported. One DLT has occurred: a pt with Gr 3 neutropenia at study entry which worsened (cohort 1). A dose-response relationship has been observed with TGR-1202. 28/32 are evaluable for efficacy with best response in the table below. To date, of all 32 pts, 89% (16/18) in the higher dose cohorts remain progression-free compared to 57% (8/14) in the lower dose cohorts. Of the 10 CLL pts, all remain progression-free at a median of 8 months (range 2 – 12+ months). **Conclusions:** The combination of UTX + TGR-1202 is well tolerated with activity in rel/ref NHL and CLL with a dose-response relationship observed. Dose escalation continues with enrollment ongoing at the highest dose cohort and in recently opened expansion cohorts. Clinical trial information: NCT02006485.

	TGR-1202 Higher dose					TGR-1202 Lower dose				
	Pts			ORR		Pts			ORR	
Type	(n)	CR	PR	n (%)	PD	(n)	CR	PR	n (%)	PD
CLL/SLL	3	-	3	3 (100%)	-	7	-	4	4 (57%)	-
DLBCL	4	2	1	3 (75%)	1	3	-	-	-	2
FL	6	1	2	3 (50%)	-	4	-	-	-	-
Richter's	1	-	-	-	-	-	-	-	-	-
Total	14	3	6	9 (64%)	1	14	-	4	4 (29%)	2

Higher dose, 1200 original and 600/800 micronized; Lower dose, 800 original and 400 micronized.

8549 Poster Session (Board #367), Sun, 8:00 AM-11:30 AM

Clinical significance of radiotherapy in the treatment of limited stage NK/T cell lymphoma. *First Author: Soo Jung Lee, Department of Oncology/Hematology, Kyungpook National University Medical Center, Kyungpook National University School of Medicine, Daegu, South Korea*

Background: For the treatment of limited-stage natural killer (NK)/T-cell lymphoma, combined treatment modality including radiotherapy (RT) is widely recommended. However, the best standard has not been clearly determined. In this study, we analyzed the role and the optimal timing of RT, and the difference of clinical outcome among patients with limited-stage NK/T-cell lymphoma. **Methods:** We retrospectively analyzed patients with limited-stage NK/T-cell lymphoma, diagnosed between January, 2004 and April, 2013 from six Korean institutes. These patients were categorized into 3 groups, i.e., 1) anthracycline or non-anthracycline-based chemotherapy followed by radiotherapy (CTx/RT), 2) concurrent chemoradiotherapy (CCRT) followed by non-anthracycline-based chemotherapy (CCRT/CTx), and 3) CTx alone group. **Results:** In total 104 patients, the median age was 52 years (range 28~85). According to therapeutic modalities, 29 (27.9%) and 44 (42.3%) patients were treated by CTx/RT and CCRT/CTx, respectively, and the remaining 31 (29.8%) patients were managed by CTx alone as initial therapy. Overall response (OR) rate was 80.8% including complete response (CR) rate 70.2% after initial therapy. Patients who had CTx/RT or CCRT/CTx achieved high CR rate (76.7%) comparing to those had CTx only group with 54.8% (p = 0.009). With median follow up of 47.6 months, the 5-year progression free survival (PFS) was 44.2% and overall survival was 75.1%. The 5-year PFS of patients with RT containing protocol and those with CTx only group were 52.1% and 25.8%, respectively (p = 0.003). Among patients treated with RT containing protocol, the 5-year PFS was superior in CTx/RT group as 60.6% than CCRT/CTx group as 48.8% (p = 0.001). All patients treated with CTx/RT could finish the planned protocol. **Conclusions:** Our results show the role of RT for treating limited stage NK/T cell lymphoma. Although CCRT showed a higher CR rate compared CTx followed by RT, the optimal timing of RT should be determined carefully considering the possibility of progression outside RT field prior to systemic chemotherapy or failure to complete planned treatment related with radiotherapy in particular in case of RT at upper aerodigestive tract.

8550 Poster Session (Board #368), Sun, 8:00 AM-11:30 AM

Breast implant-associated anaplastic large cell lymphoma: Proposal for optimal management. *First Author: Mark Warren Clemens, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) is a newly identified lymphoma arising around breast implants placed for cosmetic or reconstructive indications. Patterns of disease progression and optimal treatment strategies have not been described. **Methods:** The literature was reviewed for all published cases of BI-ALCL from 1997 to November 2014, contacted corresponding authors to update clinical follow up, management, and combined data with institutional cases. A novel clinic-pathologic TNM staging system is proposed and was compared to traditional Ann Arbor staging to determine prognostic value for overall survival (OS) and progression free survival (PFS). A Prentice, Williams and Peterson (PWP) model was used to assess treatment effect on progression events. **Results:** We identified 128 unique cases of BI-ALCL, including 91 previously reported and 37 unreported cases.Pathologic slides were available in 56 patients for pathologic staging.Average follow up was 45 months (30-217 months). The median OS was 13 years, OS rate 93% at 3-years and 89% at 5-years. 18 progression events were noted and median PFS was 13 months, with 3-year and 5-year PFS at 79.4%. Total capsulectomy with implant removal (TCIR) prolonged OS (p = 0.022) and improved PFS (p = 0.014), and the effect of definitive surgery was statistically significant for PFS benefit (HR = 0.14, 95%, CI = 0.05-0.46, p = 0.001). After definitive surgery, patients had 4% of risk of having events by the end of the first year while the rates were 18%, 24% and 60% when patient had radiation, chemotherapy or limited surgery. The PFS was significantly different by Ann Arbor staging (p = 0.013) and by the newly proposed clinical staging (p = 0.030). **Conclusions:** Advanced stage, presence of mass, incomplete resection, and delay in definitive surgical treatment were associated with poor OS and PFS in patients with BI-ALCL. Surgical management with definitive excision and oncologic surveillance is adequate for most patients with BI-ALCL. The role for chemotherapy, targeted immunotherapy, and/or radiation for advanced disease requires further research in larger series.

8551 Poster Session (Board #369), Sun, 8:00 AM-11:30 AM

Rituximab maintenance Therapy in B-cell lymphoma: A meta-analysis. *First Author: Yucai Wang, Rutgers New Jersey Medical School, Newark, NJ*

Background: The role of rituximab (R) maintenance therapy (MT) in B-cell lymphoma is controversial. We reviewed data from clinical studies and conducted a meta-analysis to evaluate the efficacy and safety of R MT in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). **Methods:** PubMed, ASCO and ASH databases were searched for eligible clinical studies to date that investigated survival outcomes (OS, PFS, EFS and/or TTP) and adverse events of R MT in FL, DLBCL and MCL. Pooled hazard ratios (HRs) for survival outcomes and risk ratios (RRs) for dichotomous data with 95% CI were calculated using Comprehensive MetaAnalysis (v2). **Results:** 22 clinical studies of 6785 patients, including 15 randomized controlled trials (RCTs) enrolling 5029 patients, were included in this meta-analysis. In RCTs, R MT significantly prolonged PFS (HR = 0.60, 95% CI = 0.52-0.68, $P < 0.001$) and OS (HR = 0.79, 95% CI = 0.69-0.93, $P = 0.005$) in B-cell lymphoma. Improvement of PFS with R MT was demonstrated in all types of lymphoma studied. R MT increased OS in FL (HR = 0.76, 95% CI = 0.61-0.94, $P = 0.010$) but not DLBCL (HR = 0.88, 95% CI = 0.64-1.21, $P = 0.425$) or MCL (HR = 0.77, 95% CI = 0.47-1.27, $P = 0.303$) in RCTs. The survival benefits remained after including non-randomized clinical studies and retrospective studies. R MT increased the risks of neutropenia (RR = 1.82, 95% CI = 1.40-2.37, $P < 0.001$) and infection (RR = 2.49, 95% CI = 1.61-3.85, $P < 0.001$) but not cardiac dysfunction (RR = 1.61, 95% CI = 0.73-3.57, $P = 0.242$). **Conclusions:** R MT significantly improved PFS in FL, DLBCL and MCL as well as OS in FL. Whether R MT improves OS in DLBCL and MCL needs further study.

Survival benefits of rituximab maintenance therapy in B-cell lymphoma.

Study type	Survival	Type	# of trials	HR	95% CI	*P* value
RCT	PFS	FL	9	0.52	0.42-0.64	0.000
		DLBCL	4	0.70	0.57-0.86	0.000
		MCL	3	0.55	0.41-0.73	0.000
		All	15	0.60	0.52-0.68	0.000
	OS	FL	7	0.76	0.61-0.94	0.010
		DLBCL	2	0.88	0.64-1.21	0.425
		MCL	1	0.77	0.47-1.27	0.303
		All	10	0.79	0.69-0.93	0.005
All	PFS	FL	10	0.53	0.44-0.65	0.000
		DLBCL	6	0.71	0.59-0.86	0.000
		MCL	7	0.53	0.32-0.86	0.010
		All	22	0.62	0.54-0.70	0.000
	OS	FL	8	0.77	0.64-0.92	0.005
		DLBCL	3	0.85	0.63-1.15	0.284
		MCL	4	0.62	0.42-0.91	0.015
		All	15	0.76	0.66-0.88	0.000

8552 Poster Session (Board #370), Sun, 8:00 AM-11:30 AM

CD30+ expression in Peripheral T-cell lymphomas (PTCLs): A subset analysis from the international, prospective T-Cell Project. *First Author: Massimo Federico, Dept of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy*

Background: CD30 is a member of TNF-alpha receptor family that might have important therapeutic implications with the advent of targeted therapies. Several PTCLs subtypes have been reported in literature to be associated to variable CD30 expression. We investigated the frequency of CD30 expression among PTCLs subtypes registered in the T-Cell Project and correlated it with clinical features and outcome. **Methods:** The T-cell Project is a prospective, international study in patients (pts) with newly diagnosed aggressive PTCLs. Clinical, laboratory and disease localization data at diagnosis as well as therapy details and follow-up information are collected at a dedicated website via secure HTTP protocols. Central review of diagnostic biopsy is planned. **Results:** From Sept 2006 to Jan 2015, 1308 pts were registered in the T-Cell Project by 73 sites from 14 countries world-wide. As from the 792 pathology forms filled out by site local staff CD30 expression was tested in 490 pts (62%) and reported as CD30+ in 349 (71%) and CD30- in 141 (29%). Frequency of CD30 expression in different subtypes is shown in the Table. CD30+ pts tended to be younger (54 vs 58 yrs, P = .03) with less extranodal involvement (65% vs 78%, P = .01) than CD30-. CHOP like regimens were the most common irrespective of CD30 status (63% in both groups, P = 1.0). In the group of pts with any histology but ALCL, no difference in CR rate (44% vs 51%, P = .26), 5-yr PFS (29% vs 22%, P = .57) and OS (44% vs 29%, P = .17) was observed between CD30+ and CD30- pts. Brentuximab use in first line was noted in only 5 pts enrolled in clinical trials. **Conclusions:** Data from the T-cell project confirm that CD30 is expressed in many PTCLs other than ALCL, thus suggesting a routine assessment for all PTCLs. Again, this analysis suggests that CD30 expression has no prognostic significance. The very limited use of anti CD30 targeted therapy in this sample doesn't allow to establish the predictive value of CD30 expression in PTCLs.

	CD30- N, %	CD30+ N, %
PTCL,NOS	85, **41**	120, **59**
AITL	16, **42**	50, **76**
ALCL	0, **0**	145, **100**
NKTCL	13, **48**	14, **52**
EATL	11, **46**	13, **54**
Other	16, **70**	7, **30**

8553 Poster Session (Board #371), Sun, 8:00 AM-11:30 AM

A phase I trial of lenalidomide maintenance after autologous stem cell transplant (ASCT) in patients with high-risk relapsed/refractory lymphomas. *First Author: Jakub Svoboda, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Lymphoma patients (pts) with residual hypermetabolic lesions on PET imaging after salvage chemotherapy have extremely poor outcomes and may benefit from continued therapy after ASCT. Lenalidomide (len) has been used as maintenance in other hematologic malignancies, but its toxicity and efficacy are not well known in lymphoma pts following ASCT. **Methods:** We conducted a phase I trial of len maintenance after ASCT in lymphoma pts at high risk for relapse defined by residual PET positive lesions of SUV $>$ 2.5 immediately prior to ASCT. Our primary objective was to determine the safety and dose-limiting toxicity (DLT) of len maintenance. A 3+3 de-escalation design was utilized with a starting dose of len at 10 mg on days 1 through 28 of each 28 day cycle (C). Len was initiated 28-100 days post-ASCT and planned for twenty four Cs. DLT was defined as non-hematologic toxicity $\geq$ grade (G)3 or hematologic toxicity $\geq$ G4 during the first 28 days of len. Enrollment began in 5/2012; reported data were collected through 1/2015. **Results:** Eight pts were enrolled and 6 pts are evaluable (4 diffuse large B-cell and 2 Hodgkin lymphomas). One pt withdrew consent and one progressed prior to initiation of len. Median age was 51 yrs (29-61), ECOG PS 0 (0- 1), prior therapies 3 (2-5). Median time on len was 7 Cs (2-24). Len was well tolerated and no DLT was observed at the 10 mg dose. Two pts required dose reduction to 5 mg due to treatment-related toxicities (after C7 and C3). Four pts had $\geq$ G2 non-hematologic adverse events possibly related to len including fatigue, bronchitis, and thrush. Three pts had transient $\geq$ G3 neutropenia. Two pts discontinued len (1 due to progression, 1 at investigator's discretion). No secondary malignancies or study-related deaths were observed. Four of 6 pts remain on len and are progression free; 5 of 6 pts are alive with median follow-up of 195 days. **Conclusions:** We established safety of len after ASCT in pts with relapsed/refractory lymphomas and determined that len 10 mg daily is a well-tolerated maintenance dose in this setting. Preliminary clinical outcomes observed in this cohort of high-risk lymphoma pts are encouraging and will be validated in the ongoing phase II trial. Clinical trial information: NCT01575860.

8554 Poster Session (Board #372), Sun, 8:00 AM-11:30 AM

Outcomes and prognostic factors in marginal zone lymphoma: Case comprehensive cancer center cumulative experience of 358 cases. *First Author: Adam Starr, Case Western Reserve University, Cleveland, OH*

Background: MZL are uncommon B-cell lymphomas. The outcomes and prognostic factors of MZL remain poorly defined. **Methods:** We retrospectively identified 485 cases of MZL diagnosed between 1994-2014 from 2 institutions. Diagnoses had been confirmed by expert hematopathologists. We excluded 127 cases because of limited data and overlapping features with other lymphoma subtypes. **Results:** Of the 358 patients (pts) included in the analysis, 216 (60%) had extranodal MZL (EMZL) with most EMZL arising from stomach (32%), 56 (16%) nodal MZL (NMZL), 64 (18%) splenic MZL (SMZL), and 22 (6%) had typical MZL phenotype but were unclassifiable. Median age was 66 (range 13-95) years, 171 (48%) pts had stage III/IV disease at diagnosis. B-symptoms were present in 33 (9%) pts and 65 (18%) had $>$ 4 nodal sites (LN) involved. Median time from diagnosis to treatment was 33 (2-1883) days and median duration of follow-up was 40.3 (2.2-236.4) months. Among treated pts, initial treatment was rituximab (R) (33%), chemotherapy +/- R (22%), radiation (16%), surgery (16%), and antibiotics (13%). Progression-free survival (PFS) and overall survival (OS) for the whole group was 5.15 (95% confidence intervals; C.I. = 2.8-10) and 19 (95% C.I. = 10-19) years respectively and there was no significant difference in PFS or OS between EMZL, NMZL, SMZL, or atypical MZL. On univariate analysis, age $>$ 60 (p = 0.002), elevated serum lactate dehydrogenase (LDH) (p = 0.003), involvement of $>$ 4 LN (p = 0.019), follicular lymphoma International Prognostic Index (FLIPI) score (p = 0.0005), and hemoglobin (Hb) level $<$ 12 g/dL at presentation (p = 0.003) were associated with inferior OS. In a multivariate analysis, only age (hazard ratio (HR) = 5.48, p = 0.002) and Hb (HR = 2.97, p = 0.009) retained significance. Transformation to aggressive lymphoma occurred in 29 (8%) pts and was associated with high serum LDH and higher FLIPI at diagnosis. In pts treated with R +/- chemotherapy, R maintenance was associated with improved OS (p = 0.04). **Conclusions:** In our MZL series, one of the largest reported, prognosis of MZL is good with a median OS of over 19 years. Age $>$ 60, Hb $<$ 12 g/dL, elevated LDH, and $>$ 4 LN involved are associated with inferior OS.

8555 Poster Session (Board #373), Sun, 8:00 AM-11:30 AM

Exercise patterns and quality of life among survivors of aggressive lymphoma. *First Author: Raina Mahajan Ferzoco, Mayo Clinic, Rochester, MN*

Background: Aerobic exercise has been associated with improved QOL in the general population, but has not been studied in non-Hodgkin lymphoma (NHL) survivors. **Methods:** Newly diagnosed patients with aggressive lymphoma were prospectively enrolled in the University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource and systematically followed. Patient reported exercise patterns and QOL (FACT-G) were assessed at 3 years after diagnosis; patients with active disease or recent treatment were excluded from this analysis. QOL scores were normalized to a 0-100 scale for analysis. **Results:** From 2002-2009, 625 eligible patients completed the 3 year questionnaire.Themedian age was 62 years (range 18-87), 59% were male, and diagnoses included DLBCL (60%), FL grade III (11%), mantle cell (12%), other B-cell (7%), and T-cell (10%) lymphomas. Overall, 49% of 3-year survivors met CDC exercise recommendations defined as 30 minutes of moderate activity at least 5 days/week, which was comparable to the general population estimate (50%). Since their diagnosis of lymphoma, 10% of patients reported an increase in exercise and 49% reported a decrease in exercise. Males were more likely to meet exercise recommendations than females (54% v 41%, p = 0.002). Young patients (18-39 years) were more likely to increase physical activity after diagnosis than patients age $>$ 70 (16% vs. 4%; p = 0.002). Those meeting exercise recommendations had higher median functional well-being (WB) (89 vs.75), physical WB (93 vs. 88), emotional WB (88 vs. 83), social/family WB (89 vs. 86), and overall QOL (89 vs. 80) (all p $<$ 0.0001). Similarly, compared to those who reported decrease in exercise since diagnosis, patients with increased physical activity had higher median functional WB (89 vs. 75), physical WB (96 vs. 86), emotional WB (88 vs. 83), social/family WB (88 vs. 86) and total QOL (90 vs. 81) (all p $<$ 0.0001). **Conclusions:** In this cohort, half of aggressive lymphoma survivors are meeting recommendations for exercise, similar to the general population. Meeting exercise recommendations and increasing exercise are associated with significantly higher QOL. Lymphoma patients should be counseled on exercise, and studies of activity interventions and outcomes are needed.

8556 Poster Session (Board #374), Sun, 8:00 AM-11:30 AM

A new class of anti-cancer drugs targeting the tyrosine kinase receptor ROR1 in CLL. *First Author: Hakan Mellstedt, Karolinska Univer. Hosp. Solna, Stockholm, Sweden*

Background: RTK families are attractive therapeutic candidates. One of the families is the ROR receptors. ROR1 is of importance during embryogenesis but down-regulated in most adult human tissues.ROR1 has been shown to be expressed in CLL as well as in other hematological malignancies and solid tumors and is constitutively phosphorylated. ROR1 siRNA transfection of CLL cells induced apoptosis. We have produced and explored the activity of a new class of compounds, acting as inhibitors of phosphorylation of the tyrosine kinase domain of ROR1 (ROR1-TKI). We describe for the first time the activity of a lead ROR-TKI, KAN0439834. **Methods:** ROR1 inhibitors were derived from a high-through-put screen (HTS) using HTRF assay based on recombinant intracellular kinase domain of ROR1. A chemical lead series was optimized for activity on target, in vitro ADME and in vivo pharmacokinetic properties. **Results:** KAN0439834 induced apoptosis in vitro of fresh CLL cells from patients with non-progressive and progressive disease as well as from patients with fludarabine resistant disease with and without 17p abnormalities (EC50 for CLL cells $<$ 200 nM and for normal PBMC $>$ 14 μM). In vitro incubation resulted in dephosphorylated ROR1, Src, PIKδ, AKT, mTOR and CREB. 6 h incubation was sufficient to induce full apoptosis at 24 h. In NOD-SCID mice xenografted with human CLL cells orally bioavailable KAN0439834 induced a significant reduction of ROR1$^+$cells, dephosphorylated pROR1, downregulated Mcl-1 and upregulated cleaved PARP. PK analyses showed a blood concentration of KAN0439834 to be sufficient to induce apoptosis of CLL cells. Minimal animal toxicity could be noted. **Conclusions:** The RTK ROR1 is expressed in CLL cells and of importance for survival. Targeting ROR1 by a TKI induced a strong killing of leukemic cells in vitro. The drug dephosphorylated ROR1 as well as PI3K/AKT/mTOR. In an animal CLL model the lead ROR1 inhibitor compound significantly reduced xenotransplanted CLL cells with minimal animal toxicity. This is a first report of a novel class of candidate drugs targeting ROR1. The candidate drug will be further evaluated in preclinical in vivo efficacy and safety models before proceeding to clinical evaluation.

8557 Poster Session (Board #375), Sun, 8:00 AM-11:30 AM

BRD4 degraders produce long-lasting loss of BRD4 Ppotein and robust efficacy in Burkitt's lymphoma cells. *First Author: Kevin Coleman, Arvinas, New Haven, CT*

Background: We have created specific BRD4 degraders using PROTAC (PROteolysis TArgeting Chimera) technology. This involves creating bifunctional molecules, with one end having a ligand for BRD4 and the other end a recruiting element for the E3 ligase cereblon. These PROTACs promote the interaction of BRD4 with cereblon, resulting in its degradation via the proteasome degradation machinery. **Methods:** Treatment of NAMALWA, Ramos, CA-46 and Daudi Burkitt's lymphoma cells with BRD4 PROTACs leads to rapid loss of BRD4, with near complete loss observed within 4 hours. This effect is potent and long lasting, with the most effective molecules having DC_{50}s in the pM range, and with 1 hour treatment of cells resulting in BRD4 loss over a 3 day period. We examined the functional effects of BRD4 PROTACs in several Burkitt's lymphoma cell lines, comparing their effects to those observed with the clinical BRD4 inhibitor OTX015. **Results:** We found that treatment of cells with the BRD4 inhibitor OTX015 led to a rapid and robust hyper-accumulation of BRD4 that, together with the reversible nature of binding to BRD4, may have accounted for the observed moderate suppression of MYC expression, modest inhibition of cell proliferation and lack of cellular apoptosis. In contrast, BRD4 PROTACs maintained suppression of BRD4 protein throughout the several day experiment, maintained near complete MYC suppression and caused both pronounced suppression of proliferation and robust apoptotic responses, as measured by PARP cleavage. **Conclusions:** These data imply that degradation of BRD4 can provide a more robust therapeutic approach to MYC-driven hematological cancers.

8558 Poster Session (Board #376), Sun, 8:00 AM-11:30 AM

A phase 1 study of INCB040093, a PI3Kδ inhibitor, alone or in combination with INCB039110, a selective JAK1 inhibitor: Interim results from patients (pts) with relapsed or refractory (r/r) classical Hodgkin lymphoma (cHL). *First Author: Andres Forero-Torres, University of Alabama at Birmingham, Birmingham, AL*

Background: Efficacy of treatment options for pts with r/r cHL is limited. Evidence suggests blocking the PI3K or JAK-STAT pathways may be efficacious in cHL directly and through modulation of the tumor microenvironment. Blocking both pathways may provide synergistic efficacy. **Methods:** Adult pts with r/r B-cell malignancies were enrolled in this ongoing open-label, dose escalation study. INCB040093 was given at doses of 100–300 mg QD or BID alone or 150–300 mg QD or BID with INCB039110 400–600 mg QD. Safety, efficacy, and pharmacodynamics were evaluated. Data from the r/r cHL pts are reported herein. **Results:** A total of 17 pts with r/r cHL have been enrolled: median age = 34 yrs, 59% men, median of 5 prior regimens, 82% underwent HSCT, and all had failed brentuximab vedotin. Median exposure was 209 days (range: 22+ [ongoing] – 388). The most common nonhematologic AEs (all grades) in this cHL cohort were fatigue (41%), headache (35%), and decreased appetite (35%). One nonhematologic grade $\geq$ 3 AE occurred in $>$ 1 pt, pneumonia (12%). All grade neutropenia, thrombocytopenia, and anemia occurred in 47%, 47%, and 41%, respectively. Grade $\geq$ 3 thrombocytopenia occurred in 18%. Of 6 evaluable pts receiving INCB040093, ORR was 50% (1 CR); of 9 evaluable pts receiving INCB040093 + INCB039110, ORR was 67% (2 CRs). In this limited dataset of proximate dose cohorts, a dose response in efficacy was not evident. In the overall study population, INCB040093 100 mg BID and INCB040093 100 mg BID + INCB039110 400 mg QD were selected for expansion based on pharmacodynamics and the safety profile of higher dose levels. At the selected doses, ORR in the cHL cohort was 50% for INCB040093 and 75% (1 CR) for INCB040093 + INCB039110. **Conclusions:** INCB040093 $\pm$ INCB039110 was tolerable in this heavily pretreated population of pts with r/r cHL. Although the number of evaluable pts is limited, efficacy compares well to approved and promising investigational agents. These results warranted further investigation of INCB040093 alone and in combination with INCB039110 in pts with r/r cHL, leading to the initiation of a phase 2 study. Clinical trial information: NCT01905813.

8559 Poster Session (Board #377), Sun, 8:00 AM-11:30 AM

High throughput in vitro combination sensitivity screen in hematologic malignancies with the phosphoinositide-3 kinase (PI3K)-δ,γ inhibitor, duvelisib. *First Author: Kerrie Faia, Infinity Pharmaceuticals, Cambridge, MA*

Background: Signaling via PI3K-δ and PI3K-γ has distinct and complementary effects on the tumor cell/ tumor microenvironment in hematologic malignancies (HM). Duvelisib (IPI-145) is an orally active inhibitor of the PI3K-δ and PI3K-γ isoforms in clinical development in HM. To gain mechanistic insights into the cellular response to duvelisib and identify novel pairings for duvelisib in HM, a high-throughput in vitro combination screen was conducted. **Methods:** Duvelisib was evaluated alone and in combination with 35 compounds comprising a diverse panel of standard-of-care agents and emerging drugs in development for HM. These compounds were tested in 20 cell lines including diffuse large B-cell (DLBCL), follicular, T-cell, and mantle cell lymphomas, and multiple myeloma. Growth inhibition (GI) was measured by ATPLite (Perkin Elmer) in a 6x6 or 9x9 dose combination matrix. **Results:** Single agent activity was seen in 14 cell lines treated with duvelisib, with a median GI_{50} of 0.59 μM. A scalar measure of the strength of synergistic drug interactions (Synergy Score) was devised and filtering on scores exceeding the mean self-cross plus twice the standard deviation revealed a synergy hit rate of 19.3% across the matrix of drug combinations and cell lines. Synergy was most prominent in DLBCL and follicular lymphoma cell lines and seen with approved and emerging drugs used to treat HM, including, but not limited to, dexamethasone, inhibitors of the B-cell receptor signaling pathway, such as ibrutinib, and the BCL-2 inhibitor venetoclax (ABT-199). In select cell line GI studies and in vivo DoHH2 lymphoma murine xenograft models, the combination of selective PI3K-δ and PI3K-γ inhibitors showed enhanced effects compared to either inhibitor alone. Combination effects with select drugs and duvelisib were also seen in DoHH2 murine xenografts. **Conclusions:** These studies support enhanced activity of combined PI3K-δ and PI3K-γ inhibition in lymphoma models and identified synergistic pairings with the PI3K-δ and PI3K-γ inhibitor, duvelisib. These results provide a rationale for exploring the combination of duvelisib and other therapeutic agents in clinical studies.

8560 Poster Session (Board #378), Sun, 8:00 AM-11:30 AM

Early high-dose therapy and autologous stem-cell transplantation in angioimmunoblastic T-cell lymphoma: Outcome study using the National Cancer Data Base. *First Author: Pawan Kumar Karanam, Gundersen Health System, Lacrosse, WI*

Background: Angioimmunoblastic T-cell lymphoma (AITL) is a rare aggressive non-Hodgkin lymphoma with a poor outcome. The role of high-dose therapy followed by autologous stem-cell transplantation as a consolidation strategy (early SCT) remains undefined. We studied the outcome of AITL patients who received early SCT using the National Cancer Data Base (NCDB). **Methods:** Patient level data were obtained from the NCDB Participant User File. The NCDB collects hospital cancer registry data representing 70% of newly diagnosed cancer cases in the US population. We identified AITL patients (ICD-O: 9705) diagnosed in 1998-2011 for demographics, disease and treatment characteristics. We included patients diagnosed from 1998-2006 in the overall survival (OS) analyses. Patients who received SCT as part of their first course of treatment were considered to have early SCT. **Results:** From 1998-2011, 515,026 patients were diagnosed with NHL and 3,160 (0.6%) had AITL. The median age at diagnosis was 69 years (range, 18-90+) and 52.8 % were males. The stage distribution was as follows: I (5.8 %), II (6.7%), III (35.4%), IV (34.8%), and unknown (17.3%). The median overall survival (OS) for the entire cohort was 17.7 months. Compared to those diagnosed in 1998-2000, patients diagnosed in 2001-2003 (HR: 1.09; 95% CI: 0.94-1.28) and 2004-2006 (HR: 0.99; 0.86-1.16) had similar OS. There were 201 patients (6.4%) who received early SCT. The use of early SCT steadily increased over time from 1.0% in 1998 to 9.5% in 2011 ($P < 0.001$). The unadjusted OS was superior among patients who had early SCT (median 94.8 versus 16.7 months; HR: 2.46; 1.68-3.60). On multivariable analysis, age > 70 years (HR: 1.65; 1.40-1.95), Black race (HR: 1.35; 1.10-1.67), stage III/IV (HR 1.24; 1.04-1.50) and not having early SCT (HR 1.89; 1.28-2.79) were associated with inferior OS. **Conclusions:** This is the largest series of AITL reported to date. The OS remains poor and has not improved during the study period. The use of early SCT has increased ten-fold in the past decade. Early SCT may improve long term outcome and warrants further evaluation.

8561 Poster Session (Board #379), Sun, 8:00 AM-11:30 AM

Association of hemophagocytic lymphohistiocytosis (HLH) with poor outcomes in adults with NK- and T-cell lymphoma (NKTCL). *First Author: Mithun Vinod Shah, Mayo Clinic, Rochester, MN*

Background: HLH is a rare life threatening disorder characterized by extreme activation of immune system. In adults, HLH may be secondary to malignancies, including NKTCL. There is limited knowledge about the differences in presenting features and outcomes of patients with NKTCL when associated with HLH and in those without HLH. **Methods:** All adult patients diagnosed with HLH per HLH-04 criteria seen at Mayo Clinic, Rochester were identified. Cases of NKTCL-associated HLH comprised of those with biopsy-proven NKTCL and a diagnosis of HLH within 1 month of each other. The comparison cohort comprised of adult patients with newly diagnosed NKTCL without HLH enrolled on the University of Iowa/Mayo Clinic Lymphoma SPORE prospective study. The study was approved by Mayo Clinic IRB. **Results:** We identified 20 patients with NKTCL-associated HLH; median age at diagnosis was 61 years, and 80% were male. At diagnosis, median serum ferritin was 4392 mcg/L (range, 1409-107100). In contrast to 147 NKTCL patients without HLH identified from the SPORE study, patients with NKTCL-associated HLH were more likely to be males, and have low serum albumin, high LDH, elevated creatinine, and ECOG performance status ≥ 2 at presentation. Of the 20 patients with NKTCL-associated HLH, 7 received CHOP, 4 received etoposide in addition to CHOP, and 5 received other intensive chemotherapy. Two patients received therapy according to the HLH-04 protocol, and 2 did not receive any NKTCL- or HLH-specific treatment. The median OS for NKTCL-associated HLH was 2.3 months vs. 45.1 months for NKTCL without HLH ($p < 0.0001$). After a median follow-up of 1.4 months, 14 (70%) patients with NKTCL-associated HLH had died. Death was secondary to progressive lymphoma in 12 (86%) patients. After adjusting for International Prognostic Index (IPI), the diagnosis of HLH in patients with NKTCL was independently associated with significantly shorter survival (HR = 8.5, $p < 0.0001$). **Conclusions:** Adult patients with NKTCL-associated HLH have an extremely poor outcome, even after adjusting for the IPI score. Standard therapy for NKTCL-associated HLH is ineffective and novel approaches are needed.

8562 Poster Session (Board #380), Sun, 8:00 AM-11:30 AM

Role of radiation (RT) in primary mediastinal large B-cell lymphoma (PMBCL): An analysis of the Surveillance, Epidemiology, and End Results (SEER) database. *First Author: Smith Giri, The University of Tennessee Health Science Center, Memphis, TN*

Background: In the rituximab era, patients with PMBCL demonstrate high complete remission rate and a plateau in survival curve beyond 2-3 years. The use of RT in these young patients may predispose to the risk of cardiopulmonary toxicities and secondary malignancies. **Methods:** We used SEER 18 database and histology code 9679/3 to identify adult patients with PMBCL between 1973 and 2011. FDA approved rituximab for diffuse large B cell lymphoma in 2006. Hence, using the year 2006 as a cutoff, we compared the survival differences among patients treated with and without radiotherapy. Kaplan Meier survival curves with log rank test were plotted to compare survival statistics. Chemotherapy regimen could not be ascertained. Cox proportional hazard regression model was done to adjust for other covariates including age, year of diagnosis, race, Ann Arbor stage and gender. All p-values were two-sided and level of significance was chosen at 0.05. **Results:** Of 358 PMBCL patients, 50.5% patients (n = 181) received RT. Those who received radiation were more likely to be younger than 50 years (90% vs. 81%, p = 0.01) but were similar in terms of gender, race and stage at diagnosis. The unadjusted five-year overall survival (OS) was higher for RT vs. non-RT group (84% vs. 74%, p = 0.02). When stratified by year of diagnosis, OS was higher for RT vs. non-RT group in pre-rituximab era (before 2006) but not in post-rituximab era (after 2006). In multivariate analysis, RT remained an independent predictor of improved OS in pre-rituximab era (HR 0.36; 95% CI 0.17-0.79; p = 0.01) but not in post-rituximab era (HR 0.96; 95% CI 0.45-2.05; p = 0.93) after adjusting for age, year of diagnosis, gender, race and stage at diagnosis. **Conclusions:** Our study suggests that the effect of rituximab may reduce the benefit of RT in select patients such as patients treated with R-EPOCH or those with important risk factors for breast cancer/coronary artery disease. However, select patients such as those with large masses, positive PET scan after chemotherapy or those treated with R-CHOP may still benefit from RT. Resolving these questions is an important topic for future research.

8563 Poster Session (Board #381), Sun, 8:00 AM-11:30 AM

Outcomes of anticoagulant (AC) or antiplatelet (AP) use in patients (pts) with chronic lymphocytic leukemia (CLL) or indolent non-Hodgkin's lymphoma (iNHL) in idelalisib (IDELA) trials. *First Author: Jacqueline Claudia Barrientos, Hofstra North Shore - LIJ School of Medicine, New Hyde Park, NY*

Background: IDELA, a selective oral PI3Kδ inhibitor, is approved for use in relapsed CLL (in combination with rituximab [R]) and iNHL (as monotherapy). Both diseases occur mainly in the elderly, who have comorbidities that increase thrombotic risk. This post hoc analysis characterized the use and outcomes of AC/AP therapy, which was allowed in IDELA registrational clinical trials. **Methods:** In the phase 3 Study 312-116 (NCT01539512), frail pts with relapsed CLL (including those with any degree of thrombocytopenia) were randomized to receive a combination of continuous IDELA 150 mg BID or placebo (PBO) with 8 R doses. In the phase 2 Study 101-09 (NCT01282424), pts with refractory iNHL received IDELA 150 mg BID until disease progression or unacceptable toxicity. Grade 1, 2, and ≥3 bleeding events were analyzed using MedDRA preferred terms and CTCAE. **Results:** The 2 trials included 343 pts. In the CLL study, 18 pts (16%) on IDELA + R and 31 (29%) on PBO + R had grade ≥3 thrombocytopenia at baseline. Concomitant AC/AP use was frequent (45% in each study); the most common were aspirin, enoxaparin, and warfarin. AC/AP use was more frequent in pts treated with IDELA + R vs PBO + R. The incidence of bleeding events was similar with IDELA, IDELA + R, and PBO + R. Grade ≥3 bleeding events occurred in 1 IDELA + R, 1 PBO + R, and 3 IDELA pts. **Conclusions:** AC/AP use involved 45% of the IDELA registrational trial population. Overall, rates of bleeding events were moderate and similar with IDELA + R vs IDELA + PBO; grade ≥3 events were uncommon. There was no specific trend with regard to AC/AP and bleeding events in the 2 arms of the CLL study. Clinical trial information: NCT01282424 and NCT01539512.

	CLL		iNHL
n (%)	IDELA + R n=110	PBO + R n=108	IDELA Monotherapy n=125
Pts receiving AC/AP	60 (55)	38 (35)	56 (45)
Aspirin	42 (38)	21 (19)	30 (24)
Enoxaparin	11 (10)	6 (6)	19 (15)
Warfarin	8 (7)	9 (8)	11 (9)
Pts with ≥1 bleeding event (any grade)			
Overall	15 (14)	20 (19)	17 (14)
Grade 1/2	14 (13)	19 (18)	14 (11)
Pts on AC/AP	n=60	n=38	n=56
Event at any time	10 (17)	6 (16)	14 (25)
Event on AC/AP	7 (12)	5 (13)	8 (14)
AC at any time	9	4	13
AP at any time	5	3	6
Patients not on AC/AP	n=50	n=70	n=69
Event at any time	5 (10)	14 (20)	3 (4)

8564 Poster Session (Board #382), Sun, 8:00 AM-11:30 AM

The outcome of ALK positive and ALK negative anaplastic large cell lymphoma (ALCL) following DA-EPOCH. *First Author: Catherine Lai, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: Systemic anaplastic large cell lymphoma (ALCL) is a clinically and molecularly heterogeneous type of peripheral T-cell lymphoma (PTCL). It may be sub-divided into cases with or without translocation of the anaplastic lymphoma kinase gene (*ALK*), leading to overexpression of ALK. While the outcome for patients with ALK positive ALCL - particularly in pediatric patients - has been very favorable following doxorubicin-based therapy, ALK negative cases have fared more poorly. Approaches such as autologous transplantation have been studied in this group in an attempt to improve outcome (d'Amore et al. J Clin Oncol. 2012). **Methods:** 23 patients with newly diagnosed ALK positive (15) and ALK negative (8) ALCL underwent treatment with 6 to 8 cycles of dose-adjusted infusional etoposide, vincristine and doxorubicin with prednisone and cyclophosphamide (DA-EPOCH). Both groups had similar IPI characteristics (shown below). **Results:** 19/23 (83%) patients achieved CR or CRu; 3/23 (13%) a PR and 1 patients had PD. At the median potential follow-up time of 13 years, event free survival (EFS) in ALK positive and ALK negative ALCL was 72% and 62.5% ($p = 0.50$) and overall survival was 76% and 87.5% ($p = 0.82$), respectively. Toxicity was assessed on all 135 cycles. Neutropenic fever and thrombocytopenia $< 25{,}000/mm^3$ occurred on 10% of cycles, respectively. Absolute neutrophil count (ANC) less than 500 cells/mm^3 occurred on 35% of cycles. **Conclusions:** Following DA-EPOCH, the outcome of ALK negative ALCL is equivalent to ALK positive ALCL. The incorporation of etoposide, infusional scheduling and dose adjustment may play important roles in ALCL therapeutics. DA-EPOCH should be considered a reasonable front-line regimen in ALCL and especially in older patients where approaches such as transplantation may not be feasible. Clinical trial information: NCT00001337.

Characteristics	All Patients (N = 23)	ALK + ALCL (N = 15)	ALK – ALCL (N = 8)
Median age (range)	38 (19-68)	36 (19-68)	43 (27-60)
Male sex	16 (70%)	9 (60%)	7 (87%)
Stage III or IV	17 (74%)	12 (80%)	5 (62%)
Elevated LDH	12 (52%)	8 (53%)	4 (50%)
Extranodal sites	12 (52%)	8 (53%)	4 (50%)
Bone/Bone marrow	5 (22%)	3 (20%)	2 (25%)
Lung	5 (22%)	3 (20%)	2 (25%)
Bowel	3 (13%)	2 (13%)	1 (12%)
IPI ≥ 2	14 (61%)	10 (67%)	4 (50%)

8565 Poster Session (Board #383), Sun, 8:00 AM-11:30 AM

Phase II study of rituximab plus high-dose ara-C (HDAC)-containing chemotherapy (CTX) followed by ASCT in untreated mantle cell lymphoma (MCL): Japan Clinical Oncology Group study (JCOG0406). *First Author: Michinori Ogura, National Hospital Organization Suzuka National Hospital, Suzuka, Japan*

Background: Although HDAC-containing CTX with rituximab (R) followed by high-dose CTX (HDC) with autologous stem cell transplantation (ASCT) has been recommended in younger untreated MCL patients (pts), no standard regimen has been established. **Methods:** Eligibility criteria included untreated MCL; stage II bulky, III or IV; and aged 20 to 65. In R-High-CHOP, doses of CPA and DXR were 1,500 and 75 mg/m^2, respectively. Pts received 1 cycle of R-High–CHOP followed by 3 cycles of CHASER {CPA 1,200 mg/m^2 on day (d)3, Ara-C 2 g/m^2 on d4-5, ETP 100 mg/m^2 on d3-5, R on d1 and d15} every 3 weeks. Peripheral blood stem cells (PBSCs) with $> = 2 \times 10^6$ cells/kg were harvested during CHASER. ASCT was performed to pts in CR or PR after R-High-CHOP/CHASER. HDC of LEED consisted of L-PAM 130 mg/m^2 on d1, CPA 60 mg/kg on d-4 to d-3, ETP 500 mg/m^2on d-4 to d-2. The primary endpoint was 2 yr-PFS. The planned sample size was 45 pts, which provided at least 90% power with the expected 2 yr-PFS of 50%, threshold of 30%, and a one-sided α of 10%. **Results:** From June 2008 to June 2012, 45 pts with a median age of 59 (38-65) yrs were enrolled. The numbers of pts with low-, intermediate- and high-risk group by the simplified MCL International Prognostic Index (MIPI) was 28, 15 and 2. 40 and 35 pts completed induction CTX and HDC. A median number of harvested PBSCs was 3.8 (0.4 to 38.4) x 10^6/kg in treated 43 pts. Among 36 pts with successfully harvested PBSCs, 35 pts completed HDC. At a median follow-up period of 46 (1-71) months among censored pts, 2-yr PFS was 77% (95% CI; 62-87), which met the primary endpoint. 5-yr PFS was 52% (95% CI; 34-68) and 5-yr OS was 71% (95% CI; 51-84). Overall response rate and %CR after induction CTX were 96% and 82%. Most common G4 toxicities were hematologic: %G4 neutropenia and thrombocytopenia were 80% and 0% in R-High-CHOP, 91% and 89% in CHASER, and 94% and 77% in LEED. 4 pts developed secondary malignancies; AML, prostate cancer, DLBCL, and ATL. **Conclusions:** In younger pts with untreated MCL, R-High-CHOP/CHASER/LEED with ASCT demonstrated high efficacy with durable PFS and OS and acceptable toxicity profiles, and is considered to be a standard treatment option. Clinical trial information: 000001220.

8566 Poster Session (Board #384), Sun, 8:00 AM-11:30 AM

Outcome comparison of allogeneic vs. autologous stem cell transplantation in transformed low grade lymphoid malignancies: A meta-analysis of comparative studies. *First Author: Seongseok Yun, University of Arizona, Tucson, AZ*

Background: Low grade lymphoid malignancy is incurable disease with a chronic relapsing disease course, requiring recurrent therapeutic interventions. Stem cell transplantation (SCT) has become the cornerstone in the cure of this disease. While both allogeneic and autologous SCTs have been shown to improve survival compared to conventional chemotherapy, allogeneic SCT is associated with higher treatment related mortality (TRM) and autologous SCT with higher post-transplantation relapse. We report a meta-analysis of the clinical outcomes of allogeneic vs. autologous SCT in patients with transformed low grade lymphoid malignancies. **Methods:** We searched PubMed, MEDLINE, EMBASE and Cochrane databases for comparative studies of allogeneic vs. autologous SCT in adult patients with low grade lymphoid malignancies including follicular lymphoma (FL), chronic lymphocytic lymphoma (CLL), small lymphocytic lymphoma (SLL) and marginal zone lymphoma (MZL). Relative risks (RR) and 95% CI were calculated using random effects models. **Results:** Four comparative studies were retained for the meta-analysis, and a total of 526 patients were included in the analysis. Of these, 124 underwent allogeneic SCT and 402 autologous SCT. Overall survival (OS) was 50.0% vs. 66.4% (RR 1.47, 95% CI 1.17-1.84, p= 0.001), relapse rate 37.3% vs. 35.3% (RR 1.04, 95% CI 0.70-1.55, p= 0.84), and TRM 31.5% vs. 6.7% (RR 4.53, 95% CI 2.89-7.09, $p<$ 0.00001) for allogeneic and autologous SCT, respectively. Previous rituximab treatment or a reduced intensity conditioning regimen prior to SCT did not have independent prognostic impact. **Conclusions:** Autologous SCT may be the better therapeutic option in patients with transformed low grade lymphoid malignancies regardless of previous rituximab treatment or prior SCT conditioning regimens.

8567 Poster Session (Board #385), Sun, 8:00 AM-11:30 AM

Is rituximab sub-optimally dosed in indolent B cell lymphoma? *First Author: Yazeed Sawalha, Cleveland Clinic, Cleveland, OH*

Background: Rituximab (R) pharmacokinetics (PK) are affected by gender, age and weight (Wt) and can affect outcomes in aggressive B cell lymphoma (Pfreundschuh JCO 2014). Less is known about PK of R in indolent B cell lymphoma (iNHL). **Methods:** We analyzed effects of gender, age, Wt, BSA and BMI on outcomes for 303 consecutive patients (pts) at the Cleveland Clinic treated with 1st line R-based regimens for iNHL from 1997-2014. We divided pts into 3 treatment cohorts: R only (N = 119), R + Chemotherapy (CTX) (N = 120) and R-CTX followed by R maintenance (Rm) (N = 64); and by follicular (FL) (N = 184) or non-FL (N = 119) histology. Event-free survival (EFS) was based on date of relapse, progression, transformation, loss of follow-up, initiation of 2nd therapy or death. Characteristics among the 3 cohorts were compared using ANOVA, Chi-square and Fisher's exact tests. Time to event data was summarized using proportional hazards models. Recursive partitioning survival trees were used to find the cut points for continuous variables. **Results:** Characteristics for the entire group were (mean ± SD): age 62 ± 12 yrs, Wt 83 ± 20 kg, BSA 2.0 ± 0.3 m^2, BMI 24.3 ± 5.2, and 49% were male. There were no significant differences in baseline characteristics among the 3 cohorts. An event has occurred in 52%. Cut points determined were Wt ≥ 81.8 kg, BSA ≥ 2m^2 and age ≥ 70. For all pts combined, higher Wt was significantly associated with inferior EFS (HR = 1.75, p = .007) with or without adjustment for gender and age. Univariable analysis by cohort revealed outcome differences only in the R-CTX cohort, with higher Wt associated with lower EFS (HR = 2, p = .008). For FL within the R-CTX cohort, Wt (HR 2.54, p = .003) and BSA (HR 2.02, p = .024) were associated with worse EFS. Elderly females in this group had better EFS (HR = 0.32) though this did not reach statistical significance (p = .098). **Conclusions:** Our results concur with DLBCL studies in which higher Wt was associated with faster R clearance and worse outcomes for R-CTX. As this is not observed in pts after R alone or R-CTX followed by Rm, we hypothesize that higher levels of weekly R and/or prolonged R exposure exceed therapeutic threshold despite more rapid clearance. Pts with iNHL, and FL specifically, treated with R-CTX may be sub-optimally dosed with R.

8568 Poster Session (Board #386), Sun, 8:00 AM-11:30 AM

Relationship of distinct B-cell receptor (BCR) isotype in diffuse large b-cell lymphoma (DLBCL) with ABC and GCB genetic signatures and association with signaling molecules of clinical significance. *First Author: Abid Qureshi, University of Calgary, Calgary, AB, Canada*

Background: DLBCL is a heterogeneous disease. Gene expression profile (GEP) based distinction into ABC and GCB sub-types, provides basis for risk stratification in DLBCL patients. GEP is an intricate platform, which is not routinely available in clinical laboratories. Hence, surrogate markers for distinction between ABC vs GCB subtypes of DLBCL are needed. **Methods:** We used Nanostring nCounter system for gene expression analysis, utilizing RNA from diagnostic biopsy tissues. We correlated, flow-cytometry based BCR-isotype (IgM/IgG) expression with mRNA levels in a series of ABC/GCB related genes (n = 54). We also investigated gene set (n = 48) related to TLR, NF-kB and JAK/STAT pathways to determine, if BCR- isotype expression has distinct influence on specific cell signaling pathways. Median expression for each gene was compared across two BCR isotype groups utilizing fisher's exact test. **Results:** Our cohort (n = 44) comprised of IgG^+ (n = 13; 30%) and IgM^+ (n = 31; 70%) DLBCL patients. BCR-isotype expression showed significant association with specific molecular signature related to cell of origin. IgG expression was linked with GCB genetic profile and IgM expression allied with ABC related genes ($P<$ 0.001), thus confirming a previous single report (*Leukemia. 2011 Apr; 25 (4):681-8*). IgM expression related well with higher median expression of BLNK, LYN, BCL10, CARD 11 ($P<$ 0.001); while SYK/BTK expression showed no significant differences ($P<$ 0.091). In NF-kB pathway, expression levels of p100, p52, IKKα were significantly higher in IgM^+ DLBCL, compared to IgG^+ DLBCL patients ($P<$ 0.001); thus suggesting higher NF-kB activity. Genes related to TLR and PI3K/AKT pathway showed no significant differences between two BCR-isotype groups ($P=$ 0.182). In relation to JAK/ERK/STAT signaling pathway, IgM^+ DLBCL showed significantly higher expression of STAT3/JAK2 genes ($P<$ 0.001). **Conclusions:** Our data stipulates some preliminary observations that BCR-isotype is distinct between ABC and GCB subtypes of DLBCL. We have also shown linkage of BCR-isotype with some critical pathways related to disease biology in DLBCL.

8569 Poster Session (Board #387), Sun, 8:00 AM-11:30 AM

Overall survival in patients with Hodgkin lymphoma: Disparities by insurance status. *First Author: Rahul Parikh, Mount Sinai Beth Israel; Mount Sinai Health System, New York, NY*

Background: The association between insurance status and outcome has not been well established for patients with Hodgkin Lymphoma (HL). The purpose of this study was to examine the disparities in overall survival (OS) by insurance status in a large cohort of patients with HL. **Methods:** We used a prospectively collected nationwide database-the National Cancer DataBase (NCDB) to evaluate clinical features and survival outcomes among patients diagnosed with stage I-IV HL from 1998 to 2011. The association between insurance status, co-variables, and outcome was assessed in a multivariate Cox proportional hazards model. Survival was estimated using the Kaplan-Meier method. **Results:** Among the 76,672 patients with HD within the NCDB, a total of 45,777 patients with stage I-IV disease were eligible for this study, with a median follow-up of 6.0 years. The median age was 39 years (range: 18-90). The insurance status was as follows: 3,247(7.1%) uninsured; 7,962 (17.4%) Medicaid; 30,334 (66.3%) private insurance; 3,746 (8.2%) managed care; 488 (1.0%) Medicare. Patients with unfavorable insurance status (uninsured or Medicaid-insured) were found to be older ($>$ 50), more advanced stage at diagnosis, with higher co-morbidity score, more commonly with "B" symptoms, and lower income and education quartiles (all $p < 0.01$). These patients were also less likely to receive radiotherapy, start chemotherapy promptly ($<$ 30 days from diagnosis), and less commonly treated at academic/research centers (all $p < 0.01$). Patients with unfavorable insurance had a 10-year OS of 37% vs. 80% for those with favorable insurance ($p < 0.01$). When adjusting for all co-variates, unfavorable insurance status was associated with a significantly decreased OS (HR = 3.32; 95% CI, 3.02-3.64, $p <$ 0.01). Unfavorable insurance status steadily increased from 22.8% to 28.8% between 1998 and 2011. **Conclusions:** Our study reveals that HL patients with Medicaid or uninsured status have inferior outcomes than patients with more favorable insurance. To our knowledge, this study represents the largest dataset examining the role of insurance status on survival for patients with HL. Targeting this subset of patients with limited access to care may help improve outcomes.

8570 Poster Session (Board #388), Sun, 8:00 AM-11:30 AM

Distinct early response dynamics of circulating tumor DNA and circulating tumor cells during therapy of B-cell NHL. *First Author: David Matthew Kurtz, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Both circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) have been used for disease monitoring in non-Hodgkin lymphoma (NHL) (Armand BJH 2013; Kurtz ASCO 2014; Roschewski ASH 2014). However, it remains unclear how these compartments compare during induction of active therapy in NHL. Using immunoglobulin high-throughput sequencing (Ig-HTS), we compared the dynamics of ctDNA and CTCs in response to systemic therapy. **Methods:** We performed 206 Ig-HTS assays from 104 serial blood samples in diverse patients with NHL receiving their first cycle of systemic therapy at Stanford University. Tumor samples were used to define tumor specific DNA sequences by Ig-HTS. Identified sequences were used to track ctDNA and CTCs. **Results:** A total of 17 patients with NHL were enrolled (DLBCL = 10, FL = 3, transformed FL = 4). All patients received Rituximab-containing regimens. In patients with high-grade disease, CTCs and ctDNA decreased by a mean of 94% (61%-100%) and 95% (68%-100%) after 1 cycle of therapy respectively. CTCs and ctDNA became undetectable in 7/10 and 5/11 patients by cycle 2. However, a dramatic increase or 'spike' was seen in ctDNA levels within hours of Rituximab (median increase 8.0x, range 0.3x to 264x). In contrast, a dramatic decrease was seen in CTCs (median decrease 72%, range -23% to 93%), indicating their rapid clearance. This ctDNA spike was observed in 6/6 FL/tFL patients, but only 1/5 DLBCL patients ($p =$ 0.02). The size of the ctDNA spike was significantly associated with the burden of pretreatment CTCs ($p < 0.001$) and the magnitude of decrease in CTCs ($p < 0.001$), but was not associated with the pretreatment ctDNA level ($p = 0.88$). Four of eight patients achieving CR and 2/3 patients not achieving CR had a spike in ctDNA ($p = 1.0$). **Conclusions:** While ctDNA and CTCs can be used to monitor NHLs, their dynamics in response to therapy are distinct. Although both clear during therapy, a rapid increase in ctDNA is seen in response to Rituximab, indicating cell death of CTCs. This ctDNA spike is associated with therapeutic effect on CTCs, but not with outcome in this small cohort. Circulating tumor DNA is a potentially useful method to measure cell death in NHL and other malignancies.

8571 Poster Session (Board #389), Sun, 8:00 AM-11:30 AM

Effect of prednisone and rituximab prephase on early toxicity in older DLBCL patients (pts) receiving RCHOP within a NHL specific comprehensive geriatric assessment (CGA) trial. *First Author: Colette Ngozi Owens, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Older pts with DLBCL are increasing in the US and are most vulnerable to treatment related toxicities and mortality (TRM). Effective tools to predict and mitigate toxicity are essential in these pts. The RICOVER-60 trial implemented a "pre-phase" of vincristine and prednisone (Pred) to reduce disease symptoms and improve KPS, reporting decreased early TRM. This prospective pilot study in older DLBCL pts employs a pre-phase of Pred and rituximab (R) as part of a larger CGA validation study in NHL (n = 200; NCT01829958). **Methods:** Eligible pts (n = 30) had de novo DLBCL/tDLBCL, age $\geq$ 70 yrs or $\geq$ 60 yrs with KPS $<$ 80%, and planned RCHOP-like therapy for 2+ cycles. CGA consisted of CARG and CRASH scores as largely self administered assessments. CGA was assessed at baseline, post pre-phase, with each cycle, and at end-of-therapy. Pre-phase included Pred 50-100mg x 5-10 days and R 375mg/m2 x1 day completed in the 14 days pre-RCHOP. The study is powered to show a 15% change in CGA risk score, with secondary endpoints of toxicity, TRM, PFS/OS. **Results:** Of 30 pts: median age 75 (range 65-85), female 59%, DLBCL 87%, Stage III/IV 60%, aaIPI high-int/high 57%, cell of origin GC/non-GC 55%/45%, median ki67 70% (range 60-90%). 97 % completed pre-phase and 2+ cycles of chemotherapy. Median followup is 6m (range 1-18m) with 28/30 pts alive. **Impact of pre-phase:** KPS median increased from 70% to 80% ($p = .057$)post pre-phase; Timed up-and-go was not significantly changed ($p = .484$), but 4/7 normalized post-pre-phase; Pre-phase therapy (n = 29) improved CGA risk scores compared to baseline ($p = .024$). CGA predicted risk of G3+ toxicity was 65%(range 32-89%). Toxicity risk score reduced in 31% (9/29) pts, mean 16% risk reduction for G3+ toxicity. Focusing on early toxicity (C1-C3), actual non-heme grade 3+ events were 41% and heme G4+ events 16%. Hospitalization occurred in 37%. There was no reported TLS or early TRM (n = 30). 1 pt pursued hospice after pre-phase. **Conclusions:** A pre-phase intervention of Pred and R may mitigate early toxicity, resulting in improved KPS and CGA risk score, with no TLS or early TRM in this pilot. Clinical trial information: NCT01829958.

8572 Poster Session (Board #390), Sun, 8:00 AM-11:30 AM

Prognostic value of interim 18F-FDG PET/CT in patients with diffuse large B-cell lymphoma treatment with R-CHOP: SUVmax reduction-based assessment at two cycles of chemotherapy. *First Author: Xu Zhang, Sun Yat-Sen University Cancer Center, Guagnzhou, China*

Background: The prognostic value of interim positron emission tomography/computer tomography (PET/CT) interpreted according to visual criteria is a matter of debate in diffuse large B-cell lymphoma (DLBCL). The purpose of this study was to investigate whether maximal standardized uptake value reduction (△SUVmax) may help to improve the prognostic value of PET/CT, compared with Deauville criteria, after 2 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). **Methods:** To compare the prognostic value of both methods, we analyzed PET/CT done at baseline and after 2 cycles of R-CHOP in 306 DLBCL patients enrolled on this retrospective study. All images were reviewed and interpreted visually according to the Deauville criteria (as negative or positive), and by computing △SUVmax for positive patients. Optimal cutoff to predict progression was 58%. Survival curves were estimated using Kaplan–Meier analysis and compared using the log-rank test. **Results:** By the Deauville criteria, the rate of 2-yearprogression-free survival (PFS) for patients with negative and positive PET/CT was 79.1% and 30.9%, respectively ($p < 0.001$). For positive patients according to Deauville criteria, △SUVmax analysis ($> 58\%$ vs $\leq 58\%$) identified patients with significantly different outcomes (2-year PFS:64.5% vs 15.9%, $p < 0.001$;2-year OS: 83.4% vs. 45.1%, $p < 0.001$). Seventy patients considered as positive by the Deauville criteria could have been reclassified as good responders. **Conclusions:** △SUVmax analysis of interim PET/CT is feasible for DLBCL during first-line chemotherapy and better predicts outcome than Deauville criteria.

8573 Poster Session (Board #391), Sun, 8:00 AM-11:30 AM

A randomized phase II study of bortezomib (Btz)/dexamethasone (dex) with or without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *First Author: Andrzej J. Jakubowiak, University of Chicago Medical Center, Chicago, IL*

Background: Elo, a monoclonal antibody (mAb) targeting Signaling Lymphocytic Activation Molecule F7 (SLAMF7), kills myeloma cells with minimal effects on normal tissue. Elo showed enhanced activity when combined with Btz in a preclinical myeloma model, (van Rhee F, et al. *Mol Cancer Ther* 2009;8:2616–24) and encouraging clinical activity in a Ph 1 study (Jakubowiak A, et al. J Clin Oncol 2012;30:1960–65). This Ph 2 open-label study (NCT01478048, CA204-009) investigated the efficacy and safety of Elo + Btz/dex (Bd) in pts with RRMM. **Methods:** Pts with RRMM, 1–3 prior therapies, were given Elo + Bd (EBd) or Bd in 21-d (Cycles 1–8) or 28-d cycles (9+) to disease progression/unacceptable toxicity. Elo (10 mg/kg IV): wkly Cycles 1–2, D1+11 Cycles 3–8, then D1+15; Btz (1.3 mg/m^2 IV/SC): D1, 4, 8+11 Cycles 1–8, then D1, 8+15; dex 20 mg non-Elo days, 28 mg PO + 8 mg IV Elo days. Primary endpoint: PFS (ITT population). A 2-sided 0.30 significance level was specified (80% power, 103 events) to detect a hazard ratio (HR) of 0.69. **Results:** 152 pts were randomized; 77 EBd, 75 Bd. At data cut-off (12 Sep 2014), 18% (EBd) vs 10% (Bd) of pts remained on therapy. Discontinuation was mainly for disease progression (52%). Median PFS was 9.7 mo (EBd) vs 6.9 mo (Bd) (HR 0.71; 70% CI 0.58, 0.87; $p = 0.08$). PFS HR, adjusting for prognostic factors, was 0.58 (70% CI 0.47, 0.72; $p = 0.01$). ORR was 66% (EBd) vs 63% (Bd). Early overall survival (OS) results revealed a HR of 0.61 (70% CI 0.43, 0.85); 40 deaths (17 EBd, 23 Bd) were observed, mainly from disease. Common ≥ G3 adverse events (EBd, Bd): thrombocytopenia 7 (9%), 13 (17%); infections 14 (19%), 11 (15%). Infusion reactions (IRs; all grade 1–2, none at max 5 mL/min rate) occurred in 7% of pts with EBd. **Conclusions:** This study met the primary endpoint. PFS was longer with EBd than with Bd (HR 0.71). More pts continue on EBd vs Bd and early OS data favor EBd vs Bd. A low rate of IRs was seen with EBd. In patients with RRMM, Elo, an immunotherapeutic mAb, provides clinical benefit with limited added toxicity when combined with Bd vs Bd alone. Clinical trial information: NCT01478048.

8574 Poster Session (Board #392), Sun, 8:00 AM-11:30 AM

A phase I/IIa study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma (rrMM). *First Author: Marc S. Raab, University Hospital Heidelberg, Heidelberg, Germany*

Background: MOR202 is a HuCAL-derived fully human IgG1 anti-CD38 antibody, with high efficacy in preclinical models of MM. **Methods:** This is an open-label, dose-escalation study (3 + 3 design) to evaluate the safety and preliminary efficacy of MOR202 in adult patients (pts) with rrMM. We present the data of pts previously treated with ≥ 2 prior therapies including an immunomodulatory drug and a proteasome inhibitor. Pts received 2-hour IV MOR202 every 2 weeks (q2w) (8 dose levels [DLs] from 0.01–16 mg/kg) without dexamethasone (DEX), or 4 or 8 mg/kg (DLs 6 and 7), weekly (q1w) +/- DEX. MOR202 16 mg/kg (DL 8) q1w +/- DEX and combination cohorts with lenalidomide (LEN)/pomalidomide (POM) + DEX are planned, as well as confirmation cohorts. **Results:** As of December 31st 2014, 38 pts had been treated; 29 and 9 pts in the q2w and q1w DLs, respectively. Median age was 70 (44–80) yrs. The median number of prior treatment lines was 4 (2–10) for all pts. 36 pts (94.7%) developed AEs. The most frequently reported AEs (> 10%) of any grade were anemia (31.6%), fatigue (28.9%), WBC decreased (21.1%), lymphocyte count decreased (LCD) (21.1%), diarrhea (21.1%), nasopharyngitis (18.4%) and leukopenia (13.2%). Grade ≥ 3 hematologic AEs were LCD (15.8%), WBC decreased (7.9%), leukopenia (5.3%), thrombocytopenia (2.6%) and lymphopenia (2.6%). Infusion-related reactions occurred in 13 pts (34%) receiving MOR202 without DEX, mainly during the first infusion. All were grade 1-2 except for 1 pt grade 3. There have been no treatment-related deaths. PK data demonstrate a significant target-mediated drug disposition effect for most pts treated q2w. In 4/6 pts in the q1w 4 mg/kg cohort MOR202 trough levels show the start of target saturation. Only 1 pt (MOR202 0.15 mg/kg q2w) generated a transient anti-drug antibody response to MOR202. **Conclusions:** The MTD has not been reached. MOR202 is safe and well tolerated. PK data show the potential for full target occupancy in the majority of pts receiving 8 and 16 mg/kg q1w. These latter DLs of MOR202 will be tested as monotherapy or in combination with DEX, LEN + DEX and POM + DEX in the upcoming cohorts. Efficacy analyses are ongoing. Clinical trial information: NCT01421186.

8575 Poster Session (Board #393), Sun, 8:00 AM-11:30 AM

Analysis of outcomes based on response for patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 PANORAMA 1 study. *First Author: Vania T.M. Hungria, Irmandade da Santa Casa de Misericordia de São Paulo, São Paulo, Brazil*

Background: Panobinostat (PAN) is the first pan-deacetylase inhibitor (pan-DACi) to demonstrate a statistically significant and clinically relevant increase in median progression-free survival (PFS) in patients (pts) with relapsed or relapsed and refractory multiple myeloma (MM) in a phase 3 clinical trial. In the PANORAMA 1 trial, pts randomized to receive PAN + bortezomib (BTZ) and dexamethasone (Dex; PAN-BTZ-Dex) demonstrated a median PFS of 12.0 months vs 8.1 months for pts who received placebo + BTZ and Dex (Pbo-BTZ-Dex; HR, 0.63; $P < .0001$). Here, we present a detailed analysis of the effect of response on clinical outcomes. **Methods:** Response outcomes, including rate of near complete/complete response (nCR/CR) and duration of response (DOR), were analyzed. A landmarkanalysis at 6, 12, 18, and 24 weeks using a Cox regression model was conducted to determine PFS in pts who achieved nCR/CR or partial response (PR) per mEBMT and IMWG criteria. **Results:** The nCR/CR rate was significantly higher with PAN-BTZ-Dex vs Pbo-BTZ-Dex (27.6% vs 15.7%; $P = .00006$ post hoc testing).The DOR for pts with nCR/CR and PR was 18.4 and 9.0 months, respectively, in the PAN-BTZ-Dex arm and 14.5 and 8.8 months, respectively, in the Pbo-BTZ-Dex arm. The landmark analysis by mEBMT criteria at 12 weeks demonstrated a median PFS of 16.5 months for pts with CR/nCR and 10.3 months for pts with PR in the PAN-BTZ-Dex arm (HR, 0.40; 95%CI, 0.25-0.65) and a median PFS of 14.1 months for pts with CR/nCR and 9.7 months for pts with PR in the Pbo-BTZ-Dex arm (HR, 0.62; 95%CI, 0.36-1.07). By IMWG criteria, the landmark analysis at 12 weeks demonstrated a median PFS of 15.9 months for pts with ≥ very good PR (VGPR) and 8.1 months for pts with PR in the PAN-BTZ-Dex arm (HR, 0.36; 95%CI, 0.21-0.62) and a median PFS of 14.4 months for pts with ≥ VGPR and 7.6 months for pts with PR in the Pbo-BTZ-Dex arm (HR, 0.39; 95% CI, 0.22-0.68). Similar results were observed the other landmarks tested. **Conclusions:** A higher proportion of pts in the PAN-BTZ-Dex arm achieved higher-quality responses, which are associated with longer PFS. Overall, these data support achievement of higher-quality responses as a treatment goal in relapsed/refractory MM. Clinical trial information: NCT01023308.

8576 Poster Session (Board #394), Sun, 8:00 AM-11:30 AM

Phase I interim safety and efficacy of venetoclax (ABT-199/GDC-0199) monotherapy for relapsed/refractory (R/R) multiple myeloma (MM). *First Author: Shaji Kumar, Mayo Clinic, Rochester, MN*

Background: The anti-apoptotic protein BCL-2 has been implicated in mediating the survival of MM cells. Venetoclax (VEN) is a potent, selective, orally bioavailable small-molecule BCL-2 inhibitor. VEN induces cell death in MM cell lines and primary samples in vitro, especially in t(11;14)-positive (pos) cells, which express a high ratio of *BCL2* to *MCL1*(VEN resistance factor). The current Ph 1 study evaluates safety and efficacy of VEN in pts with R/R MM. **Methods:** Primary objectives are to evaluate safety, PK, and RPTD; other objectives include preliminary efficacy and impact of chromosomal abnormalities. In dose-escalation cohorts, VEN was given PO daily at 300, 600, 900, or 1200 mg after a 2-week dose ramp-up. Pts were monitored for tumor lysis syndrome (TLS). **Results:** As of 12/19/2014, there were 28 pts with median age 65 (12/16 F/M); 9 ISS stage I, 11 stage II, 6 stage III. Median (range) prior therapies: 6 (1–13). 23 had prior bortezomib (15 refractory), 26 lenalidomide (12 refractory), and 13 auto-HSCT. 10 pts were t(11;14)-pos. AEs in ≥20% pts: diarrhea (32%), nausea (32%), neutropenia (21%), fatigue (21%). Grade 3/4 AEs (≥10%): thrombocytopenia (18%), anemia (14%), neutropenia (14%). 7 pts had SAEs, with 1 (epigastric pain) possibly related to VEN. 17 pts have discontinued (D/C): 14 due to PD, 2 for AEs (worsening shortness of breath, hypokalemia), and 1 withdrew consent; 11 still receiving therapy. 2 deaths occurred (both PD). 2 DLTs were seen at 600 mg (cohort was expanded): epigastric pain, nausea with abdominal pain. No pt had TLS. Preliminary PK (n=11; 300 and 600 mg): mean C_{max} and AUC_{24} were ~dose-proportional with high intra-dose variability. 21 of 28 pts were evaluable for preliminary efficacy. Best response by t(11;14) status shown in Table. **Conclusions:** VEN monotherapy was well tolerated in heavily-pretreated R/R MM. Responses (including CR) and longer ToS were observed in t(11;14)-pos pts. RPTD was achieved; study is now enrolling in the safety expansion cohort at 1200 mg (with 2-week ramp-up). Clinical trial information: NCT01794520.

n (%)	t(11;14)-pos (n=7)	t(11;14)-neg (n=14)
CR	1 (14)	0
PR	1 (14)	0
MR	1 (14)	0
SD	2 (29)	9 (64)
PD	1 (14)	2 (14)
D/C	1 (14)	3 (21)
ORR (CR+ PR)	2 (29)	0
Median (range) time on study (ToS)	5.1 (1.2–8.6)	1.9 (0.4–6.8)

8577 Poster Session (Board #395), Sun, 8:00 AM-11:30 AM

The prognostic significance of CD45 expression by clonal bone marrow plasma cells in multiple myeloma. *First Author: Wilson I. Gonsalves, Mayo Clinic, Rochester, MN, Rochester, MN*

Background: Evaluation of clonal plasma cells (cPCs) in the bone marrow (BM) of multiple myeloma (MM) patients (pts) reveals two distinct cPC populations based on CD45 expression, i.e. CD45- and CD45+. We explored the prognostic significance of CD45 expression by cPCs in the BM of MM pts using flow cytometry. **Methods:** All MM pts seen at the Mayo Clinic, Rochester from 2009 to 2011 who had BM PCs evaluated by flow cytometry were included. For flow cytometry, a 6-color method was used with each sample stained with antibodies to CD45, CD19, CD38, CD138 and cytoplasmic Kappa and Lambda Ig light chains. Samples where > 20% of the cPCs detected expressed CD45 were classified as CD45+ and the rest were CD45-. Survival analysis was performed by the Kaplan-Meier method and differences assessed using the log rank test. **Results:** There were 604 consecutive MM pts who had their BM PCs evaluated by flow cytometry. Of these pts, 156 were newly diagnosed and 448 were previously treated with systemic therapy. Among newly diagnosed pts, the median follow up was 42 mos and 41 pts (27%) had high risk disease by FISH. The median time to next therapy (TTNT) for pts in the CD45+ group was 12 mos (n = 26, 17%) versus 29 mos for pts in the CD45- group (n = 130, 83%) (P = 0.002). The median overall survival (OS) for pts in the CD45+ group was 23 mos versus not reached for the CD45- group (P < 0.001). Among previously treated pts, the median follow up was 44 mos and 45% had a prior ASCT. There were 240 previously treated pts that were actively relapsing at the time of their bone marrow analysis. The median OS for actively relapsing pts classified as CD45+ was 11 mos (n = 61, 14%) versus 29 mos (n = 386, 86%) for CD45- (P < 0.001). In a multivariable analysis, CD45+ status and PCLI > 3 were independent predictors of worse OS among the newly diagnosed and actively relapsing pts. Increasing age and elevated LDH were independent predictors of worse OS in newly diagnosed and actively relapsing pts, respectively. **Conclusions:** The presence of > 20% cPCs in the BM expressing CD45 appears to bear negative prognostic value in newly diagnosed and actively relapsing MM pts. This may be a surrogate for a more aggressive phenotype of MM.

8578 Poster Session (Board #396), Sun, 8:00 AM-11:30 AM

Outcome at first relapse after frontline RVD regimen plus lenalidomide maintenance in transplant eligible MM patients. *First Author: Murielle Roussel, Hematology Department, IUCT Oncopole- CHU Purpan, Toulouse, France*

Background: The IFM 2009 trial recruited 700 MM pts between 2010-2012. Pts were randomly assigned to received RVD (5-8 cycles) and 1-yr Len maintenance +/- upfront ASCT. More than 250 pts relapsed. We aimed to analyze response rates (RR) and survival outcomes after salvage therapy. **Methods:** Pts who relapsed during RVD cycles or first 2 months of maintenance (group 1) were considered Relapsed and Double Refractory and were likely to receive CVAD or DCEP regimen. Pts who relapsed during or early after maintenance (Group 2) were considered Relapsed and Len Refractory and were likely to receive VCD, CPAD or pomalidomide based regimen (PCD). Pts who relapsed during FU (Group 3) were standard Relapsed. Eligible pts could receive SCT (auto and/or allo). **Results:** 83 pts were retrospectively analyzed. Median age was 56 years (28-65), ISS 2/3=37/22. 27 pts had High Risk (HR) cytogenetics. Group 1 comprised 15 pts (10 relapsed during RVD induction/consolidation). Eight pts received CVAD, 3 DCEP and 1 PD. Three pts died before any tx. Group 2 comprised 40 pts; 14 received VCD, 8 CPAD, 4 DCEP and 11 PCD. Group 3 comprised 28 pts; 12 received VCD, 3 CPAD and 11 PCD. RR and survival outcomes are listed in table 1. ORR was 40, 67.5 and 75% in groups 1,2,3, respectively. 46 pts proceeded to SCT (allo, n = 5). Median FU is 42 months from initial therapy: 64% pts relapsed again and 29% died. Median PFS2 is 11 months and 3-year OS 74%. Pts from group 1 had the poorest prognosis with 60% death, median OS 11.7 months. Median PFS2 was 3.5 months. **Conclusions:** Relapsed pts within 1 year after RVD induction/consolidation have impaired prognosis after salvage therapy.

	Salvage Tx	n	ISS 2/3	PFS 1 mos	BRA	SCT	Relapse 2	PFS 2 mos	Death	3-y OS
1 Double Refractory	all	15	3/6	7.2	CR2/VGPR1/PR3	8 (57%)	9* (60%)	3.5	9 (60%)	40%
	CVAD	8	1/4	7.2	CR 1/PR 3	6	6	2.6	3	62,5%
	DCEP	3	2/1	3.0	CR 1/VGPR 1	2	2	5.0	2	-
2 Len Refractory	all	40	21/10	15	CR 10/VGPR 9/ PR 8	25 (62.5%)	30 (75%)	13.2	13 (32.5%)	70.5%
	VCD	14	8/3	13	CR 3/VGPR 3/PR 2	9	12	15.6	5	78.5%
	CPAD	8	4/3	16	CR 3/VGPR 3/PR 2	7	5	13.5	1	87.5%
	DCEP	4	2/1	9.7	CR 2/PR 1	3	3	8.3	2	50%
	PCD	11	6/2	19	CR 1/VGPR 3/PR 3	4	7	9	3	70%
3 Relapsed	all	28	13/6	30	CR 6/VGPR 7/PR 8	13 (46.5%)	14 (50%)	14	2 (7%)	100%
	VCD	12	7/2	25.6	CR 2/VGPR 3/PR 3	6	7		2	90%
	CPAD	3	1/0	30.5	CR 2/PR 1	2	1		0	100%
	PCD	11	5/2	30.9	CR 2/VGPR 3/PR 4	5	4		0	100%

8579 Poster Session (Board #397), Sun, 8:00 AM-11:30 AM

Preliminary safety and efficacy of evofosfamide (TH-302), an investigational hypoxia-activated prodrug, combined with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma (RR MM). *First Author: Jacob Laubach, Dana-Farber Cancer Institute, Boston, MA*

Background: The presence of hypoxia in the diseased bone marrow presents a new therapeutic target for multiple myeloma (MM) (Colla, *Leukemia* 2010). Evofosfamide (EVO; formerly TH-302) is a novel 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide mustard that is selectively activated under hypoxia and is investigated in multiple Phase 1-3 trials. Synergistic induction of apoptosis in MM cells by EVO and bortezomib (Bor) was shown *in vivo* and *in vitro* (Hu et al, *Mol Cancer Ther*2013). An ongoing phase 1/2 study investigates EVO in combination with Bor and dexamethasone (D) in RR MM (NCT01522872). **Methods:** This phase 1/2 open-label multicenter study investigates IV EVO (240-480 mg/m^2), IV or SC Bor (1.3 mg/m^2), plus PO D (40 mg) on Days 1, 4, 8 and 11 of a 21-day cycle. At the maximum tolerated dose, a Simon two-stage optimal design was implemented to pursue a regimen with ≥ 50% response rate or discontinue if ≤ 25% (85% power, 10% alpha). **Results:** Nine patients (pts; 4 male, 5 female) have been reported (3 at 240 mg/m^2 EVO and 6 at 340 mg/m^2 EVO). Pts were heavily pre-treated; median number of prior therapies was 8 (4 – 12). Median age was 57 years (45 – 68). All had previously received Bor and lenalidomide or thalidomide. No pt had a dose limiting toxicity and the recommended phase 2 dose (RP2D) was established at 340 mg/m^2 EVO. The most common ≥ Gr 3 adverse events (AEs) were thrombocytopenia (5 pts), lymphopenia (2 pts), leukopenia (2 pts) and anemia (2 pts). Limited skin toxicity has been observed (2 pts, grade 2 rash or skin lesions). Four pts had SAEs; one SAE of thrombocytopenia was related to EVO. Seven pts discontinued for progressive disease; no pts have discontinued due to an AE. IMWG assessments were 1 CR, 2 PR, 4 SD and 2 PD (1 CR and 2 PRs out of 6 pts at 340 mg/m^2 EVO). Two pts with a CR and PR continue on study. To date, 17 of 24 pts have been enrolled to evaluate safety and efficacy at the RP2D. **Conclusions:** EVO can be administered at 340 mg/m^2 twice a week with Bor and D. Preliminary clinical activity has been noted in pts with heavily pre-treated RR MM. Data from pts treated at the RP2D will be updated and presented at the meeting. Clinical trial information: NCT01522872.

8580 Poster Session (Board #398), Sun, 8:00 AM-11:30 AM

Phase 1b interim results: Venetoclax (ABT-199/GDC-0199) in combination with bortezomib (BTZ) and dexamethasone (Dex) in relapsed/refractory (R/R) multiple myeloma (MM). *First Author: Cyrille Touzeau, CHU de Nantes, Hotel Dieu—HME, Nantes, France*

Background: The anti-apoptotic proteins BCL-2 and MCL-1 promote MM cell survival. BTZ can inhibit MCL-1 activity by elevating the MCL-1 antagonist, NOXA. Venetoclax (VEN) is a selective, orally bioavailable, small-molecule BCL-2 inhibitor, which enhances BTZ efficacy in MM xenograft models. This Ph 1 study evaluates VEN with BTZ and Dex in patients (pts) with R/R MM. **Methods:** Objectives include safety, PK, preliminary efficacy, and MTD of VEN with BTZ and Dex. Pts received VEN (50-500 mg PO daily) in cycles (C) 1-11 per designated dose escalation (DE) cohorts (continual reassessment); BTZ (1.3 mg/m^{2}SC, days [D] 1, 4, 8, 11) and Dex (20 mg PO, D1, 4, 5, 8, 9, 11, 12) in C1-8 (21D), BTZ+Dex D1, 8, 15, 22 in C9-11 (35D), and VEN alone ≥ C12. **Results:** 32 pts were enrolled as of 12/18/2014: median age 65; 12/20 F/M. 12 were ISS stage I, 7 stage II, 10 stage III. Median (range) prior therapies: 5 (1–15). 26 pts received prior BTZ (10 refractory), 26 had prior lenalidomide, and 20 auto-HSCT. AEs in ≥ 20% pts: constipation (41%), diarrhea (38%), peripheral edema (28%), thrombocytopenia (31%), peripheral neuropathy (28%), insomnia (28%), dyspnea (25%), anemia (22%). Grade 3/4 AEs (≥10%): thrombocytopenia (25%), anemia (13%). 14 pts had SAE: none VEN-related. Reason for discontinuation (D/C; n = 17): PD (n = 14), AEs (n = 2: adenocarcinoma, cardiac and respiratory decompensation), consent withdrawal (n = 1). 3 deaths occurred (due to PD); 1 DLT at 300 mg (cardiac decompensation attributed to Dex). No TLS occurred. Dose-normalized exposure when given with BTZ+Dex (n = 30) was similar to VEN alone. Preliminary efficacy (best response) by BTZ status. **Conclusions:** Venetoclax with BTZ and Dex has an acceptable safety profile in heavily pretreated MM. This combination targeting BCL-2 and MCL-1 resulted in anti-tumor activity and longer ToS in pts naïve or sensitive to prior BTZ. DE continues at 600 mg. Clinical trial information: NCT01794507.

n (%)	Refractory (n=10)	Sensitive (n=16)	Naïve (n=6)
sCR	0	1 (6)	0
CR	0	0	2 (33)
VGPR	0	2 (13)	1 (17)
PR	0	7 (44)	2 (33)
MR	1 (10)	0	0
SD	3 (30)	4 (25)	0
PD	4 (40)	1 (6)	1 (17)
D/C	2 (20)	1 (6)	0
ORR (sCR+CR+VGPR+PR)	0	10 (63)	5 (83)
Median (range) time on study (Tos), months	1.3 (0.3–4.8)	5.0 (0.7–9.5)	5.0 (1.4–9.4)

8581 Poster Session (Board #399), Sun, 8:00 AM-11:30 AM

Total marrow irradiation (TMI) with helical tomotherapy and peripheral blood progenitor cell rescue (PBPC) following high-dose melphalan (Mel) and PBPC as part of tandem autologous transplant (TAT) for patients with multiple myeloma. *First Author: George Somlo, City of Hope, Duarte, CA*

Background: Ablative dose total body irradiation (TBI) of 800 cGy in combination with high-dose melphalan (MEL) was found to be too toxic. TMI, an image-guided targeted TBI using TomoTherapy intensity modulated radiotherapy , given as the sole ablative regimen for the second cycle (C) of TAT was tested in patients (pts) with stable (SD)/responsive MM, in a phase I-II trial. Here we provide long-term update on outcome. **Methods:** We enrolled pts with Durie-Salmon stages (DS) I-III MM in response or with SD, who were ≤ 70 years old and ≤ 18 months from diagnosis. Pts received MEL 200 mg/m^2 and AT (C 1), and, after recovery, TMI (MTD : 1600 cGy) and AT (C 2) followed by maintenance with dexamethasone and an IMiD. **Results:** 54 pts started treatment (23 F/31M). The median age was 54 years (31-67). DS stages were:I (N = 4), II (N = 18), III (N = 32). 44 of the 54 pts received TMI (28 of 36 pts enrolled at the MTD received TMI). 10 pts did not receive TMI due to post-MEL toxicities or pt or doctor's choice. The median time between MEL and TMI was 65 days (range 47-125). All pts engrafted. 9/54 (17%) experienced febrile neutropenia (FN) following MEL, and 8/44 (18%) experienced FN after TMI; less frequent grade 3 or 4 non-hematologic toxicities were similar between MEL and TMI. Best responses included CR (N = 22, of which 3 were in CR prior to MEL), very good partial response (VGPR, N = 8, of which 2 were in VGPR prior to MEL) and PR or SD (N = 14). Median follow-up of alive pts is 73 months (27-117). Second malignancies included 2 skin, 1 breast, 1 thyroid carcinoma, and 1 acute myeloid leukemia. In intent-to-treat analysis median PFS for the 54 pts is 52 months (95% CI 34.4-NR), and median OS is not reached. PFS and OS at 5 years is 43% (95% CI 31-59) and 66% (95% CI 54-81), respectively. For pts enrolled at 1600cGy, the PFS and OS at 5 years were 48% (34-69) and 73% (59-90). **Conclusions:** TMI of 1600 cGy is feasible following MEL in MM patients. The long-term safety and PFS/OS are encouraging, and further assessment of TMI is warranted. Clinical trial information: NCT00112827.

8582 Poster Session (Board #400), Sun, 8:00 AM-11:30 AM

Overall survival in newly diagnosed MM patients with del(17p): A report from the Connect MM Registry. *First Author: Jatin J. Shah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Del(17p) is detected in 10%-15% of patients (pts) with MM and is associated with early relapse and short survival. There are limited data, no uniform or optimal treatment (Tx) approach, and questions on role of autologous stem cell transplant (ASCT). Connect MM, a prospective, observational, US, multicenter disease registry, contains the largest cohort of pts with newly diagnosed MM (NDMM) and del(17p). Disease characteristics and OS were analyzed in this cohort. **Methods:** Connect MM was initiated in Sep 2009. Data from pts (diagnosed ≤ 2 mo before study entry) enrolled up to Dec 2011 (N = 1493) at 234 sites were collected at baseline and quarterly thereafter. Outcomes data through Jun 30, 2014 for 1450 treated pts were analyzed. Survival analysis was adjusted for sex, race, therapy received, and ASCT. OS was estimated using Kaplan-Meier methods and comparisons were assessed using the log-rank test. **Results:** Del(17p) was detected (mainly by FISH) in 108 of the 1450 pts (7.4%). Median age was 69 y (range 27-89), 58% were male, 82% were Caucasian, and 33.3% had ISS stage III MM. Median follow-up was 33.5 mo (0.03-55.9 mo). Pts with del(17p) had lower median survival (38.6 mo vs not reached [NR], $P < 0.001$). Of pts initially treated with transplant intent, 44% (19/43) with del(17p) and 45% (274/615) without del(17p) received ASCT during first-line therapy. ASCT vs no ASCT was associated with a higher median OS in pts with del(17p) (NR vs 31.3 mo, $P = 0.0177$). By multivariate analysis of various baseline characteristics and therapy modalities, front-line ASCT was associated with a lower risk of death (HR 0.14, $P = 0.008$); hypercalcemia was associated with a higher risk of death (HR 3.06, $P < 0.01$) in pts with del(17p). **Conclusions:** Among pts with NDMM across a range of clinical practices, del(17p) was associated with inferior OS. Hypercalcemia may be a negative prognostic factor. Pts with del(17p) seem to benefit from ASCT. Analyses of the impact of novel combination therapies are being done and will be reported, as there is clear need to improve outcomes in this pt segment.

8583 Poster Session (Board #401), Sun, 8:00 AM-11:30 AM

Outcomes of high, t(11;14), and standard cytogenetic risk multiple myeloma following early high dose therapy and autologous hematopoietic cell transplantation (SCT). *First Author: Gregory Peter Kaufman, Mayo Clinic, Rochester, MN*

Background: Current cytogenetic risk stratification in newly diagnosed multiple myeloma (NDMM) is not derived from recent patients (pts) treated with novel agents. High dose melphalan and SCT is a preferred management strategy for transplant eligible NDMM pts following novel agent induction. We investigated outcomes of high cytogenetic risk (HR), t(11;14), and standard cytogenetic risk (SR) NDMM treated with early SCT. **Methods:** Following Mayo Clinic IRB approval and in accordance with the Declaration of Helsinki, all pts treated at Mayo Clinic Rochester with SCT for NDMM between 2003 and 2012 were identified (n = 941). We excluded pts without FISH cytogenetics from diagnosis (dx) and those who did not undergo SCT within 12 months of dx. HR was defined as a composite of mSMART high and intermediate risk abnormalities including del(17p), t(4;14), t(14;20) or t(14;16). Response and progression were defined per IMWG criteria. Overall survival (OS) and progression free survival (PFS) were calculated from dx. **Results:** The study cohort had 409 pts [SR = 244, t(11;14) = 69, HR = 96], with a median estimated follow up of 43 months from dx. Novel agents (IMiDs or proteasome inhibitors) were used in 95% of pts prior to SCT, and 80% of pts achieved partial response. Median PFS for HR, t(11;14), and SR pts was 24.9 (23,30), 28.1 (21,31), and 30.4 (28-34) months respectively (p = 0.034). Median OS for HR, t(11;14), and SR pts was 60.5 (46,71), 73.4 (54,89), and 103 (98,113) months respectively (log rank < 0.0001). When only pts who received post-transplant maintenance therapy were evaluated (IMiDs or proteasome inhibitors), there was no difference in OS at 5 years from diagnosis between HR and SR pts treated with early SCT (p = 0.19). **Conclusions:** Following novel agent induction and early SCT, pts with t(11;14) NDMM have inferior OS compared to a SR cohort of similarly treated pts. This is contrary to the current classification scheme. HR pts have similar OS at 5 years from diagnosis compared to SR pts with the use of early SCT and maintenance therapy.

8584 Poster Session (Board #402), Sun, 8:00 AM-11:30 AM

A phase I/II trial of very low to low-dose continuous azacitidine in combination with standard doses of lenalidomide and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma. *First Author: Frederic J. Reu, Cleveland Clinic, Cleveland, OH*

Background: Azacitidine (AZA) may overcome drug resistance of relapsed or refractory multiple myeloma (RRMM).Continuous administration should maximize epigenetic effects and safety. **Methods:** Lenalidomide (len) 25mg (10mg if GFR 30-59 ml/min) d1-21 every 28d and dexamethasone (dex) 40mg weekly (len-dex) were combined with escalating doses of AZA from 30mg/m^2 SC weekly to 50mg/m^{2}SC twice a week. Dose limiting toxicity (DLT) was assessed during cycle 1. IMWG uniform response criteria (partial response, PR) and adapted EBMT criteria (minor response, MR) were used. Plasma activity of the AZA inactivating enzyme cytidine deaminase (CDA) was measured by HPLC at Zymo Research Corp., CA. **Results:** Forty patients (pts) with relapsed (n = 3) or refractory (n = 37) MM were enrolled after a median of 4 prior regimens (range 1-10). Their disease was refractory to len (n = 32), bortezomib and / or carfilzomib (n = 32), or both len and proteasome inhibitors (n = 28). The target phase II dose of 50mg/m2 SC twice a wk was reached. One DLT (neutropenic fever without documented infection) occurred in 1 of 6 pts treated with 40mg/m2 AZA twice a week);. Grade 3/ 4 toxicities possibly drug related were seen in 23 pts (58%), neutropenia (13), thrombocytopenia (5), fatigue (3), infection (2), anemia (2), pleural effusion (1), fever (1), and atrial fibrillation (1). Twelve pts achieved > MR, 9 > PR (3 VGPR) yielding 30% clinical benefit response (CBR) and 22.5% response rates. Median time on study was 90 days. Responses lasted between 3 months and 2 years. Five pts remain on study. Plasma CDA activity at screening and during the study (q wk x4, then q 28d) inversely correlated with achieving > MR ($p < 0.03$, $p < 0.01$, respectively, Wilcoxon exact test) and varied by median 17%. Pts with screening CDA activity < 1000 mU/mL had 50% CBR, vs. 21% if > 1000mU/mL. **Conclusions:** AZA was well tolerated up to target 50mg/m^2 SC twice a week in combination with len-dex . Inverse correlation of CDA activity with response suggests AZA contributed to benefit and supports development of the HPLC assay to select patients for aza nucleoside treatment and guide development of CDA inhibitors. Clinical trial information: NCT01155583.

8585 Poster Session (Board #403), Sun, 8:00 AM-11:30 AM

The therapeutic benefit and toxicity from multiple myeloma phase I trials, 2004 through 2014. *First Author: Ehsan Malek, Division of Hematology and Oncology, University of Cincinnati, Cincinnati, OH*

Background: Despite the therapeutic benefit of novel agents, majority of multiple myeloma (MM) patients inevitably relapse leading to poor clinical outcomes. During the past decade, there has been an unprecedented pace of new anti-myeloma compound discovery tested through phase I trials, mostly in relapse/refractory setting. In the same period of time, at least 9 agents have been FDA approved for relapse MM that makes the decision making between standard therapy vs. recruitment on phase I trial poorly defined and occasionally ethically challenged. Further, the current perception of low therapeutic benefit from participation in phase I trials is the main obstacle for patient recruitment and make the phase I trial as a "last resort" in overall therapeutic plan. Here, we present a global assessment of therapeutic benefit and toxicity of all MM phase I studies over the past decade that may lead to optimal timing of patients recruitment on phase I trials. **Methods:** We reviewed 43 phase I trials from 2004 until 2014 in a systematic fashion. Quality and rate of response, adverse effects and mortality from single agents as well as combination of the experimental agents with immunomodulators (IMiDs) and proteasome inhibitors (PIs) are reported. **Results:** 41 trials with total of 946 participants were analyzed. 21 were single agents and the reminder tested a combined regimens. Overall response rate (ORR), i.e., partial response or better, was observed in 34% of all patients, 16% with single agents and 42% with combination therapy. Patients participated in trials with combination therapies had more grade III-IV toxicity than single agents (HR: 1.35, p-value: 0.04). There were only 5 patients (less than 1% of all participants) who have therapy-related death. Single agents with anti-CD38 agent, daratumumab and oral PI, ixazomib, had the best single agent response rate, 45% and 36%, respectively. **Conclusions:** Median ORR from MM phase I trials even with single agents is higher than reported response rate from classic chemotherapy phase I trials (i.e. 5%), therefore phase I participation should not count as the "last resort" and MM patients should be offered the opportunity to participate in these trial at any stage after failure on IMiDs and PIs.

8586 Poster Session (Board #404), Sun, 8:00 AM-11:30 AM

Impact of total therapies on clinical outcome of myeloma stratified by risk and molecular subgroups. *First Author: Christoph Johann Heuck, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Despite the introduction of new agents multiple myeloma (MM) is a disease with unpredictable clinical course consistent with it being composed of a variety of subtypes with distinct molecular features. In order to shed light on the impact of this molecular heterogeneity on treatment response we examined clinical outcomes in our series of Total Therapy (TT) trials, stratified by risk status and molecular subgroup. **Methods:** We included 1318 patients with available baseline gene expression profiling (GEP) data enrolled on Total Therapy 2–5, stratified by GEP70-defined risk and molecular subgroup. We analyzed their effect on outcomes and timing of treatment failure in relation to protocol phase. **Results:** For GEP70-defined low risk (LR) MM, PFS and OS has incrementally improved with addition of thalidomide in TT2 and bortezomib (Bz) in TT3a and 3b. While Bz improved outcomes for LRMM within the MS molecular subgroup, it had no significant impact on MF cases. Outcomes for patients treated on TT4 designed for LRMM were similar to TT3a/b. The lower intensity treatment arm TT4-L had inferior outcomes compared to the standard arm. However patients with adverse cytogenetics had improved outcomes on TT4-L. Treatment failures in LRMM were rare and not correlated to treatment phase. CR rates in high-risk (HR) MM are similar to LRMM. Yet a more dose-dense chemotherapy in Total Therapy (TT) 5 failed to improve survival in HRMM. For HRMM treated on TT2 and 3, treatment failures occurred early in the inter-transplant or consolidation phases. Interestingly with dose dense therapy in TT5 treatment failure was not seen until the maintenance phase. **Conclusions:** HRMM has a distinct clinical course with high rates of primary refractory disease and early relapse. Changing therapy for HRMM from dose intense to dose dense has shifted treatment failure from the inter-transplant to the maintenance phase, which is now a setting where novel approaches can be used. For LRMM we can define distinct clinical response and outcome patterns dependent upon GEP-defined molecular subgroups. This differential response dependent upon treatment used at induction opens the potential for adjusting maintenance to take account of the disease subtype. Clinical trial information: NCT00869232.

8587 Poster Session (Board #405), Sun, 8:00 AM-11:30 AM

Pre-clinical translational studies of daratumumab in patients with myeloma or AL amyloidosis undergoing autologous hematopoietic stem cell transplantation (SCT). *First Author: Chakra Pani Chaulagain, Cleveland Clinic Florida, Weston, FL*

Background: Daratumumab (DARA) is a human IgG1 that binds to CD38 and kills tumor cells expressing CD38 through immune-mediated cytotoxicity. CD38 is expressed on plasma cells in multiple myeloma (MM), AL amyloidosis (AL) and on myeloid progenitor cells. Since SCT remains a standard therapy for MM and AL the effect of DARA on progenitor cells was evaluated. Ability of DARA to induce complement dependent cytotoxicity (CDC) of progenitor cells was assessed in progenitor cell assay (PCA). DARA-mediated antibody-dependent cytotoxicity (ADCC) of progenitor cells, its correlation with FcγRIIIA polymorphism and stem cell potential were examined using NK-cells from post-SCT patients (n = 10, n = 6 MM and n = 4 AL) as effectors against a MM target cell line. **Methods:** ADCC was performed with post-SCT NK cells and MM.1S cells in the presence of 100 ng/ml DARA or isotype control (ICA). DARA-mediated CDC was evaluated in PCA: unselected or CD34-selected mobilized cells were incubated in complement-rich serum with no antibodies, or DARA or anti-CD59 (BRIC 229) or both. The effects of these antibodies on CFU-GM and BFU-E were evaluated two weeks later. The results were analyzed by two-tailed paired t tests with $P < 0.05$ as significance level. **Results:** MedianADCC of MM.1S target cells by primary post-SCT NK cells was 39% and 7% using DARA or ICA, respectively ($P < 0.05$). Of the 10 NK donors, 6 were V/F or V/V and lysed 60% of targets, while 4 F/F lysed 17% ($P< 0.05$). In the PCA, there was no decrease in CFU-GM or BFU-E: with unselected mobilized cells, with CD34-selected cells with DARA, or with CD34-selected cells incubated with DARA (500 or 1000 ng/ml) +/- BRIC 229 indicating that DARA did not induce CDC on the CD34-selected progenitor cells. **Conclusions:** DARA is active in ADCC assays with post-SCT NK cells from patients with MM or AL and its activity correlates with *FCGR3A-158V/F* polymorphism. DARA did not inhibit progenitor cell growth by CDC in unselected or CD34-selected cells suggesting that administration of DARA may not cause undue harm to the progenitor cells after SCT. These findings support consideration of clinical trials of DARA consolidation post-SCT in MM and AL. CPC: MMRF fellow.

8588 Poster Session (Board #406), Sun, 8:00 AM-11:30 AM

Effect of IMiD compounds on CD38 expression on multiple myeloma cells: MOR202, a human CD38 antibody in combination with pomalidomide. *First Author: Rainer Boxhammer, MorphoSys AG, Martinsried/Planegg, Germany*

Background: MOR202 (MOR03087), a human CD38 antibody currently under evaluation in a phase I/IIa trial, mediates antibody-dependent cell-mediated cytotoxicity/phagocytosis (ADCC/ADCP) of multiple myeloma (MM) patient-derived cells with high potency (EC50 ~200 pM). IMiD compounds such as lenalidomide (LEN) or pomalidomide (POM), both approved in MM, were evaluated *in vitro* for their ability to modulate CD38 expression and enhance the cytotoxicity of MOR202. **Methods:** CD38 expression +/- LEN and +/- POM on MM cell lines was analyzed by flow cytometry. The antitumor activity of POM combined with MOR202 was evaluated *in vitro*; analyses included the induction of direct cytotoxicity of MM cells and the activation of immune effector cells. On a functional level, the combinatorial effects of MOR202 with POM were assessed in ADCC assays. Different incubation schemes were used to separate the effect of POM on target and effector cells, as well as in the evaluation of the combined effects. The observed combination effects were analyzed for synergistic potential using the fractional product concept. **Results:** POM and LEN mediated a substantial CD38 upregulation on MM cell lines. POM as a single agent showed activation of effector cells and with high potency (EC50 ~150 nM), cytotoxic effects on MM cell lines. Additionally, POM dose-dependently induced an up to 3-fold CD38 upregulation (EC50 ~20 nM) on CD38-expressing MM cell lines. POM-mediated effects were time-dependent, with the most pronounced effects after 72 h incubation. Combining MOR202 with POM led to a synergistic enhancement of cytotoxic activity. The synergy benefit ranged between 1.2–3.1-fold above theoretical additivity, depending on the cell line used, and was most prominent in the case of strong CD38 upregulation. **Conclusions:** Upregulation of CD38 was mediated by both LEN and POM and may represent a class effect of IMiD compounds. The cytotoxic activity of MOR202 on MM cells was enhanced by POM via multiple mechanisms: direct cytotoxicity, CD38 upregulation and activation of effector cells. These results provide a mechanistic rationale for the combination of MOR202 with IMiD compounds and warrant further clinical evaluation.

8589 Poster Session (Board #407), Sun, 8:00 AM-11:30 AM

Patterns of AKT, mTOR, ERK, and STAT3 pathway activation in MGUS, smoldering multiple myeloma, and multiple myeloma. *First Author: Jeremy Todd Larsen, Mayo Clinic, Rochester, MN*

Background: Constitutive activation of key signaling pathways supports proliferation in multiple myeloma (MM). However, pathway activation in MGUS and smoldering multiple myeloma (SMM) compared to MM has not been characterized. We examined the levels of phosphorylated Akt, mTOR, ERK, and STAT3 expression by immunohistochemistry (IHC) in MGUS, SMM, and MM and assessed their impact on clinical outcomes. **Methods:** FFPE bone marrow biopsy samples were obtained during routine clinical care. Primary antibodies used were p-Akt (S473), p-mTOR(Ser2448), p-ERK1/2(Thr202/Tyr204), and p-STAT3 (Tyr705). Staining intensity was scored as: 0 (no staining), 1 ($<$ 50% of cells), 2 ($>$ 50%) and 3 (dark staining of all cells). Nominal variables were compared with Fisher's exact test and time to progression (TTP) was calculated with Kaplan Meier analysis. **Results:** Twenty-one MGUS, 20 SMM, and 18 MM patients were reviewed. Strong expression of p-Akt (2-3+ IHC score) was present in 15% of MGUS cases versus 62% of SMM and 61% of MM patients ($p = 0.037$). Strong p-mTOR expression was observed in SMM and MM patients compared to MGUS patients (100% and 94% versus 45%; $p = 0.001$). 61% of MM cases exhibited strong p-ERK expression versus 34% in SMM and 15% in MGUS ($p = 0.042$). There was non-significant trend toward higher p-STAT3 expression in MM versus SMM/MGUS (39% in MM versus 12% and 10% in SMM and MGUS; $p = 0.15$). Increased p-mTOR activity correlated with high expression of p-Akt(S473) in all patients ($p = 0.023$). TTP in SMM patients with high versus low p-ERK activity was significantly shorter (76 months vs 16 months; $P = 0.046$). No other signaling pathways demonstrated statistical differences in TTP or overall survival. **Conclusions:** Comprehensive IHC analysis across the spectrum from MGUS to SMM and MM demonstrated increased activity of multiple key signaling pathways as disease progression occurs. Expression of p-Akt(S473) and p-mTOR in SMM and MM is significantly higher than MGUS patients, suggesting an upregulation of these pathways is an early event in pathogenesis. Activation of p-ERK and p-STAT3 was more frequent in MM versus MGUS/SMM, suggesting they may be more active in advanced disease.

8590 Poster Session (Board #408), Sun, 8:00 AM-11:30 AM

Assessing clinical response in multiple myeloma (MM) patients treated with monoclonal antibodies (mAbs): Validation of a daratumumab IFE reflex assay (DIRA) to distinguish malignant M-protein from therapeutic antibody. *First Author: Christopher McCudden, Dept. of Pathology & Lab. Medicine, The Ottawa Hospital University of Ottawa, Ottawa, ON, Canada*

Background: Residual therapeutic mAbs can be detected by assays intended to monitor clonal myeloma protein (M-protein). Daratumumab, a human anti-CD38 IgG1k mAb in MM clinical trials, has been detected on serum protein electrophoresis (SPE) and immunofixation (IFE) gels, interfering with IMWG response criteria requiring negative SPE/IFE for CR/sCR. As new therapeutics emerge that induce very deep responses a method is needed to confirm CR/sCR. Validation and use in clinical studies of an assay that distinguishes daratumumab from M-protein is presented. **Methods:** Mouse anti-daratumumab antibody is used to shift daratumumab's IFE migration away from M-protein. Commercial and daratumumab-treated MM patient samples were evaluated to assess specificity, reproducibility and concordance. Detection of M-protein depletion by DIRA triggered additional clinical testing to confirm CR/sCR. **Results:** Daratumumab was identified on IFE in 10/10 samples when added to commercial MM serum in a 1:1 ratio with anti-daratumumab. Reproducibility was tested in 3 independent DIRA runs on 10 samples from daratumumab treated patients (16 mg/kg). 2 independent reviewers assessed daratumumab and M-protein levels and observed 100% concordance. Specificity was evaluated in commercial ($n = 16$) and daratumumab-treated patient samples ($n = 36$) by scoring whether the malignant M-protein was shifted with the anti-idiotype antibody. 94.4% (34/36) of samples had no shift in M-protein with anti-daratumumab. 33 daratumumab patient samples (from single-agent or combination studies) were DIRA tested and clinical responses assessed; 13 (39%) had no M-protein (DIRA -ve) and 10 were confirmed as CR. 20 patients had malignant M-protein remaining (DIRA +ve) and monitoring continued. **Conclusions:** DIRA, a robust and reproducible tool, determines if residual IgGk on IFE is caused by the mAb daratumumab or actual M-protein. DIRA results can trigger further assessments to confirm clinical CR. This first approach to distinguish therapeutic mAb from M-protein in MM will be needed for clinical research and eventually MM treatment.

8591 Poster Session (Board #409), Sun, 8:00 AM-11:30 AM

Safety and efficacy of pomalidomide (POM), dexamethasone (DEX), and pegylated liposomal doxorubicin (PLD) for patients with relapsed/refractory multiple myeloma (RRMM). *First Author: James R. Berenson, Institute for Myeloma & Bone Cancer Research, Los Angeles, CA*

Background: Treatment with POM and DEX has shown efficacy in RRMM patients (pts), even in those refractory to lenalidomide (LEN). In this phase (Ph) 1/2 trial, we investigated the POM-DEX-PLD combination using a modified dose and schedule (28-days) for RRMM pts. **Methods:** Ph1 pts had progressive MM at study entry. Ph2 pts were refractory to LEN (progressive disease (PD) while receiving LEN or relapsed within 8 weeks of last dose). POM was administered orally on days 1-21 of a 28-day cycle, while DEX (40 mg) and PLD (5 mg/m^2) were infused on days 1, 4, 8, and 11. The maximum tolerated dose (MTD) of POM was established at 4 mg; however, because 58.8% of the pts enrolled in Ph2 developed $\geq$ grade 3 (Gr3) neutropenia, the dose of POM was reduced to 3 mg. **Results:** As of December 1st 2014, 56 pts were enrolled, 44 of them in Ph2 and 45 pts had discontinued treatment. Pts had received a median of 4 prior treatments (range, 1-18). Median number of cycles for all pts and those enrolled in Ph2 was 3 (range, 1-8). Median follow-up time for all pts was 4 months (range, 0.2-22 months), whereas that of Ph2 pts was 3.8 months (range, 0.2-12 months). Overall response (ORR) and clinical benefit rates (CBR) were 35%and 47%, respectively. Nine pts (16%) showed stable disease (SD) while 13 (24%) pts exhibited PD. For LEN refractory pts ($N = 44$), ORR and CBR were 32 % and 48%, respectively, with 6 pts (14%) showing SD and 15 pts (34%) displaying PD.Ph2 pts receiving POM at 3 mg ($N = 28$) showed an ORR and CBR of 43% and 61%, respectively. Progression-free survival was 5.23 months. Common $\geq$ Gr3 adverse events were neutropenia (38.2%), lymphopenia (20.0%), hyponatremia (9.1%), and thrombocytopenia (5.5%). One pt died of Gr5 sepsis. **Conclusions:** The combination of POM at 3 mg, PLD and DEX given in 28-day cycles is safe and effective for the treatment of MM pts refractory to LEN. Clinical trial information: NCT01541332.

8592 Poster Session (Board #410), Sun, 8:00 AM-11:30 AM

Clinical outcomes in t(11;14) multiple myeloma. *First Author: Muhamad Alhaj Moustafa, Mayo Clinic, Rochester, MN*

Background: Chromosomal translocations involving the immunoglobulin heavy chain region on chromosome 14 are common abnormalities in multiple myeloma (MM); with translocation t(11;14) being the most common (15-20%). Our study focuses on the outcomes of this group and response to different therapies. **Methods:** We identified 254 patients with MM, who had fluorescence in situ hybridization (FISH) performed between 2004 and 2012 for MM and had t(11;14) abnormality. We included 199 patients who had FISH studies before MM diagnosis or within 2 years of diagnosis. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. **Results:** The median age at diagnosis was 63 years (range, 22-95) and 129 (65%) were male. The estimated median follow up for the whole cohort was 69 months; 100 (50%) patients are alive. The PFS for the whole cohort was 15 months (95% CI; 11, 18) and the OS was 68 months (95% CI; 54, 88). Twenty-seven (14%) patients received conventional therapies for induction, whereas 172 (86%) received novel agents (116 IMiDs, 33 proteasome inhibitors, 23 both); 115 had stem cell transplant (SCT). Partial response (PR) or a better response to induction was seen in 55%. Median OS was similar for patients receiving conventional drugs or novel agents for initial therapy; 68 months vs. 70.5 months, p= 0.53. Median OS for those receiving an SCT was 72 months compared with 35 months for the remainder. The median OS for 33 patients with a 17p deletion was 26 months vs. 73 months for the remainder, p< 0.01. The OS for the 91 patients diagnosed before 2009 was similar to the 108 patients diagnosed later; p= 0.2. **Conclusions:** The median survival of patients with t(11;14) abnormality is 5-6 years, and does not appear to have changed significantly within the last decade.

8593 Poster Session (Board #411), Sun, 8:00 AM-11:30 AM

Analyzing the relationship of response and survival in patients with refractory or relapsed and refractory multiple myeloma (RRMM) treated with pomalidomide plus low-dose dexamethasone (POM + LoDEX) in the MM-003 trial. *First Author: Katja Weisel, University Hospital of Tuebingen, Tuebingen, Germany*

Background: RRMM patients (pts) previously exposed to bortezomib (BORT) and lenalidomide (LEN) have short overall survival (OS). The phase 3 MM-003 trial (NCT01311687) demonstrated significantly longer OS in RRMM pts treated with POM + LoDEX vs HiDEX (HR, 0.74 [95% CI, 0.56-0.97], P = .0285). This post hoc analysis investigated OS based on the response status of pts at different cycles. **Methods:** Landmark analyses at the start of cycles (C) 3, 5, and 7 were performed using Kaplan-Meier methods and unadjusted Cox regression models. Time-dependent survival analyses captured response status over time. For both approaches, survival of ptswith stable disease (SD) was compared to that of pts with progressive disease (PD) or overall response (OR; ≥ partial response). **Results:** At C3, 38.4% of pts (116/302) randomized to POM + LoDEX attained SD, 14.6% PD, and 19.2% OR; 28% had no response data, most due to early discontinuation. The median OS from randomization by response status at C3 was 15.3 mos for SD, 6.3 for PD, and 17.5 for OR. The difference in OS at C3 between pts with PD or SD was significant (P < .001); that between pts with OR or SD was not (P = .32). A similar pattern was observed at C5 and C7. The time-dependent survival model showed a lower risk of death for pts with SD or OR vs PD (HR, 0.27 [95% CI, 0.17-0.44] and HR, 0.06 [95% CI, 0.02-0.16], respectively). For the HiDEX arm, small pt numbers per group (due to the lower response rate, 2:1 randomization, and shorter OS vs POM + LoDEX) made interpretation challenging. **Conclusions:** In the POM + LoDEX group, pts with SD at C3, C5, and C7 had OS comparable to pts who achieved a response by those times. Pts with either SD or OR had a longer OS than those with PD at the same time points. Clinical trial information: NCT01311687.

		POM + LoDEX (N = 302)		
Beginning of C		**SD**	**PD**	**OR**
C3	n	116	44	58
	Median OS, mo	15.3	6.3	17.5
	HR vs SD (95% CI)	-	3.83 (2.39-6.14)	0.75 (0.43-1.31)
	***P* value vs SD**	-	< .0001	.320
C5	N	57	31	56
	Median OS, mo	16.6	11.0	18.0
	HR vs SD (95% CI)	-	2.81 (1.38-5.71)	0.74 (0.33-1.66)
	***P* value vs SD**	-	.004	.462
C7	n	40	18	47
	Median OS, mo	Not reached	16.4	18.0
	HR vs SD (95% CI)	-	2.66 (0.89-7.94)	0.90 (0.3-2.67)
	***P* value vs SD**	-	.080	.843

8594 Poster Session (Board #413), Sun, 8:00 AM-11:30 AM

Outcomes and treatment of patients with POEMS syndrome experiencing progression or relapse after first line treatment. *First Author: Taxiarchis Kourelis, Mayo Clinic, Rochester, MN*

Background: While clinical improvement is almost universal with first line chemotherapy and/or radiation therapy in patients with POEMS syndrome, outcomes and management of patients who relapse or progress (R/P) after first line treatment have not been described. **Methods:** We identified 291 patients with POEMS syndrome treated at the Mayo Clinic from 1974-2014. Median follow-up for survival and R/P were 68 months and 51 months, respectively. **Results:** For the 78 documented R/P patients (27%), 2ndline treatments included: novel agents, n = 16 (21%), chemotherapy, n = 23 (30%), radiation, n = 15 (19%), ASCT, n = 12 (15%), other, n = 5 (6%) and uncertain type of therapy, n = 5 (6%). The 5 year PFS for the 291 patients was 68%. For patients with documented R/P, median time to R/P was 42 months (range 3-327 months). The 5 year OS for patients with and without an R/P was 85% vs 77%, p = NS. Excluding 9 patients with refractory disease, 47 (60%) patients experienced a clinical R/P and 22 (28%) R/Ps were identified by a combination of worsening VEGF, hematologic or radiographic evaluations. Eighteen (23%) patients relapsed with symptoms that were not present at diagnosis. Outcomes after second line treatment are shown in the table. Thirty patients (30%) went on to experience a second R/P (R/P-2) at a median of 17 months from the end of second line treatment/diagnosis of the first R/P (range 0-96 months). **Conclusions:** One quarter of patients with POEMS had a documented R/P after first line chemo-or radiation therapy, some of whom with symptoms not present at initial diagnosis. The vast majority of patients with R/P responded to subsequent therapy.

Types of relapses/progressions with respective second responses.

		2nd responses N (%)			
Type of relapse/progression	**N=78**	**CR**	**PR**	**NR**	**NE**
Hematologic (VGPR included)	23	39%	17%	26%	17%
PET	44	16%	23%	7%	55%
VEGF	26	62%	15%	8%	15%
	N	Response	Mixed response or stable disease	Progression	NE
Neuropathy	39	41%	26%	10%	23%
Fluid overload	27	48%	15%	30%	7%
Erythrocytosis/ Thrombocytosis	12	67%	8%	8%	17%
Endocrinopathy	20	15%	40%	5%	40%
Skin Changes	20	45%	10%	15%	30%
Lung function	16	38%	6%	13%	44%
Organomegaly/ Lymphadenopathy	15	53%	20%	0	27%
Papilledema	9	56%	0	0	44%
Other	6	67%	0	17%	17%

8595 Poster Session (Board #414), Sun, 8:00 AM-11:30 AM

Phase III trial of stem cell transplantation compared to melphalan and dexamethasone in the treatment of immunoglobulin light chain amyloidosis (AL). *First Author: Morie A. Gertz, Mayo Clinic, Rochester, MN*

Background: Autologous stem cell transplant is widely performed for the management of select patients with AL amyloidosis in the United States. There are no phase III trials that document improved overall survival. This phase III trial allowed patients to select between melphalan and dexamethasone or autologous stem cell transplantation. **Methods:** Eighty-nine patients with biopsy-proven AL amyloidosis elected to receive melphalan and dexamethasone (n = 34) or stem cell transplantation (n = 54). Patients were selected to exclude those for whom cardiac involvement would not have permitted safe autologous stem cell transplantation. **Results:** Allowing patients to select their preferred treatment resulted in an imbalance of patients between the two arms. Patients that selected melphalan and dexamethasone were younger, were more likely to be ECOG performance status less than 2, and had a higher amyloid stage defined by increasing degrees of cardiac amyloidosis. Patients receiving melphalan and dexamethasone had a three-year progression-free survival of 29% and overall survival of 58.8%. Patients receiving stem cell transplant had a three-year progression-free survival of 51.7% and overall survival of 83.6%. An attempt to match patients between the two arms, in terms of risk, produced 24 matched triplets with no difference in hematologic response. **Conclusions:** This trial, which did not meet its accrual goals, failed to demonstrate a survival advantage for matched patients undergoing autologous stem cell transplantation. Clinical trial information: NCT00477971.

Differences between those who chose SCT and those who chose melphalan with dexamethasone.

	Arm A n = 33	**Arm B n = 52**	
Median Age (25th-75th percentile)	63 years (58-67)	57 years (53-61)	p < 0.001
Male	17 (51.5%)	37 (71.2%)	p = 0.067
ECOG performance status	24 (72.7%)	48 (92.3%)	p = 0.015
0-1	9 (27.3%)	4 (7.7%)	
2			
Risk group	20 (60.6%)	37 (71.2%)	p = 0.350
low	13 (39.4%)	15 (28.8%)	
high			
AL stage	4 (12.1%)	25 (48.1%)	p = 0.002
I	19 (57.6%)	21 (40.4%)	
II	10 (30.3%)	6 (11.5%)	
III			
Heart as dominant disease site	22 (66.7%)	18 (34.6%)	p = 0.007
yes	11 (33.3%)	34 (65.4%)	
no			

8596 Poster Session (Board #415), Sun, 8:00 AM-11:30 AM

Survival trends in young patients with Waldenstrom macroglobulinemia (WM). *First Author: Nishanth Vallumsetla, Mayo Clinic, Rochester, MN*

Background: Data in young patients (pts) with WM are sparse and the few available studies utilizing SEER database have yielded inconsistent results, possibly overestimating survival, in part related to inclusion of asymptomatic pts. Herein, we investigate trends in overall survival (OS), including the Rituximab era, in a cohort of young symptomatic WM pts, seen at Mayo Clinic over 5 decades. **Methods:** Of 1181 pts with WM seen consecutively between 1960 and 2013, 127 (11%) were ≤ 50 years (y) at diagnosis, and 123 of those received therapy. Pts were categorized into 3 equal year groups based on the timing of initiation of therapy: Group 1 (1960-77), Group 2 (1978-95) and Group 3 (1996-2013), and their OS was analyzed using the Kaplan Meier method. We also compared their outcomes with a cohort of pts, ≥ 65 y and matched (1:1) by the timing of diagnosis. **Results:** Follow-up from initiation of therapy was similar in the 2 cohorts (median: 10.8 y in young vs 10.4 y in control arm). The median OS from initial therapy was 15 y (95% CI 13-18) for the young compared to 7.3 y (CI 5-8) for the control arm. In the young pts, 92% of deaths with known causes were WM related compared to 59% in control arm (p = 0.0004). While there was no significant OS difference observed with the use of Rituximab-based initial therapy in the young [median 11.4 y (CI 6–NR*) versus 15.6 y (CI 13-21) for all other therapies; p = 0.13], the control arm showed superior OS for pts who received Rituximab based initial therapy [median 9.1 y (CI 7-NR) vs 5.8 y (CI 5-8) for other therapies; p = 0.03]. Among young pts, there was no OS improvement from initial therapy across the 3 groups (p = 0.47) while the OS trends for the controls showed improvement across the 3 groups (p = 0.002; Table). **Conclusions:** Survival of young pts with WM remains unchanged over the past 5 decades. In contrast to the patients aged ≥ 65,Rituximab use did not translate to improved survival in young pts.

Parameter	Young Pts	Control
Median Age (Range)	44 y (30-50)	73 y (65-85)
OS in years (95% CI);		
Group 1	12.7 (5-16); n=13	4.7 (2-7); n=14
Group 2	16 (12-22); n=45	5.3 (4-10); n=43
Group 3	14.8 (10-NR*); n=65	8.3 (6-11); n=66
Initial Therapy (%)		
Rituximab-based	34	33
Chlorambucil-based	38	52
Nucleoside analogue-based	16	6
Other agents	15	11

*Not Reached

8597 Poster Session (Board #416), Sun, 8:00 AM-11:30 AM

Outcomes of primary plasmacytoma (PP) in United States (US). *First Author: Guru Subramanian Guru Murthy, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Studies on multiple myeloma demonstrate an improvement in overall survival (OS) and increased risk of second primary malignancy (SPM); Population level data on OS and the risk of SPM in primary plasmacytoma (PP) is sparse. Hence, we aimed to determine the trends in OS and SPM in patients with PP in US. **Methods:** The Surveillance, Epidemiology and End Results (SEER-13) database was used to identify patients with age > 20, diagnosed with solitary plasmacytoma of bone (SPB) or extramedullary plasmacytoma (EMP) (ICD-O-3 codes –9731, 9734) as the first primary malignancy between 1992 to 2011. OS analysis was performed using Kaplan-Meier method and compared by log rank test. SPM was identified using SEERstat software (version 8.1.5) with a latency period of 6 months from radiotherapy (RT). Multivariate analysis of OS was performed using Cox proportional hazard regression method. **Results:** 2064 patients with SPB/EMP had a median age of 62 years (range 20-96). Baseline characteristics included 63.6% males, 54.2% with age > 60, 79.2% Whites, 14% African americans and 6.8% other races. About 48.4% of patients received RT alone, 23.5% had surgery and RT, 10.5% had surgery and 17.6% did not receive surgery or RT. OS at 10 years was higher in patients with age < 60 vs. age > 60 (62.5% vs. 22.2%, p < 0.01) and for other races vs. Whites vs. African americans (51.1% vs. 40.1% vs. 34.5% respectively, p = 0.01). Use of RT and surgery resulted in better 10-year OS (51.2%) than surgery alone (44.1%), RT alone (39.8%) or no RT/surgery (21.2%) (p < 0.01).On multivariate analysis, age > 60 (HR 3.01, 95% CI 2.61-3.46; p < 0.01), Whites vs. other races (HR 1.35, 95% CI 1.02-1.77; p = 0.03) and African americans vs. other races (HR 1.52, 95% CI 1.11-2.08; p < 0.01) predicted worse OS, whereas the use of RT along with surgery Vs. RT alone (HR 0.82, 95% CI 0.70-0.97; p = 0.02) predicted better OS. Patients treated with RT had more SPM as compared to general population- all sites standardized incidence ratio (SIR) 1.49, with more leukemia/lymphoma (SIR 6.37) and bone tumors (SIR 19.93) (p < 0.05). **Conclusions:** Our study demonstrates that the use of RT and surgery for PP significantly improves the OS, despite an increased risk of SPM with RT. Our study also shows a significant racial disparity in the long-term OS of PP.

8598 Poster Session (Board #417), Sun, 8:00 AM-11:30 AM

A national study on conditional survival and excess mortality after high dose therapy with autologous stem cell transplantation for non-Hodgkin lymphoma. *First Author: Knut BjÃ„ro Smeland, National Advisory Unit on Late Effects, Department of Oncology, Oslo University Hospital, Oslo, Norway*

Background: The aim of this study was to investigate conditional survival and standardized mortality ratios (SMR) after high-dose therapy with autologous stem-cell transplantation (HDT) for non-Hodgkin lymphoma (NHL) in a national population-based cohort, and to analyse cause of death and incidence of second malignancies. **Methods:** All patients ≥ 18 years treated with HDT for NHL in Norway 1987-2008 were included (n =578). Information about cause of death from Statistics Norway and second malignancies from Cancer Registry of Norway were linked with clinical data. Treatment related mortality (TRM) was defined as death from a complication to HDT in tumour free patients. Observation time was estimated from HDT to death or cut-off at June 30th 2014 (median 6.7 years, range 0-27). Data on second cancer was available until end of 2012. **Results:** The 10- and 15-year overall survival (OS) was 52% (95%CI 48%-56%) and 49% (95%CI 44%-53%). Conditional 5-year OS are shown in the table. SMR was 12.3 (95% CI 11.0-13.9) for the entire cohort and 4.9 (95% CI 4.1-5.9), 2.4 (95% CI 1.8-3.2) and 1.0 (95% CI 0.6-1.8) for patients having survived 2, 5 and 10 years after HDT respectively. Among 281 deaths the underlying causes were NHL (n = 216, 77% of deaths), TRM (n = 21, 7%), second cancers (n = 20, 7%), cardiovascular disease (n = 8, 3%), infections (n = 6, 2%), pulmonary disease (n = 5, 2%) and others/missing (n = 5). Second malignancy after HDT was diagnosed in 38 (6.6%) (non-melanoma skin excluded), including 15 leukaemia/myelodysplastic syndrome. **Conclusions:** The conditional OS improved for each additional year survived after HDT. NHL-patients undergoing HDT had 12-fold increased mortality compared to the general population, but only 2-fold conditioned on having survived 5-years. After 10 years the mortality risk was no longer elevated. TRM and second cancers are the most common non-relapse related causes of death.

	5 year OS (%) conditioned on having survived		
	0 y	2 y	5 y
All (n = 578)	61	81	97
Diffuse large cell (n = 187)	52	77	88
T-cell (n = 93)	52	88	95
Transformed (n = 87)	57	72	80
Follicular (n = 74)	68	76	74
Mantle cell (n = 67)	81	82	72
Lymphoblastic (n = 45)	76	94	100
Burkitt (n = 17)	76	100	100
Other/unspecified (n = 8)			

TPS8599 Poster Session (Board #418a), Sun, 8:00 AM-11:30 AM

A randomized, double-blind, placebo-controlled, phase 3 study of rituximab with or without ibrutinib for Waldenstrom's macroglobulinemia (PCYC-1127-CA). *First Author: Meletios A. Dimopoulos, Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece*

Background: Current treatments for Waldenstrom's macroglobulinemia (WM) are not curative, and a standard of care does not exist. A highly recurrent somatic mutation in WM, *MYD88 L265P*, signals through interleukin-1 receptor-associated kinase 1 and Bruton's tyrosine kinase (BTK) to mediate the constitutive activation of the NF-κB pathway (Yang, 2013). Ibrutinib (ibr), an oral inhibitor of BTK, impairs crosstalk between MYD88 and BTK, and blocks BTK dependent downstream signaling within the B-cell receptor pathway inducing apoptosis of WM cells (Treon, 2012).Thus, ibr offers a novel therapeutic approach for pts with WM. Pts with previously treated WM receiving different ibr doses achieved durable responses in a phase (Ph) 1 study (Advani, 2013). This was confirmed in a Ph 2 trial of ibr 420 mg daily (overall response rate [ORR] of 87%; Treon, 2014) leading to the first FDA approval in WM. Ibr + rituximab (rtx) showed activity and tolerability in high-risk CLL and MCL. This Ph 3 study evaluates the safety and efficacy of ibr + rtx vs. placebo + rtx in pts with WM. **Methods**: Approximately 150 pts will be randomized in a 1:1 ratio to receive rtx 375 mg/m^2 IV weekly for 4 weeks, followed by a second 4-weekly rtx course 3-months later, and either ibr 420 mg daily or matching placebo until progressive disease (PD) or unacceptable toxicity. Key inclusion criteria include WM with documented PD or no response (stable disease) to last treatment if previously treated; symptomatic disease requiring treatment per the 2nd International Workshop on WM; and adequate hematologic, hepatic, and renal function. Exclusion criteria include CNS involvement and clinically significant cardiovascular disease. Pts refractory to the last rtx-containing therapy excluded from the randomized study are eligible for the open-label single-agent ibr substudy (n = 30). The primary endpoint is progression-free survival assessed by an independent review committee. Secondary endpoints are ORR, overall survival, hematologic improvement, time to next treatment, and safety. Pts in the control arm may receive single-agent ibr after confirmation of PD. Enrollment began in July 2014 (NCT02165397). Clinical trial information: NCT02165397.

TPS8600 Poster Session (Board #418b), Sun, 8:00 AM-11:30 AM

Randomized, phase III trial of the efficacy and safety of lenalidomide plus R-CHOP vs R-CHOP in patients with untreated ABC-type diffuse large B-cell lymphoma. *First Author: Grzegorz S. Nowakowski, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: The activated B-cell like subtype (ABC) of diffuse large B-cell lymphoma (DLBCL) is associated with inferior PFS and OS with R-CHOP-based chemotherapy. Lenalidomide demonstrated significant single agent activity in relapsed/refractory DLBCL, predominantly in ABC-type DLBCL. In first line therapy, lenalidomide + R-CHOP (R2-CHOP) showed improved efficacy over R-CHOP historical controls in two independent single arm phase II trials from Mayo Clinic and Fondazione Italiana Linfomi groups. R2-CHOP appears primarily to improve outcomes in ABC-type DLBCL. The objective of this multicenter, international trial is to compare the efficacy and safety of lenalidomide–R-CHOP (R2-CHOP) vs placebo–R-CHOP in patients with previously untreated ABC-type DLBCL. **Methods**: In this phase III placebo-controlled, double-blinded trial (DLC002; NCT02285062), patients with ABC-type DLBCL are randomized 1:1 to oral lenalidomide (15 mg, days 1-14/21-day cycle) plus standard-dose R-CHOP or placebo–R-CHOP, every 21 days for 6 cycles $\pm$ 2 additional doses of rituximab until PD, intolerability, inadequate response, or withdrawal of consent. Key eligibility criteria include previously untreated, histologically confirmed ABC-type CD20+ DLBCL (WHO classification), age 18-80 years, IPI score $\geq$ 2, Ann Arbor stage II-IV, and adequate organ function. ABC type will be determined by central pathology lab within 3 days by real-time gene expression profiling (GEP) using the NanoString nCounter Analysis System (Scott et al. *Blood.* 2014;123:1214-1217) on FFPE biopsy samples. Primary endpoint is PFS; secondary endpoints are EFS, OS, ORR, CR, duration of CR, time to next lymphoma therapy, and health-related QOL. Additional biological analyses for MRD detection are planned. Responses will be measured by 2007 IWG criteria with PET. Approximately 560 patients will be randomized during the estimated 34 month-accrual period. Enrollment began in January 2015, with expected accrual completion in October, 2017. To our knowledge, this is the first phase III trial in DLBCL using real time GEP to assess patient eligibility, thus allowing precision therapy of patients with DLBCL. Clinical trial information: NCT02285062.

TPS8601 Poster Session (Board #419a), Sun, 8:00 AM-11:30 AM

A phase III study of ibrutinib in combination with either bendamustine and rituximab (BR) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with previously treated follicular lymphoma or marginal zone lymphoma. *First Author: Nathan Hale Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are indolent non-Hodgkin lymphomas (iNHL) and account for approximately 22% and 10%, respectively, of all NHLs. Although patients (pts) often respond to initial therapy, most relapse and suffer substantial morbidity and mortality related to persistence/recurrence of disease. For pts with relapsed iNHL, the most common chemoimmunotherapy regimens are BR and R-CHOP; however, outcomes in the relapsed setting remain suboptimal. Ibrutinib is an oral Bruton's tyrosine kinase (BTK) inhibitor that has demonstrated activity in a phase 1 study in pts with various B-cell malignancies, including iNHL. A phase 2 monotherapy study in chemoimmunotherapy-resistant FL is ongoing. Other studies have demonstrated that ibrutinib can be safely combined with BR or R-CHOP. Based on these observations, this phase 3 trial has been designed to investigate the combination of ibrutinib with BR or R-CHOP in pts with iNHL. **Methods:** The SELENE study, PCI32765FLR3001, is a randomized, double-blind, placebo-controlled, multicenter phase 3 study of ibrutinib combined with either BR or R-CHOP for previously treated FL or MZL. The study aims to enroll approximately 400 pts with disease that has relapsed, or was refractory to, prior chemoimmunotherapy. All pts will receive 6 cycles of BR or R-CHOP (based on prior treatment) and either daily oral 560 mg ibrutinib or placebo continued up to progression. The primary objective is to evaluate whether the addition of ibrutinib to BR or R-CHOP will prolong progression-free survival; secondary objectives were evaluation of OS, CR rate, ORR, patient-reported lymphoma symptoms, and safety. Exploratory objectives include minimal residual disease negative rate in FL pts, patient-reported outcomes related to general health status, and the pharmacokinetics of ibrutinib. Approximately 145 sites in Europe, Asia, Australia, USA and South America will participate. Enrollment began in Q1 2014. As of January 8, 2015, 163 pts have been randomized across 76 sites in 16 countries. Clinical trial information: NCT01974440.

TPS8602 Poster Session (Board #419b), Sun, 8:00 AM-11:30 AM

A phase I study with an expansion cohort of the combination of ipilimumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma: A trial of the ECOG-ACRIN Cancer Research Group (E4412). *First Author: Catherine S. Magid Diefenbach, New York University Perlmutter Cancer Center/New York University School of Medicine, New York, NY*

Background: E4412 is a phase 1 study with an expansion cohort of the combination of brentuximab vedotin (BV) and ipilumumab in patients with relapsed and refractory Hodgkin lymphoma (HL). Despite advances in chemotherapy, relapsed HL remains a significant problem, with over 1,000 lives lost annually. HL has a unique biology in which a small number of malignant Hodgkin Reed-Sternberg (HRS) cells propagate an immunosuppressive microenvironment. In E4412 the peri-tumoral T cells are primed with ipilimumab and the HRS cells targeted with the CD30 specific antibody-drug conjugate BV. We hypothesize that this immuno-chemotherapy approach may overcome tumor cell resistance and deepen clinical response. E4412 is the first clinical trial targeting the HL tumor microenvironment in conjunction with HRS tumor cell targeting. **Methods:** E4412 is currently open at 7 sites within ECOG. A modified 3+3 dose escalation design is used; 6 patients are tested at each dose level if no more than one DLT is observed in the first 3 patients. All DLT are evaluated within the first cycle (1 cycle = 21 days). The primary endpoint is the maximum tolerated dose (MTD) of the combination. Secondary endpoints include complete response (CR) rate, partial response (PR) rate, overall response (ORR) rate, duration of response (DOR), overall survival (OS) and progression-free survival (PFS). Response rates are reported along 95% confidence intervals. DOR, PFS and OS are estimated using Kaplan-Meier methodology. BV is given at 1.8mg/kg and ipilimumab at 1mg/kg (cohort 1) and 3mg/kg (cohort 2) every 21 days for 4 cycles. From cycle 5 BV is given q 21 days, and ipilimumab on cycles 8, 12, and 16. Once the MTD is established, 9 patients are treated in an expansion cohort with BV at 1.8mg/kg and ipilumumab at MTD. Eligibility Criteria include: age $>$ 18, relapsed HL, measurable disease, no prior relapse on BV, no active GVHD or immunosuppressive therapy, ECOG 0-2, FEV1/FVC $>$ 60%, hematology and chemistry labs within standard parameters, no uncontrolled systemic illness. Cohorts I and II have been completed. Expansion cohort enrollment opened on February 3rd, 2015. Clinical trial information: NCT01896999.

TPS8603 Poster Session (Board #420a), Sun, 8:00 AM-11:30 AM

AUGMENT: A randomized, phase 3 trial in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) to compare efficacy and safety of lenalidomide plus rituximab (R^2) versus placebo plus rituximab. *First Author: John Leonard, Weill Cornell Medical College - New York Presbyterian Hospital, New York, NY*

Background: The immunomodulatory drug, lenalidomide (Revlimid), has both anti-inflammatory and antiangiogenic properties. In preclinical studies, the immunological function of tumor-infiltrating lymphocytes is reduced in patients with follicular lymphoma (FL); lenalidomide can restore this response (Ramsay, *Blood*, 2009). In a phase 2 trial of frontline lenalidomide + rituximab (R^2), the overall response rate (ORR) reached 90% (Fowler, *Lancet Oncol*, 2014) in iNHL patients; in a second study, patients with FL achieved 93% ORR (Martin, ICML, 2013). After treatment with R^2 in phase 2 investigations, patients with R/R iNHL achieved clinical responses: ORRs of 73% (36% complete response [CR]) in R/R FL (Leonard, ASCO 2012 oral presentation), and 80% (55% CR) in marginal zone lymphoma (MZL; Raderer, EHA 2014 oral presentation) patients. Based on the results of these preclinical and phase 2 studies, further investigation of R^2 in iNHL is warranted. **Methods:** This multicenter, double-blind, phase 3, randomized study (AUGMENT) is designed to evaluate the efficacy and safety of R^2 versus placebo + rituximab (P+R) in patients with R/R iNHL. Eligibility criteria for patients include: grade 1, 2, or 3a FL or MZL; previous treatment with systemic therapy; considered refractory to or relapsed after last treatment; rituximab-sensitivity if prior rituximab therapy was administered; presentation of $\geq$ 1 measurable lesion; and adequate function in bone marrow, liver, and kidneys. An estimated 350 patients will be randomized 1:1 to either experimental or control groups. Patients enrolled in the R^2 experimental study arm will receive lenalidomide (20 mg/day; days 1 to 21 up to 12 cycles) + rituximab (375 mg/m^2; days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2 to 5) in 28-day cycles. Patients in the control study arm will receive P+R (375 mg/m^2) following the same schedule. Progression-free survival is the primary endpoint, and key secondary endpoints will include rate of durable CR, overall survival, ORR, safety, and time to next anti-lymphoma treatment. Patients are currently being enrolled for this trial (NCT01938001). Clinical trial information: NCT01938001.

TPS8604 **Poster Session (Board #420b), Sun, 8:00 AM-11:30 AM**

Phase I/II study of intratumoral injection of SD-101, an immunostimulatory CpG, and intratumoral injection of ipillumumab, an anti-CTLA-4 monoclonal antibody, in combination with local radiation in low-grade B-cell lymphomas. *First Author: Michael Siavash Khodadoust, Stanford University, Stanford, CA*

Background: Immunotherapy is a promising treatment modality for low grade non-Hodgkin's lymphomas. SD-101 (Dynavax Technologies) is an immunostimulatory synthetic CpG molecule that activates toll-like receptor 9. Intratumoral CpG injection produced local and abscopal anti-lymphoma immune responses with minimal systemic toxicity in an early phase clinical trial (Brody J et al. J Clin Oncol. 2010). Resistance to CpG is thought to be due to the induction of immune tolerance following an initial immune stimulation. Ipilimumab (Bristol-Myers Squibb) is a monoclonal anti-CTLA-4 antibody that interrupts inhibitory signaling on the surface of T cells, thus blocking the development of immune tolerance. Preclinical models show intratumoral injection of anti-CTLA-4 antibodies can produce systemic anti-tumor immune responses at a fraction of the standard systemic dose, thereby limiting adverse autoimmune side effects. This trial proposes a local low-dose immunomodulation strategy combining intratumoral CpG, intratumoral ipilimumab, and local radiation to produce systemic immune responses with minimal toxicity. **Methods:** Up to 12 patients will be enrolled in the phase 1 dose escalation design to determine maximum tolerated dose of intratumoral ipilimumab with a set dose of SD-101, and an additional 15 patients will be enrolled in the phase II expanded cohort at the chosen ipilimumab dose. All patients initially receive two fractions of 2 Gy radiation. After radiation, patients receive intratumoral SD-101 (1mg) and ipilimumab (10mg or 25mg depending on dose cohort). Weekly SD-101 intratumoral injections continue for a total of 5 doses. The primary objective is to determine the safety and tolerability of increasing dose levels of intratumoral ipilimumab with SD-101. Eligible patients must have relapsed/refractory low grade B-cell lymphoma with a disease site amenable to intratumoral injection and a second measurable disease site to assess abscopal effects. This study is currently accruing and is supported by a grant from the NIH (CA188005). Clinical trial information: NCT02254772. Clinical trial information: NCT02254772.

TPS8605 **Poster Session (Board #421a), Sun, 8:00 AM-11:30 AM**

Phase III trial of brentuximab vedotin and CHP versus CHOP in the frontline treatment of patients (pts) with CD30+ mature T-cell lymphomas (MTCL). *First Author: Owen A. O'Connor, Columbia University Medical Center, New York Presbyterian Hospital, New York, NY*

Background: MTCL including systemic anaplastic large cell lymphoma (sALCL) are aggressive neoplasms. Anthracycline-based multiagent chemotherapy regimens have demonstrated response rates ranging from 76 to 88%. Five-year overall survival rates range from 12 to 49% depending on the histologic subtype. Brentuximab vedotin is an antibody drug conjugate that has shown efficacy in a pivotal phase II study as a single agent in relapsed sALCL (Pro et al., J Clin Oncol, 2012) and evidence of clinical activity in combination with CHP in the frontline treatment of MTCL including sALCL in a phase I study (Fanale et al., ASH 2012). **Methods:** This randomized, double-blind, placebo-controlled, multicenter, phase III study (NCT01777152) is evaluating the safety and efficacy of 1.8 mg/kg brentuximab vedotin with CHP (A+CHP) vs CHOP for frontline treatment of CD30+ MTCL. Pts must have FDG-avid disease by PET and measureable disease of at least 1.5 cm by CT. Approximately 300 pts will be randomized 1:1 to receive A+CHP or CHOP for 6–8 cycles (q3wk). Randomization will be stratified by ALK+ sALCL vs other histologic subtypes and IPI score (0–1, 2–3, or 4–5). The target proportion of pts with a diagnosis of sALCL will be 75%. The primary objective is to compare progression-free survival (PFS) between the 2 treatment arms as determined by an independent review facility (IRF). Secondary objectives include comparisons of PFS per IRF in sALCL patients, safety, overall survival, and complete remission rate between the 2 arms. After completion of treatment, pts will be followed for disease progression, medical resource utilization, quality of life, and survival. Post-treatment stem cell transplant is permitted. Efficacy assessments will use the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). CT and PET scans will be performed at baseline, after Cycle 4, and after the completion of treatment. CT scans will also be performed at regular intervals during follow-up until disease progression, death, or analysis of the primary endpoint. Safety assessments will occur throughout the study until 30 days after last dose of study treatment. Enrollment for this global trial began in early 2013. Clinical trial information: NCT01777152.

TPS8606 **Poster Session (Board #421b), Sun, 8:00 AM-11:30 AM**

MAGNIFY: A randomized, phase 3b trial in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) investigating lenalidomide plus rituximab (R^2) induction followed by maintenance R^2 followed by lenalidomide versus R^2 induction followed by rituximab (R) maintenance. *First Author: David Jacob Andorsky, Rocky Mountain Cancer Centers, Boulder, CO*

Background: Combination of the immunomodulatory agent lenalidomide (Revlimid) with rituximab (R^2) is a promising therapeutic option for patients with R/R NHL. As frontline therapy, R^2 provided a 90% overall response rate (ORR) in patients with follicular lymphoma (FL), marginal zone lymphoma (MZL) and small lymphocytic lymphoma (Fowler, *Lancet Oncol*, 2014) and 89% ORR in MCL patients (Ruan, ASH, 2014). In phase 2 trials of R^2, patients with R/R MZL, FL, and MCL achieved ORRs of 80% (55% complete response [CR]), 73% (36% CR), and 57% (36% CR), respectively (Raderer, EHA, 2014; Leonard, ASCO, 2012; Wang, *Lancet Oncol*, 2012). These trials support further investigation of R^2 therapy in R/R NHL. **Methods:** The efficacy and safety of 12 cycles of combination R^2 for induction with randomization to R^2 (Arm A) vs R (Arm B) maintenance will be compared in R/R FL, MCL, or MZL patients as part of the phase 3b MAGNIFY trial. Approximately 500 patients will be randomized 1:1 to 28-day (d) treatment cycles (C). Both patient groups will receive R^2 induction with lenalidomide (20 mg/d on d 1-21; 12 C) + R (375 mg/m^2 on d 1, 8, 15, 22 in C1; d1 of C 3, 5, 7, 9, 11). Patients in Arm A will receive R^2 maintenance with lenalidomide (10 mg/d on d 1-21; C 13-30) + R (375 mg/m^2 on d1 of every other C from 13 to 29), followed by lenalidomide (10 mg/d on d 1-21) until progression. Following 12 cycles of induction with R^2, patients in Arm B will receive maintenance R (375 mg/m^2 on d1 of every other C from 13 to 29). Eligibility criteria include R/R FL grades 1-3b, transformed FL, MZL, or MCL; previous systemic therapy; $\geq$ 1 measurable lesion; and adequate bone marrow, liver, and renal function. Progression-free survival is the primary endpoint. Secondary endpoints include rate of CR/CR unconfirmed (CRu), overall survival, ORR, duration of response, duration of CR/CRu, and safety. An exploratory endpoint, health-related quality of life will be measured using the FACT-Lym questionnaire. The MAGNIFY trial is currently enrolling; 38 patients have been enrolled as of January 30, 2015 (NCT01996865). Clinical trial information: NCT01996865.

TPS8607 **Poster Session (Board #422a), Sun, 8:00 AM-11:30 AM**

A phase 2 trial of INCB040093 alone or in combination with INCB039110 in patients (pts) with relapsed or refractory (r/r) classical Hodgkin lymphoma (cHL). *First Author: Paul M. Barr, University of Rochester Medical Center, Rochester, NY*

Background: In vitro data suggest that both the PI3K and JAK-STAT pathways contribute to tumor growth and survival in HL. Therapies that block both pathways may prove more beneficial in pts with r/r cHL, where treatment options are limited. INCB040093 is an oral PI3Kδ inhibitor and INCB039110 is an oral JAK1-selective inhibitor. **Methods:** This ongoing, nonrandomized, open-label trial has a planned enrollment of 122 pts (61 per treatment arm). Eligible pts are $\geq$ 18 years of age with r/r cHL after autologous stem cell transplant (SCT) and/or after $\geq$ 2 prior chemotherapy-containing regimens who are not candidates for autologous SCT; have fluorodeoxyglucose-avid disease; ECOG performance status 0 to 2; prior brentuximab vedotin (BV) treatment (or not a candidate for BV). Pts who received prior treatment with an immune checkpoint inhibitor are eligible if disease progression or relapse is confirmed with a second assessment $\geq$ 28 days later. Pts must have adequate ANC, platelet count, hemoglobin, total bilirubin, AST and ALT levels. Before first dose of study drug, pts must not have investigational agents within 28 days or 5 half-lives (whichever is greater); autologous SCT within 28 days or allogeneic SCT within 3 months; or radiation treatment within 3 weeks. Pts will receive INCB040093 100 mg bid monotherapy or INCB040093 100 mg bid with INCB039110 300 mg qd. Pts receiving benefit may continue on therapy until they meet treatment discontinuation criteria. Pts receiving INCB040093 monotherapy who experience disease progression or relapse on study may be eligible for crossover to combination therapy. The primary endpoint is objective response rate per the Lugano Classification (Cheson et al. J Clin Oncol 2014) determined by an independent review committee. Secondary endpoints include duration of response and progression-free survival. Overall survival is an exploratory endpoint. Final analysis is planned when all pts reach at least the Week 36 disease evaluation. Clinical trial information: EudraCT 2014-005631-13.

TPS8608 Poster Session (Board #422b), Sun, 8:00 AM-11:30 AM

A randomized open-label study of bortezomib, melphalan, and prednisone (VMP) versus daratumumab (DARA) plus VMP in patients with previously untreated multiple myeloma (MM) who are ineligible for high-dose therapy: 54767414MMY3007 (Alcyone). *First Author: María-Victoria Mateos, University Hospital of Salamanca/IBSAL, Salamanca, Spain*

Background: Based on the results of the VISTA study (San Miguel JF et al. NEJM 2008), VMP is considered a standard of care for newly diagnosed patients with MM not considered suitable for high-dose chemotherapy and stem cell transplantation (SCT). DARA is a human anti-CD38 IgG1κ monoclonal antibody in clinical development for MM. DARA has shown promising efficacy and a favorable safety profile in ongoing phase I/II studies as monotherapy and in combination with chemotherapy (lenalidomide/dexamethasone) in patients with relapsed or relapsed, refractory MM (Lokhorst HM et al. ASCO 2014; Plesner T et al. ASH 2014) as well as in combination with VMP in newly diagnosed MM (Moreau P et al. ASH 2014). **Methods:** This is a phase III randomized, open-label, multicenter study of VMP versus DARA + VMP in patients aged $\geq$ 18 y with previously untreated MM who are ineligible for high-dose therapy. Main inclusion criteria are documented MM satisfying the CRAB criteria, measurable disease, and newly diagnosed and not considered a candidate for high-dose chemotherapy with SCT. Approximately 700 eligible patients will be stratified by International Scoring System, region (Europe vs others), and age ($<$ 75 vs $\geq$ 75 y) and randomized in a 1:1 ratio to VMP or DARA + VMP. All patients will receive up to 9 cycles (1 cycle = 6 wk) of VMP (bortezomib 1.3 mg/m^2 SC twice weekly [Weeks 1, 2, 4, and 5] in Cycle 1, then once weekly [Weeks 1, 2, 4, and 5] in Cycles 2-9; melphalan 9 mg/m^2 and prednisone 60 mg/m^2 PO Day 1-4 of each cycle). Patients in the DARA + VMP arm will receive DARA 16 mg/kg IV weekly x 6 wk (Cycle 1), then every 3 wk for Cycles 2-9; patients will then continue to receive DARA every 4 wk until progression. The primary endpoint is progression-free survival (PFS). An Independent Data Monitoring Committee will conduct reviews of the efficacy and safety data. The primary analysis will occur when approximately 360 PFS events have been observed. Approximately 200 sites in 24 countries will participate. The first patient was enrolled in January 2015. Clinical trial information: NCT02195479.

TPS8609 Poster Session (Board #423a), Sun, 8:00 AM-11:30 AM

Twin randomized studies of daratumumab (DARA; D) plus standard of care (lenalidomide/dexamethasone or bortezomib/dexamethasone [DRd or DVd]) versus Rd or Vd alone in relapsed or refractory multiple myeloma (MM): 54767414MMY3003 (Pollux) and 54767414MMY3004 (Castor). *First Author: Antonio Palumbo, Department of Hematology, University of Torino, Torino, Italy*

Background: Lenalidomide or bortezomib plus low-dose dexamethasone are considered standard of care for relapsed/refractory MM patients. DARA is a human anti-CD38 IgG1κ monoclonal antibody. In ongoing phase I/II studies, DARA (16 mg/kg) has shown promising efficacy and safety as a single agent (overall response rate (ORR) 35%; Lokhorst HM et al. ASCO 2014), in combination with Rd (ORR 87%; Plesner T et al. ASH 2014), as well as in combination with Vd (ORR 100 %; Moreau P et al. ASH 2014). **Methods:** MMY3003 and MMY3004 are phase III randomized, open-label, multicenter studies for patients with relapsed/refractory MM. For both studies, the main inclusion criteria are documented MM after one or more prior line of therapy, and documented evidence of progressive disease. In MMY3003, approximately 560 patients will be randomized in a 1:1 ratio to DRd (DARA 16 mg/kg IV weekly x 8 wk, every 2 wk x 16 wk, every 4 wk thereafter; lenalidomide 25 mg PO Days 1-21 of each 28-day cycle; dexamethasone 40 mg weekly) or Rd and stratified by International Staging System (ISS), number of prior lines (1 vs 2 or 3 vs $>$ 3), and prior lenalidomide exposure. In MMY3004, approximately 480 subjects will be randomized in a 1:1 ratio to DVd (DARA 16 mg/kg IV weekly x 3 cycles, Day 1 of Cycles 4-9, every 4 wk thereafter; bortezomib 1.3 mg/m^2 SC Days 1, 4, 8, and 11 of each 21-day cycle; dexamethasone 80 mg weekly) or Vd and stratified by ISS, number of prior lines (1 vs 2 or 3 vs $>$ 3), and prior bortezomib exposure. The primary endpoints for MMY3003 and MMY3004 are progression-free survival (PFS). An Independent Data Monitoring Committee (IDMC) will review data every 6 months for safety and at 2 predetermined interim analyses for both studies. First patients were dosed June/September 2014 (MMY3003/MMY3004). The primary analysis in each study will occur after 295 PFS events have been observed. Clinical trial information: NCT02076009 and NCT02136134.

TPS8610 Poster Session (Board #423b), Sun, 8:00 AM-11:30 AM

MM-007: A phase 3 trial comparing the efficacy and safety of pomalidomide (POM), bortezomib (BORT), and low-dose dexamethasone (LoDEX [PVD]) versus BORT and LoDEX (VD) in subjects with relapsed or refractory multiple myeloma (RRMM). *First Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA*

Background: Combination treatment (Tx) with immunomodulatory agents and proteasome inhibitors can provide deep and durable responses in patients (pts) with RRMM (Richardson, *Blood,* 2013). PVD showed promising activity and was well tolerated in a Ph 1 dose-escalation study (Richardson, ASCO, 2014). MM-007 is a global, multicenter, randomized, open-label Ph 3 trial designed to compare efficacy and safety of PVD vs VD in pts with RRMM (target enrollment: 782 pts; NCT01734928). **Methods:** Pts must have received 1-3 prior lines of anti-MM Tx, including $\geq$ 2 consecutive cycles (C) of a lenalidomide-containing regimen. Exclusion criteria include refractory to prior BORT 1.3 mg/m^2 twice weekly, ANC $<$ 1000/μL, platelet count $<$ 75,000/μL ($<$ 30,000/μL for pts with $\geq$ 50% bone marrow plasma cells), CrCl $<$ 30 mL/min requiring dialysis, hemoglobin $<$ 8 g/dL, and peripheral neuropathy $\geq$ grade 2. Pts will be randomized 1:1 to continuous Tx with PVD or VD q3w until progression or unacceptable toxicity. PVD (arm A): POM 4 mg on D1-14; BORT SC 1.3 mg/m^2 on D1, 4, 8, 11 for C1-8, D1, 8 for C9+; and D 20 mg (10 mg for pts $>$ 75 y) on D1, 2, 4, 5, 8, 9, 11, 12 for C1-8, D1, 2, 8, 9 for C9+. VD (arm B): BORT and D same as arm A. Thromboprophylaxis with low-dose aspirin or equivalent is required for pts treated with PVD (VD if prior history of deep vein thrombosis or pulmonary embolism). The primary endpoint is progression-free survival (PFS). Secondary endpoints are overall survival (OS), safety, overall response rate by modified IMWG criteria, and duration of response. Exploratory endpoints include evaluation of PFS2, clinical benefit rate, PK, and HRQOL. Minimal residual disease, genomic, molecular/mechanistic, and immune biomarkers will be evaluated. Upon Tx discontinuation, follow-up will continue for subsequent anti-MM Tx, OS, and second primary malignancies. As of Jan 2015, 62 sites have opened in the US and 53 pts have been enrolled. Top enrolling US sites include Dana-Farber Cancer Inst, MA; UT SW Medical Ctr, TX; Gabrail Cancer Ctr, OH; and NW Georgia Oncology Ctr, GA. Sites are planned for Italy, Spain, France, and the rest of the world. Clinical trial information: NCT01734928.

TPS8611 Poster Session (Board #424a), Sun, 8:00 AM-11:30 AM

Denosumab compared with zoledronic acid for the treatment of bone disease in adults with newly diagnosed multiple myeloma: An international, randomized, double-blind trial. *First Author: Noopur S. Raje, Massachusetts General Hospital, Boston, MA*

Background: A characteristic feature of multiple myeloma (MM) is osteoclast-mediated breakdown of the bone. Patients with MM and bone lesions often experience debilitating pain and skeletal complications including pathologic fractures, need for radiotherapy or surgery to bone, and spinal cord compression, collectively termed skeletal-related events (SREs). RANKL is the key mediator of osteoclast activity. Denosumab, a fully human monoclonal antibody specific to RANKL, inhibits the formation, function, and survival of osteoclasts, thus decreasing cancer-mediated bone destruction. The primary endpoint of this trial is to determine whether denosumab is noninferior to zoledronic acid (ZA) in delaying the time to 1st on-study SRE in patients with MM. Secondary endpoints include superiority of denosumab vs ZA in delaying the time to 1st on-study SRE and time to 1st-and-subsequent SRE and overall survival. Safety endpoints will be assessed. This trial is registered (ClinicalTrials.gov NCT01345019) and sponsored by Amgen Inc. **Methods:** Targeted enrollment is ~1520 adults with newly diagnosed MM and $\geq$ 1 bone lesion receiving first-line treatment. Patients with $\leq$ 30 days of anti-myeloma therapy, $\leq$ 1 prior dose of IV bisphosphonate, an ECOG status $\leq$ 2, and adequate organ function are eligible. Use of any approved anti-myeloma treatment is permitted. Enrolled patients are stratified by whether they intend to undergo autologous stem cell transplant; use of novel vs non-novel anti-myeloma agents as first-line therapy; stage at diagnosis per the International Staging System (I, II, or III); SRE at time of presentation; and geographic region. Randomized (1:1) patients receive either SC denosumab 120 mg + IV placebo *or* IV ZA 4 mg (adjusted for CrCl) + SC placebo once every 4 weeks. Daily calcium ($\geq$ 500 mg) and vitamin D ($\geq$ 400 IU) supplements are strongly recommended. The primary analysis is planned when ~800 patients experience an on-study SRE. Enrollment is currently ongoing and enrollment rates are as planned.

TPS8612 Poster Session (Board #424b), Sun, 8:00 AM-11:30 AM

A multicenter, randomized, open-label, phase 2 study of carfilzomib with or without ARRY-520 (filanesib) in patients with advanced multiple myeloma. *First Author: Jeffrey A. Zonder, Karmanos Cancer Institute, Detroit, MI*

Background: Immunomodulatory agent (IMiD)/bortezomib (BTZ) combinations are common frontline therapy in patients with multiple myeloma (MM). Despite high initial objective response rates (ORR) and prolonged progression-free survival (PFS), almost all patients eventually relapse. Treatment for relapsed or refractory disease typically includes regimens that maintain IMiDs and/or proteasome inhibitors (PIs) as a foundation. Filanesib is a highly selective, targeted kinesin spindle protein (KSP) inhibitor that has shown promising preliminary activity and manageable toxicity as a single agent and in combination with dexamethasone, BTZ and carfilzomib (CFZ). Due to a distinct mechanism of action, filanesib demonstrates activity in patients with myeloma that has become resistant to IMiDs and PIs, potentially addressing a significant unmet medical need. **Methods:** This multicenter, randomized (2:1), open-label Phase 2 study is designed to assess the efficacy, safety and pharmacokinetics (PK) of CFZ ± filanesib in 75 patients with measurable MM who have received at least 2 prior treatment regimens (including BTZ and an IMiD) and have disease refractory to their last myeloma therapy (NCT01989325). Patients at community and academic centers in the United States are stratified by BTZ-refractory disease status and randomized to receive CFZ + filanesib (~50 patients) or single-agent CFZ (~25 patients) in continuous 28-day cycles until disease progression or unacceptable toxicity. CFZ (20/27 mg/m^2) is administered intravenously (IV) on Days 1, 2, 8, 9, 15 and 16. Filanesib is administered as 1.25 mg/m^2/day IV on Days 1, 2, 15 and 16 with prophylactic filgrastim. Crossover from single-agent CFZ to combination treatment is permitted upon confirmed disease progression. The primary endpoint is PFS; secondary endpoints include PFS rate at 6 months, ORR, duration of response, time to best response, clinical benefit rate, disease control rate, safety, and PK. No formal comparisons will be made between treatment arms. Exploratory measurements of alpha 1-acid glycoprotein (AAG), a potential predictive biomarker for filanesib treatment, will be performed. Clinical trial information: NCT01989325.

TPS8613 Poster Session (Board #425a), Sun, 8:00 AM-11:30 AM

The AfFIRM Study: A multicenter phase 2 study of single-agent filanesib (ARRY-520) in patients with advanced multiple myeloma. *First Author: Sagar Lonial, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA*

Background: An unmet medical need exists for patients (pts) with multiple myeloma (MM) whose disease has progressed despite prior exposure to immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs), particularly if their disease has become refractory to carfilzomib (CFZ) and/or pomalidomide (POM). Filanesib is a highly selective, targeted kinesin spindle protein (KSP) inhibitor that has shown promising activity and a manageable safety profile as a single agent in heavily pretreated pts with MM. Due to a distinct mechanism of action, filanesib is expected to be active in cells that have become resistant to IMiDs and PIs, potentially addressing a significant unmet need in the treatment of patients with refractory MM. Nonclinical and prior clinical data have suggested that pts with high serum levels of α 1-acid glycoprotein (AAG) may not obtain therapeutic benefit from filanesib as a result of decreased unbound fraction of drug and ineffective therapeutic exposure. The correlation between Baseline AAG and clinical response to single-agent filanesib will be evaluated. **Methods:** This single-arm Phase 2 study is designed to assess the efficacy and safety of single-agent filanesib in ~160 pts with MM at centers in North America and Europe (NCT02092922). Eligible pts have received at least 2 prior lines of therapy; have received prior bortezomib and lenalidomide; and have disease refractory to CFZ and/or POM. Filanesib (1.50 mg/m^2/day) is administered intravenously on Days 1, 2, 15 and 16 in continuous 28-day cycles with prophylactic filgrastim until disease progression or unacceptable toxicity. Objective response is assessed by independent central review and classified per International Myeloma Working Group (IMWG) criteria. AAG is measured by a central laboratory using a validated immunoturbidimetric assay. The primary endpoint is objective response rate (ORR) in pts with low Baseline AAG. Secondary endpoints are ORR in pts with high Baseline AAG, duration of response, time to best response, clinical benefit rate, disease control rate, progression-free survival, time to next treatment, overall survival and safety. The study includes a 25-pt pharmacokinetics/QT substudy. Clinical trial information: NCT02092922.

TPS8614 Poster Session (Board #425b), Sun, 8:00 AM-11:30 AM

The VITAL study: A randomized, double-blind, placebo-controlled, global, phase III study of NEOD001 in patients with AL amyloidosis and cardiac dysfunction. *First Author: Michaela Liedtke, Stanford Comprehensive Cancer Center, Stanford, CA*

Background: Light chain (AL) amyloidosis is a rare disease caused by the deposition of misfolded proteins that cause dysfunction of vital organs (eg, heart and kidneys). There are no approved therapies. Current therapeutic approaches target the plasma cells that produce the pathogenic light chain proteins and are typically associated with significant adverse effects. Therefore, there is a substantial need for a safe and effective therapy that specifically targets the misfolded light chain proteins responsible for the underlying organ dysfunction. NEOD001 is a monoclonal antibody that targets these misfolded proteins, and it is hypothesized to neutralize circulating soluble protein aggregates and clear insoluble aggregates from organs. In an ongoing phase I/II study in 27 patients with AL amyloidosis and persistent organ dysfunction, NEOD001 was safe and well tolerated, with monthly infusions producing meaningful decreases in cardiac and renal biomarkers by best response. Supported by these positive results, the current study (VITAL; NCT02312206) is a randomized, double-blind, placebo-controlled, phase III trial of NEOD001 in patients with AL amyloidosis and cardiac dysfunction. **Methods:** Eligible patients with a diagnosis of AL amyloidosis (newly diagnosed and treatment naive) with cardiac dysfunction (N-terminal pro-brain natriuretic peptide [NT-proBNP] 650-8500 pg/mL) will be randomly assigned to receive NEOD001 (24 mg/kg q28d) or placebo. Concurrent anti-plasma cell therapy will be allowed in both arms. The primary end point is a composite evidence-based measure consisting of all-cause mortality or cardiac hospitalization. Secondary end points include NT-proBNP response, time to cardiac mortality or cardiac hospitalization, change in the 6-minute walk test, change in the Short Form-36 (SF-36) Questionnaire and Kansas City Cardiomyopathy Questionnaire (KCCQ), and renal and hepatic response. The study has 90% power to detect a $\geq$ 30% difference in events between treatment groups. An interim analysis for efficacy or futility is planned. Estimated enrollment is 236 patients. The VITAL phase III trial has commenced. Clinical trial information: NCT02312206.

9000 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Oral nicotinamide to reduce actinic cancer: A phase 3 double-blind randomized controlled trial. *First Author: Andrew James Martin, NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia*

Background: Nicotinamide (vitamin B3) enhances DNA repair and prevents cutaneous immune suppression after ultraviolet (UV) radiation exposure. It reduces photocarcinogenesis in mice, and human non-melanoma skin cancers (NMSC) in Phase 2 clinical trials. We report the outcomes of the Phase 3 Oral Nicotinamide to Reduce Actinic Cancer (ONTRAC) Study. **Methods:** ONTRAC was a double-blind RCT conducted in two tertiary treatment centers in Sydney, Australia from 2012-2014. 386 immune competent participants with ≥ 2 histologically-confirmed NMSC in the past 5 years were randomized (1:1) to oral nicotinamide 500mg bd (NIC) or matched placebo (PBO) for 12 months. The primary endpoint was the number of new NMSCs to 12 months. Secondary endpoints included number of squamous cell carcinomas (SCCs), basal cell carcinomas (BCCs), and actinic keratoses (AKs) to 12 months. Skin reviews by dermatologists were performed 3 monthly. The sample size provided 90% power to detect a 33% difference in NMSC rates. Analysis was by intention-to-treat. **Results:** The mean age of study population was 66 years, the mean number of NMSC in the past 5 years was 8, and 63% were men. Treatment discontinuation rates were 9% for PBO versus 10% for NIC. 99% of patients underwent at least one post-baseline skin assessment. The average NMSC rate was significantly lower for NIC (1.77) than PBO (2.42). The estimated relative rate reduction (RRR) was 0.23 (95% CI: 0.04 to 0.38, p = 0.02) adjusting for center and NMSC history, and 0.27 (95% CI: 0.05 to 0.44; p = 0.02) with no adjustment. Treatment effects of comparable magnitude were found for both BCCs (RRR = 0.20, 95% CI: -0.06 to 0.39, p = 0.1) and SCCs (RRR = 0.30, 95% CI: 0 to 0.51, p = 0.05). AK counts were reduced for NIC compared to PBO by 11% at 3 months (p = 0.01), 14% at 6 months (p < 0.001), 20% at 9 months (p < 0.0001) and 13% at 12 months (p < 0.005). There were no clinically relevant differences in adverse event rates between the two arms. **Conclusions:** Nicotinamide reduces NMSC formation in high risk patients and is well tolerated. Furthermore, it is widely accessible as an inexpensive over-the-counter vitamin supplement and presents a new chemopreventive opportunity against NMSCs that is readily translatable into clinical practice. Clinical trial information: ACTRN12612000625875.

9001 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Long term follow up of survival in a randomised trial of wide or narrow excision margins in high risk primary melanoma. *First Author: Andrew J Hayes, The Royal Marsden NHS Trust, London, United Kingdom*

Background: Our randomized trial of 1 versus 3 cm clinical excision margins for high risk melanoma showed that narrow margins were associated with an increase in loco-regional relapse, but with no significant difference in melanoma-specific survival (MSS). We now report long-term melanoma-specific and overall survival from that trial. **Methods:** Patients with primary cutaneous melanoma two mm or more in Breslow thickness were randomized to a 1 or 3 cm excision. **Results:** Four hundred and fifty-three patients were randomized to a 1 cm margin and 447 patients to a 3 cm margin. Median age was 58.7 (IQR 47.2-69.2), median tumour thickness and percentage ulceration were similar in both groups (1 cm group: 3.0 mm and 31.8%, 3 cm group: 3.1 mm and 34.5%) . At a median follow-up of 8.8 years (IQR 6.3-11.3), 494 patients have died, with 359 of these deaths from melanoma. There were 194 melanoma deaths in the 1 cm group and 165 in the 3 cm group. Relative rate of melanoma death was estimated to be 24% higher in the 1 cm group than the 3 cm group on univariable analysis (hazard ratio (HR) 1.24; 95% confidence interval (CI) 1.00 to 1.52; p = 0.05). This effect was similar in multivariable analysis, adjusting for known prognostic factors (table).While there was an increase in the number of overall deaths in the 1 cm group compared to the 3 cm group (253 versus 241), this difference was not statistically significant in univariable analysis (HR 1.14: 95% CI 0.96 to 1.36, p = 0.14). **Conclusions:** With longer follow up, the previously reported increase in loco-regional relapse associated with narrow excision margins has translated into a significant increase in melanoma specific mortality.

			Overall Survival	Melanoma-Specific Survival
		N (%)	HR (95% CI) p value	HR (95% CI) p value
Margin	3cm	387 (50.2)	1.00	1.00
	1cm	384 (49.8)	1.19 (0.99-1.45) 0.07	1.27 (1.02-1.59) 0.036
Sex	Female	419 (54.3)	1.00	1.00
	Male	352 (45.7)	1.38 (1.11-1.71) 0.003	1.38 (1.07-1.17) 0.013
Thickness		771 (100)	1.18 (1.10-1.27) < 0.001	1.23 (1.13-1.3) < 0.001
Ulceration	Absent	475 (61.6)	1.00	
	Present	296 (38.4)	1.68 (1.38-2.04) < 0.001	1.75 (1.39-2.20) < 0.001
Site	Distal limb	244 (31.6)	1.00	1.00
	Proximal limb	173 (22.4)	1.23 (0.93-1.63) 0.03	1.44 (1.03-2.03) 0.003
	Trunk	354 (45.9)	1.41 (1.09-1.81)	1.69 (1.24-2.29)

LBA9002 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Survival of SLNB-positive melanoma patients with and without complete lymph node dissection: A multicenter, randomized DECOG trial. *First Author: Ulrike Leiter, Department of Dermatooncology, University of Tuebingen, Tuebingen, Germany*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

9003 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Surveillance imaging with FDG-PET in the follow-up of melanoma patients at high risk of relapse. *First Author: Jeremy Howard Lewin, Peter MacCallum Cancer Centre, East Melbourne, Australia*

Background: In the modern era of melanoma treatment, approaches to imaging surveillance following surgery require reconsideration. The aim of this study was to evaluate disease sub-stage specific schedules of positron emission tomography (PET) surveillance for resected stage III melanoma. **Methods:** Between 2009-2013, patients at the Peter MacCallum Cancer Centre with fully resected AJCC stage III melanoma underwent serial whole body PET/CT scans according to schedules based on Bayesian disease sub-stage relapse probabilities. Schedules were stage IIIA: 6, 18 months; IIIB: 6, 12, 18, 24, 36, 48, 60 months; IIIC: 6, 12, 18, 24, 36 months. Descriptive statistics and contingency table analyses were used to evaluate outcomes for each schedule. **Results:** Eighty-six patients underwent PET surveillance according to schedule (IIIA: 11; IIIB: 50; IIIC: 25). In total, 232 PET scans were performed over a median follow-up of 28 months after surgery. Relapses were identified in 25 (29%) patients (IIIA: 4%; IIIB: 56%; IIIC: 40%), of which 20 (80%) were asymptomatic at the time of scanning. Incidental secondary malignancies were found in 6 (6.5%) patients. Stage IIIA/B relapses were more likely than stage IIIC to be loco-regional (IIIA/B: 42%; IIIC: 10%; p = NS). Nine (36%) relapsed patients underwent potentially curative resection (IIIA: 1; IIIB: 6; IIIC: 2), with 5 (IIIA: 1; IIIB: 4) free of disease after a median 32 months follow-up. The positive and negative predictive values (PPV, NPV) of an individual PET scan for detecting disease relapse at the same time point were: stage IIIB – PPV 69% (CI: 43-87%) and NPV 99% (CI: 95-100%), stage IIIC – PPV 73% (CI: 39-94%) and NPV 97% (CI: 90-100%). The PPV and NPV of each surveillance protocol for detecting any disease relapse were: stage IIIB – PPV 68% (CI: 43-87%) and NPV 97% (CI: 83-99%), stage IIIC – PPV 73% (CI: 39-94%) and NPV 86% (CI: 57-98%). The sensitivity and specificity of the overall approach of sub-stage specific PET/CT surveillance for detecting disease relapse were 88% (CI: 69-97%) and 84% (CI: 72-92%), respectively. **Conclusions:** FDG-PET is effective in detecting asymptomatic metastases and thus facilitating early treatment in patients who relapse after resection of stage III melanoma.

9004 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. *First Author: F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA*

Background: Combined blockade of T-cell checkpoints by NIVO and IPI demonstrated a high objective response rate (ORR), promising overall survival (OS), and a manageable safety profile in pts with advanced MEL in a phase I study, based on which an appropriate dose was selected for registrational trials. We report efficacy and safety of the NIVO + IPI combination vs IPI alone in treatment-naïve pts with advanced MEL, including pts with poor prognostic factors, in a phase II study. **Methods:** Pts (N = 142) with metastatic or unresectable MEL were randomized 2:1 to receive IPI 3 mg/kg combined with either NIVO 1 mg/kg or placebo Q3W × 4, followed by NIVO 3 mg/kg or placebo Q2W until disease progression or unacceptable toxicity. The primary endpoint was ORR in BRAF wild-type (WT) pts. Secondary and exploratory objectives included PFS in BRAF WT pts, ORR and PFS in BRAF V600 mutation-positive (MT) pts, and safety. **Results:** In BRAF WT pts (n = 109), ORR was 60% (43/72) for NIVO + IPI; 11% (4/37) for IPI alone ($P < 0.0001$); complete responses were reported in 12 (17%) and 0 pts, respectively. Median PFS was 8.9 months for the combination vs 4.7 months for IPI alone ($P = 0.0012$). Higher ORR was observed for NIVO + IPI vs IPI in predefined pt subgroups with poor prognostic factors, such as elevated baseline LDH (53% vs 0%) and M1c stage disease (62% vs 25%). Similar ORR and PFS results were observed in 33 BRAF MT pts. Grade 3–4 drug-related adverse events (AEs) were reported in 51% of pts receiving NIVO + IPI vs 20% for IPI alone. The safety profile of NIVO + IPI was similar across pt subgroups, including age. Select AEs related to the combination regimen were consistent with phase I reports and most resolved with immunosuppressive medication (> 83% across organ categories) with the exception of endocrinopathies. Updated results from a planned data analysis in March 2015 will be presented. **Conclusions:** NIVO + IPI significantly improved ORR and PFS compared with IPI alone and had a manageable safety profile. The efficacy and safety of the combination was similar across pt subgroups and provided a favorable risk-benefit ratio in treatment-naïve pts with advanced MEL. Clinical trial information: NCT01927419.

9005 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Long-term efficacy of pembrolizumab (pembro; MK-3475) in a pooled analysis of 655 patients (pts) with advanced melanoma (MEL) enrolled in KEYNOTE-001. *First Author: Adil Daud, UC San Francisco, San Francisco, CA*

Background: The anti–PD-1 antibody pembro is approved in the US for treating unresectable or metastatic MEL that progressed following ipilimumab (IPI) and, if *BRAF* ^{V600} mutant, a BRAF inhibitor. Pembro has demonstrated robust antitumor activity and manageable toxicity in IPI-treated (IPI-T) and naive (IPI-N) pts. In KEYNOTE-002, pembro significantly prolonged PFS over chemotherapy in IPI-refractory MEL. Here we present long-term follow-up data for all pts with MEL enrolled in KEYNOTE-001 (NCT01295827). **Methods:** IPI-T and IPI-N pts received pembro 2 mg/kg every 3 weeks (Q3W), 10 mg/kg Q3W, or 10 mg/kg Q2W until unacceptable toxicity, disease progression, or investigator decision. Treatment could continue beyond initial radiographic progression in eligible pts. Response was assessed every 12 wks. Pts were followed for survival every 3 mo after discontinuation. Primary end point was ORR per RECIST v1.1 by central review; secondary end points included PFS, OS, and duration of response (DOR). **Results:** 655 pts enrolled: 342 IPI-T, 313 IPI-N. Median-follow-up duration was 14.8 mo (range, 7.5-29). Median duration of exposure was 5.6 mo (range, 0.03-28.3). At the time of analysis, 217 (33%) pts remained on therapy. ORR was 34% (29% IPI-T, 38% IPI-N), with a 6% CR rate. Median time to response was 2.8 mo (range, 1.6-19.3). 80% of responses were ongoing at the time of analysis, and median DOR was not reached (range, 6+ to 98+ wk). Median PFS was 5.2 mo (95% CI 3.6-5.5) (IPI-T, 4.9 mo [3.0-5.5]; IPI-N, 5.4 mo [3.1-6.9]). PFS rates at 6 and 12 mo were 44% and 34% (41% and 32% IPI-T, 47% and 36% IPI-N). The 1-y OS rate was 67% (63% IPI-T, 71% IPI-N); the rate at 2 y was 50% (46% IPI-T, 53% IPI-N). Overall, 14% of pts experienced grade 3-4 treatment-related AEs, and there were no treatment-related deaths. In randomized cohorts, there were no significant differences in efficacy and safety between doses/schedules. **Conclusions:** Pembro provides robust and durable antitumor activity, promising long-term survival data, and a manageable safety profile in pts with IPI-T and IPI-N metastatic MEL. These results support the approved indication for pembro and its further exploration in other MEL populations. Clinical trial information: NCT01295827.

9006 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced *BRAF*-mutated melanoma. *First Author: James M. G. Larkin, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: Primary analysis of coBRIM showed significant improvement in PFS and overall response rate (ORR) in *BRAF*^{V600} mutation–positive patients (pts) with advanced melanoma treated with vem + cobi (Table). We report an updated median PFS evaluation and a correlative analysis of clinical response with baseline (BL) oncogenic mutations coexisting with *BRAF*^{V600} mutations. **Methods**: Study methods were previously described.[1] PFS and ORR were updated (cutoff Jan 16, 2015), median follow-up was ~14 months. *BRAF*^{V600} mutation and 528 known activating mutations in 17 oncogenic protein kinases were analyzed using next-generation sequencing (average-read depth > 3000×). Reverse-phase protein array (RPPA) was used to assess oncogenic pathway activation in tumors. Co-mutation data were correlated with PFS and ORR. **Results**: Updated median PFS was 12.3 mo for vem + cobi vs 7.2 mo for vem + placebo (pbo); PFS hazard ratio was 0.58 [95% CI; 0.46-0.72]. ORR data are presented (Table). In 46 of 423 (11%) pt samples, coexisting BL oncogenic mutations were seen in *H-,K-,N-Ras*, non-V600 *BRAF*, or receptor tyrosine kinases (RAS/RAF/RTK), with a median allele frequency of 8%. Co-mutations were not correlated with shorter PFS or lower ORR in pts treated with vem + pbo or vem + cobi, despite the tumors' having higher levels of ERK and MEK activation than those without coexistent mutations (detected by RPPA). **Conclusions:** Longer follow-up confirms the clinical benefit of vem + cobi in pts with advanced *BRAF*^{V600}-mutant melanoma. Co-existence of *BRAF*^{V600} and BL activating RAS/RAF/RTK mutations do not seem to affect disease progression or rate of response to vem + cobi or vem treatment. Clinical trial information: NCT01689519.

		May 9, 2014[1]		Jan 16, 2015	
		Vem + Cobi (n = 247)	Vem + Pbo (n = 248)	Vem + Cobi (n = 247)	Vem + Pbo (n = 248)
PFS	PFS events, n	79	128	143	180
	Median follow-up, mo	7.4	7.0	14.9	13.6
	Median, mo (95% CI)	9.9 (9-NR)	6.2 (5.6-7.4)	12.3 (9.5-13.4)	7.2 (5.6-7.5)
	HR (95% CI)	0.51 (0.39-0.68)		0.58 (0.46-0.72)	
Response	Pts, n	167	111	172	124
	ORR, %	68	45	70	50
	Complete response, n (%)	25 (10)	11 (4)	39 (16)	26 (11)
	Partial response, n (%)	142 (58)	100 (40)	133 (54)	98 (40)

[1]Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

9007 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

A phase Ib/II study of BRAF inhibitor (BRAFi) encorafenib (ENCO) plus MEK inhibitor (MEKi) binimetinib (BINI) in cutaneous melanoma patients naive to BRAFi treatment. *First Author: Ryan J. Sullivan, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: MEKi addition to BRAFi therapy has been reported to increase response rate (RR) and duration of response. The BRAFi ENCO (LGX818) and MEKi BINI (MEK162) have each shown promising single-agent activity in *BRAF*V600–mutant melanoma. **Methods:** Combined ENCO and BINI are being evaluated in this phase (Ph) Ib/II open-label study of patients (pts) with *BRAF*V600–mutant cutaneous melanoma. Based on Ph Ib dose-escalation findings, the safety and efficacy of ENCO 600 mg or 450 mg daily + BINI 45 mg twice daily are being investigated in the Ph II part of the study. **Results:** Fifty-five BRAFi-naive pts were enrolled in Ph Ib (n = 13) or Ph II (n = 42). Median duration of exposure was 9.7 mo; 9 pts received ENCO 400 mg or 450 mg daily (5 in Ph Ib, 4 in Ph II), and 39 pts received ENCO starting at 600 mg daily (1 in Ph Ib, 38 in Ph II), all with BINI. Among all pts starting at ENCO 600 mg, common adverse events (AEs; all grades [Grs] > 30%) were nausea (54%), diarrhea (44%), fatigue and arthralgia (33% each), and vomiting, pyrexia, and increased AST (31% each). At ENCO 400/450 mg, rates of these AEs were: nausea and fatigue (44% each), diarrhea, vomiting, and increased AST (33% each), and arthralgia and pyrexia (11% each). Gr 3/4 AEs occurred in 64% of pts treated with 600 mg, commonly including increased ALT (18%), lipase (15%), AST (13%), and creatine phosphokinase (13%). At 400/450 mg, Gr 3/4 AEs occurred in 67% of pts; increased lipase (22%) was the only event occurring in > 1 pt. Photosensitivity (n = 1, 400 mg; n = 1, 600 mg) and Gr 3/4 pyrexia (n = 2, 600 mg) were rare. The confirmed RR among pts treated at ENCO 400/450 mg was 78% (1 CR + 6 PRs) and at ENCO 600 mg was 72% (3 CRs + 25 PRs). Ph Ib and Ph II combined (all doses) median progression-free survival (95% CI) was 11.3 (7.4-14.6) mo, and in pts with baseline lactate dehydrogenase (LDH) > upper limit of normal (ULN; n = 21) and ≤ ULN (n = 32), was 6.8 (5.0-11.3) mo and 20.0 (11.0-not reached) mo, respectively. **Conclusions:** These data suggest that ENCO + BINI is well tolerated at multiple doses, with promising activity in BRAFi-naive pts with *BRAF*-mutant melanoma. A Ph III trial (COLUMBUS) is underway using ENCO 450 mg daily with BINI. Clinical trial information: NCT01543698.

9008 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

BRAF inhibitor acquired resistance: A multicenter meta-analysis of the spectrum and clinical implications of resistance mechanisms. *First Author: Douglas Buckner Johnson, Vanderbilt Univ, Nashville, TN*

Background: Acquired resistance (AR) to BRAF inhibitors (BRAFi) in melanoma is a near-universal phenomenon driven by numerous genetic and non-genetic alterations. Clinical implications of these AR mechanisms have not been described in a large cohort. We assessed the spectrum of BRAFi AR mechanisms and their associated timing of onset, pattern of disease progression (DP), and clinical outcomes. **Methods:** We compiled clinical and genetic data from 100 patients (pts) with 132 melanoma samples obtained at BRAFi DP from three previously published studies of BRAFi resistance. Whole exome sequencing and/or PCR-based genetic testing were performed on all samples. Associations between AR mechanisms and clinical features/outcomes were assessed with multivariate logistic regression models. **Results:** In 132 DP samples, putative AR mechanisms were identified in 58%, including *NRAS* or *KRAS* mutations (20%), *BRAF* splice variants (16%), $BRAF^{V600E/K}$ amplifications (13%), MEK1/2 mutations (7%), and non-MAPK pathway alterations (11%). Marked heterogeneity was observed within tumors and patients. $BRAF^{V600E/K}$ amplifications and non-MAPK alterations often co-occurred with other genetic changes, whereas *NRAS* mutations, *MEK1/2* mutations, and *BRAF* splice variants largely arose in isolation ($p = 0.02$). Of 19 pts with ≥ 2 DP biopsies, identified AR mechanisms were concordant in only 1 pt (5%). *NRAS* mutations were associated with vemurafenib use ($p = 0.045$) and baseline intracranial metastases ($p = 0.036$). Progression-free survival and patterns of DP were similar across AR mechanisms. The median survival after DP was 6.9 months, and subsequent responses to combined BRAF/MEK inhibition were uncommon (2/15; 13%); no patients responded to ipilimumab (0/24). Post-progression outcomes did not correlate with specific BRAFi AR mechanisms. **Conclusions:** This is the largest study of acquired BRAFi resistance in pts with *BRAF* mutant melanoma. Despite marked heterogeneity of AR mechanisms within pts and tumors, *NRAS* mutations were associated with vemurafenib use and intracranial disease. Further investigation into non-genetic AR mechanisms and immune features of BRAFi progression is warranted.

9009 Poster Discussion Session; Displayed in Poster Session (Board #252), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Safety and activity of pembrolizumab in melanoma patients with untreated brain metastases. *First Author: Harriet M. Kluger, Yale School of Medicine, New Haven, CT*

Background: Brain metastases (BrMs) develop in 40% of metastatic melanoma (MM) patients (pts). Untreated BrMs exclude from most clinical trials. In prior trials, treatment of MM with pembrolizumab (pembro), an IgG4 antagonist of the immune checkpoint PD-1, produced response rates of $> 30\%$. A phase 2 study (NCT02085070) was initiated to assess safety and activity of pembro in pts with previously untreated or progressing BrMs. **Methods:** Pts with BrMs from melanoma (reported here) or lung cancer are eligible if at least 1 asymptomatic 5-20mm BrM not requiring immediate local therapy or systemic steroids is present, and at least 1 BrM is amenable to biopsy or resection. Prior PD-1/PD-L1 inhibitors are excluded. Pembro 10mg/kg is administered every 2 weeks (wks). Brain MRI is repeated at 4 wks to assess safety and restaging is done every 8 wks. Primary endpoint is BrM response by modified RECIST (lesions $\geq$ 5mm are measurable on MRIs with 1mm slices; up to 5 BrMs are used to determine response). **Results:** Between April and December 2014, 17 pts were accrued, 6 with BRAF mutations, 10 previously received ipilimumab. Activity at interim analysis was sufficient to continue. Four were unevaluable for BrM response (3 due to rapid extracerebral disease progression (PD), 1 due to intralesional hemorrhage), and 1 was too early. Among 12 evaluable pts, BrM partial responses (PRs) were observed in 3 pts (1 with prior ipilimumab), stable disease in 2, PD in 7 (2 with a mixed response and 1 with PD by imaging but pseudoprogression on histology). BrM responses are ongoing at 7+, 6+ and 3+ months. One CR and 3 PRs were observed in extra-cerebral metastatic disease, 3 of these 4 with concordant BrM response. The only grade 3 adverse event clearly related to pembro was liver function abnormalities (1 pt). Two pts had seizures, 1 from perilesional edema, 1 from tumor growth, treated with anti-convulsants and a brief course of steroids. **Conclusions:** Early results from this ongoing trial suggest that pembro has promising activity in untreated melanoma BrMs. CNS symptoms were controllable with anti-convulsants and transient use of steroids. Accrual is ongoing and correlative studies from pre-treatment brain and extra-cerebral tumor samples are being conducted. Clinical trial information: NCT02085070.

9010 Poster Discussion Session; Displayed in Poster Session (Board #253), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

The use of pembrolizumab for the treatment of metastatic uveal melanoma. *First Author: Lisa A. Kottschade, Mayo Clinic, Rochester, MN*

Background: Uveal melanomas are a rare type of melanoma with only 5-7 cases per 1 million persons diagnosed each year. Patients with metastatic melanoma of uveal origin, tend to have lower response rates on traditional therapies, as well as are usually excluded from clinical trials. Herein we report our experience with 7 patients with metastatic uveal melanoma who received pembrolizumab as part Merck's expanded access program. **Methods:** Patients were considered eligible for treatment on this protocol, if they were $\geq$ 12 years old, diagnosed with unresectable metastatic melanoma, had progressed on prior ipilimumab therapy, and if BRAF mutant had progressed on BRAF inhibition therapy. Patients had to have good performance status (ECOG of 0 or 1) and adequate organ and marrow function. Patients could have CNS disease, but needed to be clinically stable, prior to enrollment and could not be receiving other concurrent therapy for their cancer. Patients were treated with 2 mg/kg of pembrolizumab IV over q3 weeks until disease progression, unacceptable toxicity or for up to 2 years. **Results:** Between 4/15/2014 and 8/6/2014, we enrolled a total of 7 patients with metastatic uveal melanoma onto study MK-3475-030. Median age at enrollment was 64, with 5 patients being female. As of the data cutoff date of 1/27/2014 median progression free survival was 12.2 weeks (range 3.14-41) with 2 patients still currently receiving therapy without progression. There was 1 CR, 1 PR and 1 patient with SD. Three patients had PD and 1 patient was excluded as she discontinued therapy after 1 dose due to grade 4 endocrine toxicity. Other toxicities were as expected and were usually grade 1 or 2 in nature. **Conclusions:** While this cohort of patients was small, to our knowledge this is the first such report of outcomes in uveal melanoma patients being treated with anti-PD1 therapy. Toxicities were acceptable and expected. Patients were all pretreated, most with 2+ regimens. Treatment with pembrolizumab appears to be a viable option for patients with metastatic uveal melanoma. Clinical trial information: NCT02083484.

9011 Poster Discussion Session; Displayed in Poster Session (Board #254), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Response to anti-PD1/PDL1 therapy in patients with metastatic desmoplastic melanoma. *First Author: Zeynep Eroglu, City of Hope, Pasadena, CA*

Background: Higher overall burden of somatic mutations in tumors may be associated with better response rates to immunotherapy. Desmoplastic melanoma (DM) is a rare subtype of melanoma comprising approximately 1% of cases. Since DM has been reported to have a higher mutational load than other sub-types of melanoma, we hypothesized that patients with metastatic DM may respond more frequently to anti-PD1 or anti-PDL1 immunotherapies. **Methods**: A retrospective analysis of over 1000 melanoma patients treated with anti-PD1/PDL1 therapies among seven institutions (UCLA, MD Anderson, UCSF, Memorial Sloan Kettering, Vanderbilt, Melanoma Institute Australia, and Westmead) was conducted to identify patients with DM. We assessed objective response rates (ORR), overall survival (OS), and progression-free survival (PFS). **Results**: We identified 23 patients with stage IV DM (either pure or mixed subtype), 2 with stage M1a, 11 with M1b, and 10 with M1c disease. Eighteen patients had received prior systemic therapy, including 12 whose disease progressed following ipilimumab. Three patients were treated with nivolumab (anti-PD1 antibody, doses 0.1 or 3 mg/kg), 1 with nivolumab (3mg/kg) plus ipilimumab (1 mg/kg), 3 with BMS-936559 (anti-PDL1, 0.1 or 0.3 mg/kg), and 16 with pembrolizumab (anti-PD1, 2 or 10 mg/kg). Patients received a median of 9 cycles of therapy. A RECIST ORR of 70% was observed, including 9 complete responses and 7 partial responses (3 with $> 75\%$ decrease in tumor size per RECIST criteria). Median length of follow-up was 13.4 months. Three patients with eventual isolated progression underwent surgical excision without further disease progression, and only 2 of 23 patients received subsequent systemic therapy. Eighteen patients were alive at last follow-up; Kaplan-Meier median OS (range 2.8 months to 3.5+ years) and median PFS (range 1.4 months to 2.7+ years) were not reached. **Conclusions**: Patients with metastatic DM appear to have higher response rates and favorable clinical outcomes to anti-PD/PDL1 therapy compared to other patients with advanced melanoma. Additional mechanistic studies are ongoing.

9012 Poster Discussion Session; Displayed in Poster Session (Board #255), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Deep profiling of tumor immune microenvironment (TME) with fluorescence activated cell sorting (FACS) in advanced melanoma. *First Author: Kimberly Loo, UC San Francisco, San Francisco, CA*

Background: Tumor PD-L1 expression by immunohistochemistry has limitations in describing the tumor immune microenvironment as it relates to treatment with PD-1/PD-L-1 antibodies. We developed a novel FACS based method to study the tumor immune microenvironment and used it in patients undergoing PD-1/PD-L-1 antibody treatment. **Methods**: Multi -parameter flow cytometry was performed on freshly harvested metastatic melanoma tumor tissue following overnight enzymatic digestion (n = 161). The gating strategy sorted tumor cells, CD4+, CD8+ and myeloid/stromal cells. CD8+ cells were further sorted for PD-1, PD-L1, CTLA-4, and HLA-DR, while CD4+ cells were sorted for FoxP3 in addition to these markers. Tumor associated macrophage and dendritic cell activation markers were also determined in samples. Overall responses were derived from investigator reported data by Response Evaluation Criteria in Solid Tumors (RECIST). Descriptive statistics for responders vs. non-responders to anti-PD-1 therapy were constructed to assess the prognostic utility of these markers. **Results:** TME-FACS was evaluable on 32 unique patients who were evaluable for response. A high percentage (> 35% of total CD8+ cells) of PD-1 and CTLA-4 expressing $CD8^+$TILs is associated with an increased response to anti-PD-1 therapy. Increased mean fluorescence intensity (MFI) of PD-1/CTLA-4 dual expression on CD8+ cells is also associated with response. Myeloid cell markers clearly stratified responders vs. non-responders to anti-PD-1 therapy. **Conclusions:** TME-FACS is a novel method to functionally define the immune microenvironment in melanoma. TME-FACS immunoprofiling revealed that an increased percentage of PD-1/CTLA-4 + CD8+ TIL populations in metastatic lesions correlates with responsiveness to anti-PD-1 therapies. Defined myeloid subsets can also be uncovered by TME-FACS.

Response Assessment	Median PD1 / CTLA4 MFI	Median % PD1+ CTLA4+ CD8 TILs
Complete Response (CR)	238	49 %
Partial Response (PR)	217.5	37.5 %
Stable Disease (SD)	199.5	32.05 %
Progressive Disease (PD)	163	26.1 %

9013 Poster Discussion Session; Displayed in Poster Session (Board #256), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Bim as a predictive T-cell biomarker for response to anti-PD-1 therapy in metastatic melanoma (MM). *First Author: Roxana Stefania Dronca, Mayo Clinic, Rochester, MN*

Background: Given the variability in response to novel immunotherapeutic agents such as anti-PD1/PD-L1 therapies and the desire to extend their long-term benefit to more patients (pts), there is an increased need for the development of biomarkers that can help predict treatment outcomes and ensure that these treatments, which may have significant toxicities, are offered to pts more likely to benefit. We evaluated Bim (BCL-2-interacting mediator of cell death) in peripheral blood (PB) tumor-reactive $CD11a^{high}PD\text{-}1^+CD8^+$cytotoxic T lymphocytes (CTL) as a marker of the status of PD-1 engagement and T-cell reversibility to identify pts with MM who are more likely to benefit from anti-PD-1. **Methods:** MM patients treated with Pembrolizumab (pembro) 2 mg/kg every 3 weeks through an Expanded Access Program (EAP) had PB collected at baseline and at radiographic tumor evaluation through a separate biomarker sub-study. Frequencies of Bim^+ T cells and Bim median fluorescence intensity (MFI) were measured by flow cytometry in gated $CD11a^{high}PD1^+$ $CD8^+$T cells. Non-parametric t-test was used to compare baseline Bim and percent change in Bim levels in pts who had a radiographic response (CR/PR/SD) compared to those who had progressive disease (PD) at 12 wks. **Results:** 29/40 ptsenrolled in the EAP had baseline samples and 14/29 pts had serial samplesavailable. Clinical benefit (CR/PR/SD) was observed in 9/27 evaluable pts at 12 wk; 18/27pts had PD. Two pts discontinued therapy for adrenal insufficiency (attribution to pembro unknown) and were not evaluable. Pts with clinical benefit after 4 cycles had higher frequency of Bim+/PD-1+ CD8 T cells at baseline compared to pts with radiographic PD (mean 60% vs. 49%, P = 0.04). In 9/9 responders who had serial PB samples available, the levels of Bim in PD-1+ CD8 T cells decreased after the first 3 months of treatment, and they increased/did not change in all 5/5 nonresponders with serial samples evaluable (P = 0.003). **Conclusions:** Measurements of Bim levels in tumor-reactive PD-1+ CD8 T cells may select patients likely to benefit from anti-PD-1 therapy, and provide a new non-invasive way to monitor response to anti-PD-1 blockade in MM. These results are being validated on a larger prospective cohort.

9014 Poster Discussion Session; Displayed in Poster Session (Board #257), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Effect of melanoma intrinsic β-catenin signaling on immune exclusion and resistance to immunotherapies. *First Author: Stefani Spranger, University of Chicago, Chicago, IL*

Background: A subset of metastatic melanoma patients shows evidence for a T cell-inflamed tumor microenvironment at baseline, which has prognostic value and is associated with clinical response to immunotherapies including anti-PD-1. However, the molecular mechanisms mediating the absence of T cell infiltration in a major subset of patients have not been defined. **Methods:** Exome sequencing and gene expression profiling of melanoma metastases (TCGA) was combined with mechanistic studies in genetically engineered mouse models. **Results:** Analysis of melanoma metastases samples using gene expression profiling and exome sequencing, revealed activation of Wnt/ß-catenin pathway in a major subset of non-T cell-inflamed tumors. Using genetically engineered mouse melanoma models ($Braf^{V600E}$/$PTEN^{-/-}$± active ß-catenin), we demonstrated a causal effect between tumor-intrinsic ß-catenin signaling and T cell exclusion from the tumor microenvironment. The mechanism was via failed production of the chemokine CCL4, which was associated with failed recruitment of Batf3-lineage dendritic cells. Mice with these non-T cell-inflamed melanomas failed to respond to anti-CTLA-4/anti-PD-L1 mAb therapy. Active Wnt/ß-catenin signature in human melanomas was associated with reduction of Batf3 dendritic cell transcripts. Clinically, a patient who responded to a melanoma vaccine then recurred showed selection for loss of the T cell signature and gain of the ß-catenin phenotype. **Conclusions:** We have for the first time identified an oncogenic pathway that directly mediates immune evasion, which is implicated in examples of both primary and acquired resistance to immunotherapies.

9015 Poster Discussion Session; Displayed in Poster Session (Board #258), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Quantitative assessment of *BRAF* V600 mutant cell-free tumor DNA from plasma as a diagnostic and therapeutic biomarker in pts with *BRAF* V600 mutant melanoma. *First Author: Max Schreuer, Vrije Universiteit Brussel (VUB), Brussels, Belgium*

Background: Analysis of *BRAF* V600 mutant cell-free tumor DNA (ctDNA) from plasma is under consideration as a biomarker in pts with advanced melanoma. **Methods:** Plasma samples were obtained from pts with advanced melanoma who participated in 3 prospective clinical trials. Quantitative allele-specific PCR analysis for *BRAF* V600 E/E2/D/K/R/M mutations was performed on cell-free DNA extracted from 1ml plasma (Idylla, Biocartis). **Results:** From 2/2014 to 12/2014, 232 plasma samples from 41 pts were analyzed. Detection of *BRAF* V600 mutant ctDNA at the time of diagnosis of metastatic disease was concordant with tumor tissue analysis in 100% of pts (*BRAF* mutant 3/10, *BRAF* wt 7/10). In the 3 *BRAF* mutant pts, ctDNA results preceded tissue results with a median of 40 days (14-93). Therapeutic monitoring of *BRAF* mutant ctDNA was performed in 33 pts (median of 7 analyses per pt [range 2-13]; median follow up of 4.8 months [0.5-9]). Treatment consisted of BRAF/MEK targeted therapy (n = 26 pts), ipilimumab (n = 5) or pembrolizumab (n = 9). In the 6 pts who had a detectable *BRAF* mutant ctDNA fraction (range 7-53%) at initiation of BRAF/MEK targeted therapy, the *BRAF* mutant ctDNA fraction became undetectable (n = 5) or < 1% (n = 1) after a median of 14 days (5-40) notwithstanding the absence of radiological CR. During BRAF/MEK targeted therapy, an increase in the *BRAF* mutant ctDNA fraction was detected prior to PD on imaging in 7/12 pts (58%; median interval of 1.1 month [0.8-1.7]) and concomitantly with PD on imaging in 2/12 pts (17%). An increase in *BRAF* mutant ctDNA fraction predicted PD during the following month in 67% of cases (n = 14/21, $p < 0.001$) and in 100% of cases within the following 2 months (n = 21/21, $p < 0.001$). Undetectable *BRAF* mutant ctDNA predicted absence of PD in the following month in 91% of analyses (n = 94/103; $p < 0.001$) and in the following 2 months in 83% of analyses (n = 77/93; $p < 0.001$). **Conclusions:** Analysis of *BRAF* mutant ctDNA from plasma allows for a rapid diagnosis of the *BRAF* status in pts with advanced melanoma. *BRAF* mutant ctDNA likely reflects the *BRAF* mutant proliferative tumor burden and holds promise as a therapeutic monitoring tool for pts with advanced *BRAF* V600 mutant melanoma.

9016 Poster Discussion Session; Displayed in Poster Session (Board #259), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Circulating melanoma cells and recurrence in stage III melanoma patients. *First Author: Anthony Lucci, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There is a need for more sensitive and specific prognostic markers for advanced stage melanoma patients to help improve the risk-benefit ratio of systemic adjuvant therapies. While it has been demonstrated that circulating melanoma cells (CMCs) can be detected in melanoma patients, there is limited data regarding the prognostic significance of CMCs. The aim of this prospective study was to determine if CMCs predicted relapse in stage III melanoma patients. **Methods:** Serial CMC assessments (7.5mL blood) were performed in 101 patients with stage III cutaneous melanoma patients using the CellSearch system (Janssen). CD146+ cells were immunomagnetically enriched; CD146+, HMW-MAA+/, CD45-/, and CD34- nucleated cells were considered CMCs. Relapse-free survival was compared between patients with ≥1 CMC detected at baseline (first presentation to our clinic) or at second blood draw (6 months after baseline), versus those with no CMCs at baseline and at the second blood draw. Log-rank test and Cox regression analysis were applied to establish the association of CMCs with relapse-free survival. **Results:** CMCs were identified in 44 of 101 (44%) patients at either baseline or at second blood draw. Median follow up was 10 months. We observed no significant association between CMC presence and primary tumor factors including Breslow thickness, number of mitotic figures, or ulceration. Relapse was observed in 10 of 44 (23%) patients with ≥ 1 CMC, versus 4 of 57 (7%) of patients with no CMCs at baseline and at second blood draw (log-rank P = 0.04, HR 3.25, 95% CI 1.01 to 10.37; P = 0.04). **Conclusions:** CMCs at baseline or at a six month follow up blood draw predicted relapse in stage III melanoma patients. This data supports larger studies to confirm that presence of CMCs could be used to identify patients at risk for relapse, with an ultimate goal of early systemic intervention.

9017 Poster Discussion Session; Displayed in Poster Session (Board #260), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Plasma-based monitoring of BRAF mutations during therapy for malignant melanoma (MM) using combined exosomal RNA and cell-free DNA analysis. *First Author: Ryan J. Sullivan, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Oncogenic mutations in the *BRAF* gene (V600E/V600K) are present in 40-50% of patients with MM and represent an important therapeutic target (e.g. vemurafenib). Blood-based, serial monitoring of BRAF and other mutations during therapy may be useful to inform time-critical treatment decisions. Plasma contains at least two sources of cell-free nucleic acids (NAs): exosomal RNA (exoRNA) and cell-free DNA (cfDNA). Combining exoRNA and cfDNA maximizes the yield of genetic material from plasma, and may enable monitoring of both biologically important sources to enhance mutation detection sensitivity and help match patients to targeted therapies. **Methods:** Blood was drawn from 10 metastatic MM patients for analysis prior to therapy initiation and up to 8 serial time points. Subsequent purification of high-quality NAs using a novel, spin-column based method (EXO52) to co-isolate all exoRNA and cfDNA allowed analysis of mutations present in both NA fractions by ultra-deep sequencing. A custom next-generation sequencing (NGS) library preparation method, with a novel bioinformatics pipeline to efficiently call the rare mutations, was used to analyze a panel of 9 mutation hotspots from 6 genes, including BRAF. Data were correlated with tissue-based mutational analysis, treatment information, and RECIST-defined response assessments. **Results:** Somatic mutations from MM tumors were readily detected in both exoRNA and cfDNA from plasma. We show that the BRAF mutation signal from patient blood reduces with BRAF inhibitor treatment and is detectable in plasma prior to observed clinical and radiographic progression. Further, mutation signal from exoRNA consistently exceeds that from cfDNA across timepoints, with rate of change during response or relapse also showing differences. Possible clinical relevance of the BRAF exoRNA:cfDNA ratio will be discussed. **Conclusions:** Co-isolation of circulating exoRNA and cfDNA with EXO52 and subsequent NGS using a targeted gene panel provides a highly sensitive approach to monitor for BRAF and other somatic mutations in MM patients over the course of treatment, and has clinical utility.

9018 Poster Discussion Session; Displayed in Poster Session (Board #261), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): A pooled analysis. *First Author: Jeffrey S. Weber, Moffitt Cancer Center, Tampa, FL*

Background: NIVO is a programmed death-1 (PD-1) immune checkpoint inhibitor which has shown durable tumor responses in multiple cancer types and prolongs overall survival in pts with MEL. The objective of the current analysis is to describe the safety profile of NIVO across recent MEL studies, including 4 studies in which guidelines for the management of adverse events (AEs) were utilized. **Methods:** A retrospective safety review was conducted for 4 ongoing phase I–III trials, in which MEL pts received NIVO 3 mg/kg Q2W until disease progression or unacceptable toxicity. Data were included from pts who received at least 1 dose of NIVO, and included assessments of AEs, select AEs (immune-related etiology), time to onset and resolution, and the use as well as impact of immune modulating agents (IMs). **Results:** A total of 576 patients received NIVO for a median of 3.7 months; 312 (54%) had received prior ipilimumab (IPI). The most frequent drug-related AEs of any grade were fatigue (25%), pruritus (17%), diarrhea (13%), and rash (13%); grade 3–4 drug-related AEs occurred in 10% of all pts, and in 8% of pts with prior IPI. No drug-related deaths were reported. Drug-related select AEs of any grade were most frequent in the skin (34%), GI tract (13%), endocrine glands (8%) and liver (4%); grade 3–4 select AEs occurred in 4% of pts. Median time to onset of drug-related select AEs ranged from 5 wks for skin AEs to 15 wks for renal AEs. IMs were administered to 166/474 pts (35%) in phase III studies to manage AEs; 114 pts (24%) received systemic corticosteroids. Among 21 pts with grade 3–4 drug-related select AEs, all but 1 pt with a skin AE resolved with IMs. Median time to resolution ranged from 3 wks for hepatic AEs to 29 wks for skin AEs. The objective response rate was 44% in pts who received an IM and 36% in those who did not; time to response was similar (median 9 wks), and the median duration of response was not reached for either pt subgroup. **Conclusions:** In this pooled analysis, drug-related AEs with NIVO monotherapy were primarily low grade and the incidence of grade 3–4 drug-related AEs was not affected by prior IPI. Nearly all drug-related grade 3–4 select AEs resolved with use of IMs, which did not appear to impact on tumor response.

9019 Poster Discussion Session; Displayed in Poster Session (Board #262), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. *First Author: Douglas Buckner Johnson, Vanderbilt Univ, Nashville, TN*

Background: Ipilimumab (Ipi) is a cornerstone of metastatic melanoma therapeutics. Since Ipi toxicities are largely immune-related, clinicians may withhold therapy in patients (pts) with pre-existing autoimmune disorders (AD). We assessed whether pts with AD treated with Ipi experienced exacerbation of their AD, excessive immune-related adverse events (irAEs), and optimal clinical activity. **Methods:** We retrospectively reviewed records from 12 pts with metastatic melanoma and pre-existing AD treated with Ipi from 4 centers. We characterized baseline AD symptoms, prior management, and disease course on therapy. We also assessed rates of classical Ipi-related irAEs, and subsequent clinical outcomes, including objective response rate (ORR), overall survival (OS), and progression-free survival (PFS). **Results:** Of 12 pts, 5 had baseline rheumatoid arthritis, 3 had psoriasis/psoriatic arthritis, 1 had systemic lupus erythematosus, 1 had Crohn's disease, 1 had transverse myelitis, and 1 had sarcoidosis. Ten (83%) had previously received corticosteroids or other systemic therapy for their AD, including 5 ongoing at the time of Ipi initiation (low-dose prednisone in 2 pts and hydroxychloroquine in 3). Following Ipi, 6 pts (50%) had symptomatic worsening or flares of their AD; all resolved with short courses of corticosteroids and none required additional immune suppression. Grade 3-5 irAEs were observed in 5 pts (42%) including colitis (n = 2), hypophysitis (n = 2), and acute angle glaucoma (n = 1). One treatment-related death occurred, presumably from colitis and possibly hypophysitis (no laboratory confirmation) following dose 3 of Ipi. ORR was 17% (2/12 pts); median OS and PFS were and 22.0 and 3.0 months, respectively. One pt experienced a durable complete response. **Conclusions:** This is the largest study of Ipi in pts with autoimmune disorders. Ipi was associated with moderate tolerability and clinical activity in this cohort of pts with mild to moderate pre-existing AD. Clinicians should monitor pts closely for irAEs and AD flares. Larger retrospective and prospective studies are ongoing to characterize this cohort further.

9020 Poster Session (Board #263), Mon, 1:15 PM-4:45 PM

Extended follow-up results of phase Ib study (BRIM7) of vemurafenib (VEM) with cobimetinib (COBI) in *BRAF*-mutant melanoma. *First Author: Anna C. Pavlick, New York University Cancer Center, New York, NY*

Background: BRIM7 formed the basis for development of the VEM + COBI regimen, which, in a randomized phase III trial, confirmed the statistically significant and clinically meaningful progression-free survival (PFS) improvement of VEM + COBI over VEM. Results of BRIM7 with extended follow-up are presented. **Methods:** Eligible patients (pts) had advanced $BRAF^{V600}$-mutated melanoma, ECOG PS 0-1, and could either have progressed on VEM (VEM-PD) or be BRAF inhibitor (BRAFi) naive. Dose escalation pts received VEM 720 mg or 960 mg twice daily (BID) continuously + COBI 60 mg, 80 mg, or 100 mg once daily (QD) 14 days on/14 days off (14/14); 21 days on/7 days off (21/7); or continuously. Two dose levels were expanded: VEM (720 mg and 960 mg BID) + COBI 60 mg QD 21/7. **Results:** Previously, we reported the 129 VEM + COBI treated pts with the following characteristics: BRAFi naive: 49%; stage M1c: 70% and 82%; LDH > ULN: 46% and 62%; and median follow-up: 13 months and 6 months, for BRAFi-naive and VEM-PD pts, respectively (Ribas A. *Lancet Oncol* 2014; 15:954-965). In this update, the median follow-up in BRAFi-naive and VEM-PD pts was 21 months and 8 months, respectively. Adverse event (AE) frequency and severity remained stable with extended follow-up. The frequencies of symptomatic MEK inhibitor AEs (serous retinopathy and cardiomyopathy) and BRAFi AEs (skin squamous carcinoma) were also unchanged. Confirmed response rate in BRAFi-naive pts remained at 87%. Four additional pts attained complete response (CR) at Cycles 16-25, increasing CR rate from 10% (6 pts) to 16% (10 pts). Median PFS was unchanged at 13.8 months. With extended follow-up, median overall survival (OS) was reached at 28.5 months and 2-year OS was 61%. Confirmed response rate in VEM-PD pts remained at 15%, 1 pt attained CR at Cycle 22. CR was not observed previously in VEM-PD pts. Median PFS and OS were unchanged at 2.8 months and 8.4 months, respectively. The 2-year OS was 15% with extended follow-up. **Conclusions:** VEM + COBI continues to show robust efficacy in BRAFi-naive pts, with a manageable and tolerable safety profile without new safety signals. Median OS in BRAFi-naive pts was > 2 years. Late CR conversions indicate persistent activity with continued therapy. Clinical trial information: NCT01271803.

9021 Poster Session (Board #264), Mon, 1:15 PM-4:45 PM

Quality-of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C). *First Author: Brigitte Dréno, Nantes University, Nantes, France*

Background: The phase 3 coBRIM study showed significant improvement in progression-free survival in pts with metastatic melanoma on V + C compared with those on V and placebo (P) (HR, 0.51; 95% CI, 0.39-0.68, $P< 0.001$ (Larkin et al. *N Engl J Med* 2014;371:1867-1876). We report the evaluation of health-related QOL in coBRIM for V + C versus V + P, as measured by the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30). **Methods:** The EORTC QLQ-C30 was evaluated in pts with baseline (BL) and ≥ 1 post-BL assessment. Assessments were conducted on Days (D) 1 and 15 in cycles (C) 1 and 2 (each C = 28 days), and every other cycle thereafter until pt withdrawal or end of study. The analysis includes assessments up to C8D1. Each domain score, assessing global health status and QOL, and symptom scales were examined at BL and for each time point (change from BL) by treatment arm descriptively; formal statistical comparisons were not conducted. Clinically meaningful (CM) change was defined as a ≥ 10-point increase or decrease from BL. **Results:** The completion rate at BL for both treatment arms was 96.7% and was consistently high (≥ 88%). Across all functioning domains (cognitive, emotional, social, role, and physical) and symptoms (appetite loss, constipation, nausea and vomiting, dyspnea, pain, and fatigue), pts in the V + C arm reported better scores at 1 or more post-BL time points evaluated versus those in the V + P arm, but mean score change did not reach CM criteria. However, pts in the V + C arm experienced a CM or marginal improvement in insomnia (C2D15, C4D1, C6D1, C8D11), while no V + P pts showed CM change from BL in insomnia. The V + C arm experienced CM worsening of diarrhea from BL only at C1D15 and C2D15; no CM change from BL for diarrhea was observed in the V + P arm. Responder analysis showed that a higher percentage of pts in the V + C arm had CM score improvements from BL for all EORTC domains; the greatest differences were observed in insomnia (16%), social functioning (11%), fatigue (9%), and pain (7%). **Conclusions:** In pts with metastatic melanoma, V + C provided superior efficacy compared with V +P and symptom improvement for insomnia, social functioning, fatigue, and pain with similar QOL. Clinical trial information: NCT01689519.

9022 Poster Session (Board #265), Mon, 1:15 PM-4:45 PM

Determination of locally advanced basal cell carcinoma (BCC) in the first 285 patients enrolled in the RegiSONIC disease registry study. *First Author: Simon S. Yoo, Northwestern University, Chicago, IL*

Background: Advanced BCC (aBCC), including metastatic (mBCC) or locally advanced BCC (laBCC), is rare, and a broadly accepted diagnostic definition of aBCC is lacking. The RegiSONIC disease registry (ClinicalTrials.gov identifier: NCT01604252) is designed to evaluate how clinicians diagnose and treat aBCC in real-world practice. **Methods:** RegiSONIC is an ongoing, multicenter, prospective observational cohort study in 3 BCC patient (pt) populations, treated according to clinician's standard of care: newly diagnosed pts with vismodegib-naive aBCC (cohort 1), pts with aBCC who previously received vismodegib in a Genentech-sponsored study (cohort 2), or pts with BCCNS who have aBCC or multiple BCCs of any stage (cohort 3). Determination of aBCC was at the clinician's discretion and not dictated by the protocol. This summary describes determination of laBCC in the first 285 pts enrolled to cohort 1 as of September 12, 2014. **Results:** Median time from initial diagnosis of the current BCC lesion to enrollment was 1.64 months and from determination of laBCC to enrollment was 0.43 months. Determination of laBCC was based on the following (sums to > 100%): lesion size (78%), histopathology (55%), location (53%), extent of disease (51%), recurrence (30%), curative resection unlikely (29%), radiotherapy contraindicated (21%), surgery contraindicated (16%), and other (8%). All pts had clinically visible locally advanced lesions; 72% had a single lesion, and 28% had multiple lesions (median, 3.0 lesions). The median size of target lesions was 20 mm; among 220 pts diagnosed on the basis of lesion size, 65% had lesions measuring ≥ 20 mm. Among 84 pts diagnosed on the basis of recurrence, 40% had ≥ 2 recurrences. Clinical/histopathologic subtype of the target lesion (sums to > 100%) was nodular (64%), morpheiform/infiltrative (29%), superficial (13%), micronodular (3%), basosquamous (3%), and other (11%). Target lesions were predominantly located on the head, including the nose (22.4%), forehead (12.6%), ear (8.3%), cheek (8.3%), and scalp (7.6%). **Conclusions:** Data from RegiSONIC will provide real-world clinical practice insight to help improve the diagnosis and care of pts with aBCC. Clinical trial information: NCT01604252.

9023 Poster Session (Board #266), Mon, 1:15 PM-4:45 PM

The RegiSONIC disease registry: Preliminary effectiveness and safety in the first 66 newly diagnosed locally advanced basal cell carcinoma (BCC) patients treated with vismodegib. *First Author: Mario E. Lacouture, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Treatment of advanced BCC (aBCC), including metastatic or locally advanced (la) BCC, is challenging, with approaches ranging from surgery to recently approved targeted Hedgehog pathway inhibitor vismodegib (VISMO). RegiSONIC (NCT01604252) is an ongoing, multicenter prospective observational cohort study designed to collect real-world data on the diagnosis and treatment of patients (pts) with aBCC and/or BCC nevus syndrome (BCCNS). Here we present preliminary effectiveness and safety results in the first 66 non-BCCNS newly diagnosed laBCC pts treated with VISMO. **Methods:** Pts are enrolling into 3 cohorts (C): newly diagnosed (VISMO-naive) aBCC pts (C1), aBCC pts who previously received VISMO in a Genentech-sponsored study (C2), or pts with BCCNS who have aBCC or multiple BCCs of any stage (C3). Determinations of disease response were investigator assessed. Pt follow-up is every ~3 months. **Results:** By Sept 12, 2014, 285 non-BCCNS newly diagnosed laBCC pts had been enrolled: median age, 68 years; male, 63%. 66 (23%) pts were treated with VISMO (received VISMO within 90 days of determination of laBCC). Median (range) of follow-up: 13.2 (0.16-26.8) months. Results are in the Table. All AEs leading to treatment discontinuation and 1 SAE (acute renal failure) were considered related to VISMO; the 4 deaths (6%) were not. **Conclusions:** Preliminary data from the RegiSONIC study demonstrate effectiveness of VISMO in non-BCCNS newly diagnosed laBCC pts, with a safety profile consistent with previous studies. Real-world data may provide clinical insights to improve the treatment of aBCC pts. Clinical trial information: NCT01604252.

	non-BCCNS Newly Diagnosed, VISMO-Treated laBCC Pts n = 66
Objective response rate, % (95% CI)	68 (56-79)
Complete response, n (%)	29 (44)
Partial response, n (%)	16 (24)
Duration of response (univariate), months, median (range)	5.95 (0.03-22.08)
Progression-free survival, median	NE
Overall survival, median	NE
AEs, n (%)	53 (80)
Ageusia/dysgeusia, %	56
Muscle spasms, %	48
Alopecia, %	38
Weight loss, %	20
Serious AEs, n (%)	8 (12)
AEs leading to discontinuation, n (%)	9 (14)
Muscle spasms, %	56
Alopecia, %	44
Ageusia/dysgeusia, %	33

9024 Poster Session (Board #267), Mon, 1:15 PM-4:45 PM

Impact of treatment breaks on vismodegib patient outcomes: Exploratory analysis of the STEVIE study. *First Author: Reinhard Dummer, University Hospital Zurich, Zurich, Switzerland*

Background: Vismodegib (VISMO) is the first Hh pathway inhibitor approved for use in adults with advanced BCC (aBCC) that is inappropriate for surgery or radiotherapy. While most VISMO-related adverse events (AEs) are mild to moderate, the presence of multiple chronic AEs may lead to treatment interruption or discontinuation. Treatment breaks are allowed in the STEVIE study (NCT01367665) for the management of toxicity, among other reasons. Herein we present an exploratory analysis assessing the safety and efficacy profile in patients (pts) with treatment breaks on study. **Methods:** STEVIE is an ongoing study focusing on safety of VISMO in pts with aBCC. Pts receive VISMO 150 mg once daily until progressive disease, unacceptable toxicity, or withdrawal. The primary objective is safety; efficacy is a secondary end point. Tumor response assessments are performed using RECIST 1.1 as assessed by the investigator. Exploratory analyses were performed using data from a planned interim analysis (data cutoff Nov 6, 2013). **Results:** 499 pts were included in the safety population and analyzed according to number of treatment breaks received. The median duration of treatment was 223.5, 299.0, 399.0, and 454.0 days in pts with 0, 1, 2, or ≥ 3 treatment breaks, respectively. Median dose intensity was 97%, 89%, 86%, and 81%, respectively. Median treatment break duration was 22 days (SD 13.92). Safety and efficacy results are presented in the Table. Patients with more treatment-emergent AEs (TEAEs) including those experiencing more grade ≥ 3 TEAEs had more treatment breaks. These were AEs known to be commonly associated with VISMO use. The most common grade ≥ 3 TEAE was muscle spasm. **Conclusions:** Increased number of treatment breaks was associated with longer median duration of VISMO treatment and did not appear to compromise efficacy. Clinical trial information: NCT01367665.

	Number of treatment breaks			
Result	0	1	2	≥ 3
n (%)	368 (74)	76 (15)	41 (8)	14 (3)
Any TEAE, %	98	100	100	100
Dysgeusia	51	58	63	93
Muscle spasms	59	70	81	93
Alopecia	59	63	78	79
Grade ≥ 3 TEAEs, %	39	45	66	79
Deaths due to TEAEs, n (%)	19 (5.2)	4 (5.3)	0	1 (7.1)
Best overall response rate, %	61	65	95	85
Complete response, %	30	33	51	39
Partial response, %	31	32	44	46
Median progression-free survival, mo	19.8	19.0	Not estimable	Not estimable

9025 Poster Session (Board #268), Mon, 1:15 PM-4:45 PM

De novo versus nevus-associated melanomas: Differences in associations with prognostic indicators and survival. *First Author: Rachel M. Cymerman, NYU School of Medicine, New York, NY*

Background: Although 20%-30% of melanomas may be histopathologically "nevus-associated," implying direct transformation of a nevus into melanoma, the majority of melanomas arise in clinically normal skin with no detectable precursor lesion. We aimed to determine whether nevus-associated and de novo melanomas differ in their associations with histopathologic features and survival. **Methods:** 1,048 melanoma patients prospectively enrolled in the NYU Melanoma Cooperative Group registry between 1972 and 1982 (NYU1) were analyzed to detect associations between type of melanoma (de novo vs nevus-associated) and age, anatomic site, ulceration, thickness, mitotic index, histological type, stage, and survival. We tested the significant associations in a replication cohort of 1,202 melanoma patients prospectively enrolled between 2002 and 2009 in the NYU Interdisciplinary Melanoma Cooperative Group registry (NYU2). **Results:** In the NYU1 dataset, de novo melanomas were more likely to be associated with older age (54 vs 47 years, $p < 0.01$), non-axial location (OR 1.53, $p < 0.01$), tumor thickness > 1.0mm (OR 1.95, $p < 0.01$), ulceration (OR 1.61, $p = .026$), nodular subtype (OR 2.79, $p < 0.01$), stage > 1 (OR 2.35, $p < 0.01$), and shorter overall survival ($p < 0.01$). In the NYU2 replication dataset, de novo melanoma was again significantly associated with older age (61 vs 54 years, $p < 0.01$), non-axial location (OR 2.29, $p < 0.01$), tumor thickness > 1.0mm (OR 2.22, $p < 0.01$), ulceration (OR 2.92 $p < 0.01$), nodular subtype (OR 2.23, $p < 0.01$), stage > 1 (OR 2.43, $p < 0.01$), and shorter overall survival ($p < 0.01$). In multivariate analysis, de novo histopathology was an independent, poor prognostic indicator in the NYU2 cohort only (HR = 1.69, $p < 0.01$). The NYU2 cohort has patients with thinner tumors (56.2% have tumors < 1.0mm) compared to the NYU1 cohort (41.8% have tumors < 1.0mm), which may contribute to the differing impact of the de novo histopathology on the survival models for these cohorts. **Conclusions:** These data suggest that de novo melanomas may be more aggressive than nevus-associated melanomas, and may differ in their molecular pathogenesis. These findings may also have implications for early detection programs.

9026 Poster Session (Board #269), Mon, 1:15 PM-4:45 PM

PD1/PDL-1 and VEGF expression in lymph node microenvironment and relation with tumor burden and survival in cutaneous melanomas. *First Author: Vinicius L Vazquez, Barretos Cancer Hospital, Barretos, Brazil*

Background: The regional lymph nodes are the most common site for melanoma metastasis. The understanding of lymph node microenvironment may lead to the comprehension of the metastasis development and factors related to tumour progression. The aims of this study are to characterize the PD1 (programmed cell death-1), VEGF (Vascular endothelial growth factor) A and C expression in the regional lymph nodes of melanoma patients with and without metastasis; PDL-1 (PD1 ligand) in the lymph node metastasis; and their relation to tumour burden and survival. **Methods:** We retrospectively researched the sentinel nodes, both negative, (pn0) positive (pN1+), and the negative nodes retrieved from the lymph node dissection of the sentinel positive patients (pN1-); Immunohistochemistry was performed looking for the expression of PD-1, VEGFA and C in the lymph node normal/surrounding tumor tissue and their correlation to clinical findings. **Results:** 20 negative sentinel lymph nodes (pN0), 20 positive sentinel nodes (pN1+) and 18 negative lymph nodes from patients with lymph node metastasis (pN1-) were analysed. Follow up ranged from 5.91 to 85.45 months; mean 38.77 (SD 16.13). PD-1 was expressed in 94.7% of pN0, 77.8% of pN1- and 47.1% of pN1+ ($p = 0.006$). PDL-1 was expressed in 68.7% of the tumor cases. VEGF A was expressed in 6.7% of pN0, 16.7% of pN1- and 72,2% of pN1+ ($p < 0.001$). VEGF C expression was present in 89.5% of pN0, 55.6% of pN1- and 80% of pN1+ ($p = 0.101$). Five years survival of PD1 negative patients was 42.9% and PD1 positive 77.1% ($p = 0.034$). PDL1 (only N1+) Five years survival was 33.3% in positive cases versus 24.2% in negative ones ($p = 0.566$). VEGF A five years survival was 78.4% for negative cases and 43.4% for positive ones ($p = 0.008$). VEGF C was 68.6% for negative cases and 66.9% for positive ($p = 0.746$) **Conclusions:** PD-1 expression in the regional lymph node is associated to absence or low tumour burden what is related to higher survival rates. VEGFA expression in the regional lymph node is associated to presence or high tumour burden what is related to low survival. Further studies should be performed to confirm this data and look at their clinical implications. Supported by *CNPQ grant #447590/2014-6*

9027 Poster Session (Board #270), Mon, 1:15 PM-4:45 PM

Effect of nivolumab (NIVO) on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): Results of a phase III study (CheckMate 066). *First Author: Georgina V. Long, Melanoma Institute Australia, North Sydney, NSW, Australia*

Background: While treatments exist that extend survival in advanced MEL, the quality of that survival is not often evaluated. There is a need for treatments that demonstrate increased survival while preserving long-term QoL. In a phase III, randomized, double-blind study, NIVO (a PD-1 immune checkpoint inhibitor; 3 mg/kg every 2 weeks [wks; Q2W]) improved overall survival compared with dacarbazine (DTIC; 1,000 mg/m^2 Q3W) in treatment-naïve pts with advanced MEL. **Methods:** In this study, QoL measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQol-five dimension questionnaire (EQ-5D) was evaluated at baseline (BL) and at treatment cycles Q6W. Mean changes and non-parametric comparisons are reported. Further analyses are planned to examine longitudinal QoL and the relationship between clinical and pt outcomes. **Results:** A total of 418 pts were randomized to NIVO (n = 210) or DTIC (n = 208). Adjusted completion rates at BL for EQ-5D utilities were 69.5% with NIVO and 64.9% with DTIC, and those for EORTC QLQ-C30 were 70.0% with NIVO and 64.9% with DTIC. While rates remained similar throughout the study, analysis of QoL involving DTIC was not feasible after wk 13 due to a high attrition rate in the DTIC arm (n ≤ 41). Mean BL QoL scores were similar for NIVO versus DTIC (EQ-5D utilities: 0.778 vs 0.711; EQ-5D visual analog scale [VAS] scores: 70.9 vs 69.1; EORTC Global Health: 68.9 vs 66.2). No QoL change was noted for DTIC prior to study dropout. For NIVO, improvements from BL were noted in EQ-5D utilities from wk 7 (0.027; n = 132; P= 0.011) through wk 49 (0.045; n = 38; P= 0.034), and in EQ-5D VAS scores at wks 25, 31, 37, 49 and 61 (P≤ 0.03). EORTC subscale scores did not change over time. **Conclusions:** These results demonstrate that NIVO does not impair QoL and may enhance it compared with BL, while also conferring survival benefits, in treatment-naïve pts with advanced MEL. Dropout rates with DTIC after wk 13 limited QoL data interpretation for this treatment group. Clinical trial information: NCT01721772.

9028 Poster Session (Board #271), Mon, 1:15 PM-4:45 PM

Nivolumab in resected and unresectable melanoma: Immune-related adverse events and association with survival outcomes. *First Author: Morganna L Freeman-Keller, Moffitt Cancer Center, Tampa, FL*

Background: In metastatic melanoma, immune checkpoint blockade has generated excellent response rates and prolonged survival. As the depth of immune activation may correlate with occurrence of immune related adverse events (irAEs), an association between irAEs and disease outcomes might also exist. We describe herein the irAE toxicity profile of 148 patients with resected and unresectable melanoma treated with nivolumab at our institution, and the association of irAEs with progression-free (PFS) and overall survival (OS). **Methods:** Data was pooled from 148 patients (33 resected, 115 unresectable) treated at 1-, 3-, or 10mg/kg doses (with or without peptide vaccine) every 2 weeks for 12 weeks, then an additional 12 weeks if stable or better, and up to 2 additional years if stable or better. Frequency, grade, and irAE characteristics were analyzed, including kinetics of onset, resolution, and need for steroid therapy. We conducted a 12-week landmark OS analysis, with a multivariate time-dependent Cox proportional hazard model to assess differences in PFS (for 115 unresectable patients) and OS (all 148 patients) in the presence or absence of irAEs. **Results:** IrAEs of any grade were observed in 68.2% of patients (101/148). Grade III/IV irAEs were infrequent: 3 patients (2%) had Grade III rash, 2 (1.4%) had asymptomatic Grade III amylase/lipase elevation, and 2 (1.4%) had Grade III colitis. Of the irAEs, colitis and pneumonitis required steroids (median duration = 5 wks). Statistically significant PFS and OS differences were seen in patients who experienced any grade of irAE ($p = < 0.001$ and $p = 0.078$, respectively). Improved PFS was associated with rash ($p = < 0.001$ [HR 0.237, 95% CI 0.098 to 0.573]) and vitiligo ($p = 0.005$ [HR 0.121, 95% CI 0.024 to 0.62]). Rash was associated with improved OS ($p = 0.005$ [HR 0.098, 95% CI 0.006 to 1.711]), with non-significant association between vitiligo and OS ($p = 0.081$ [HR 0.146, 95% CI 0.009 to 2.488]. No survival differences were seen with other irAEs (endocrinopathies, diarrhea, or pneumonitis). **Conclusions:** Rash and vitiligo are associated with prolonged PFS and OS in melanoma patients treated with nivolumab, which should be validated in subsequent prospective analyses.

9029 Poster Session (Board #272), Mon, 1:15 PM-4:45 PM

Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): Results of a phase II study (CheckMate 069). *First Author: Amy Pickar Abernethy, Duke Cancer Institute, Durham, NC*

Background: New therapies in advanced MEL improve survival, but QoL preservation is uncertain. NIVO (a PD-1 immune checkpoint inhibitor) and IPI are each approved as monotherapy for advanced MEL. In a phase II, randomized, double-blind study, NIVO (1 mg/kg every 3 weeks [wks; Q3W]; 4 doses) combined with IPI (3 mg/kg Q3W; 4 doses) followed by NIVO (3 mg/kg Q2W) significantly improved response rate and progression-free survival (PFS) versus IPI (3 mg/kg Q3W; 4 doses), with a manageable safety profile, in treatment-naïve pts with advanced MEL. **Methods:** In this study, QoL measured by EORTC QLQ-C30 and EQ-5D was evaluated at baseline (BL) and Q6W treatment cycles for the first 6 months. Mean changes and non-parametric comparisons are reported. Further analyses are planned to examine longitudinal QoL and the relationship between clinical and pt outcomes. **Results:** Pts received NIVO + IPI (n = 95) or IPI (n = 47). Adjusted completion rates at BL for EQ-5D utilities and EORTC QLQ-C30, respectively, were 64% and 65% with NIVO + IPI and 77% and 79% with IPI; rates remained stable throughout the study except a notable reduction at wk 13 in NIVO + IPI (48%). While completion rates remained similar to BL in the 2 arms after wk 13, pt numbers for IPI were substantially reduced after wk 13 ($n \leq 14$) due to disease progression (median PFS: 3.7 months) or toxicity. NIVO + IPI and IPI had similar mean EORTC QLQ-C30 global health scores at BL (76.9 vs 80.9), wk 7 (69.2 vs 74.5) and wk 13 (78.5 vs 72.2), and similar mean EQ-5D utility index scores at BL (0.861 vs 0.847), wk 7 (0.788 vs 0.789) and wk 13 (0.894 vs 0.834). A transient deterioration in EQ-5D utilities was noted at wk 7 for NIVO + IPI (−0.071; n = 53; *P*= 0.023) and IPI (−0.055; n = 35; *P*= 0.140), but scores returned to BL levels at wk 13 and were maintained with NIVO + IPI beyond wk 13 after the switch to NIVO alone. Similar results were noted with EORTC QLQ-C30 scales. **Conclusions:** NIVO + IPI and IPI alone maintained QoL to a similar level in treatment-naïve pts with advanced MEL, with NIVO + IPI providing superior tumor response and PFS. Studies with increased follow up and pt numbers are needed to confirm these results. Clinical trial information: NCT01927419.

9030 Poster Session (Board #273), Mon, 1:15 PM-4:45 PM

Final data from CALM: A phase II study of Coxsackievirus A21 (CVA21) oncolytic virus immunotherapy in patients with advanced melanoma. *First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: CVA21 (CAVATAK) is a novel bio-selected oncolytic and immunotherapeutic strain of Coxsackievirus A21. Intratumoral (i.t) CVA21 injection initiates preferential tumor cell infection, cell lysis and enhancement of a systemic anti-tumor immune response. Presented are the final data of the open-label, multicenter Phase II CALM (***CA***VATAK in ***L***ate stage ***M***elanoma) study. **Methods:** The CALM study investigated the efficacy and safety of i.t CVA21 in 57 patients with treated or untreated unresectable Stage IIIC-IVM1c melanoma. Pts received up to 3×10^8 $TCID_{50}$CVA21 i.t on study days 1,3,5, 8 and 22, and then every three weeks for a further 6 injections. Pts displaying immune-related progression-free survival (irPFS) or better at 6 mos were eligible for 9 additional injections. Key eligibility criteria were ≥ 18 yrs old, ECOG PS 0-1, and at least 1 injectable cutaneous, subcutaneous, or nodal melanoma metastasis ≥ 1.0 cm. The primary endpoint was to achieve > 9 of 54 evaluable pts with irPFS at 6 mos. Secondary endpoints included irRECIST overall response rate, durable response rate (continuous response ≥ 6mos), median time to response and 1-year survival. **Results:** The primary endpoint of the study was achieved with 21 of 57 (38.6%) evaluable pts displaying irPFS at 6 mos with a median irPFS of 4.2 mos. The overall response rate (irRECIST) was 28.1% (16 of 57 evaluable pts) with a ≥ 6 mos durable response rate of 19.3 % (11 of 57 pts). The median time to response was 2.8 mos, and the 1-year survival rate 75.4% (43 of 57 pts). After a median follow-up of ~16.5 mos, median duration of response in responders and median OS for all pts was not reached. The most common AE's were Grade 1 fatigue, chills, local injection site reactions and fever. No Grade 3 or 4 product-related AE's were observed. **Conclusions:** Intralesional CVA21 is a promising novel oncolytic immunotherapeutic agent for the treatment of unresectable Stage IIIC-IVM1c melanoma and the CALM study met its primary endpoint of irPFS at 6 mos. CVA21 was well tolerated and exhibited both local and distant durable tumor responses. Further clinical studies using CVA21 in combination with other immunotherapies are underway. Clinical trial information: NCT01227551.

9031 Poster Session (Board #274), Mon, 1:15 PM-4:45 PM

Clinical characteristics predictive of response to pembrolizumab in advanced melanoma. *First Author: Katy K. Tsai, UC San Francisco, San Francisco, CA*

Background: Anti-PD-1 therapy has shown significant clinical activity in advanced melanoma and in other cancers. Factors predictive of response remain vaguely defined. We report on clinical characteristics correlated with higher response rates to therapy in a phase I trial of pembrolizumab. **Methods:** Advanced melanoma patients (n = 110, enrolled Dec 2011 to Oct 2013, data analysis July 2014) received pembrolizumab in 1 of 3 dosing regimens: 2Q3W, 10Q3W, or 10Q2W. Tumor responses were evaluated by RECIST 1.1 criteria. Sites of metastases were determined based on CT imaging, and this analysis was not limited to RECIST target lesions. The overall response rate (ORR) and exact two-sided 95% CI were calculated. Demographic and clinical variables were compared between responders and progressors. **Results:** In this cohort, ORR to pembrolizumab was 40%. Factors correlated with significantly higher ORR were: LDH ≤ normal (ORR 52.2%), no previous ipilimumab (ORR 48.3%), and presence of lung metastasis (ORR 52.8%). Patients with liver metastasis had worse response (ORR 18.4%), as did those with liver and lung metastases (ORR 31.3%). Data for associations of subgroup variables with ORR in univariate analyses are shown (Table). **Conclusions:** Normal LDH, no previous ipilimumab, and presence of lung metastasis are correlated with better response to pembrolizumab in advanced melanoma patients. The presence of liver metastasis is correlated with lower response to pembrolizumab, both in the presence and absence of lung metastasis. These correlations were observed regardless of BRAF status, presence of brain metastasis, or site of primary melanoma (cutaneous vs. uveal). Clinical trial information: NCT01295827.

Clinical characteristic	ORR, % (95% CI)	p-value
All patients	40 (30.7-49.3)	
Age <65	36.2 (23.5-49)	0.39
ECOG 0	41.1 (29.5-52.7)	0.741
LDH ≤ normal	52.2 (40-64.5)	0.009
BRAF WT	40.7 (30.1-51.3)	0.416
No previous ipilimumab	48.3 (35.3-61.4)	0.0049
Brain metastasis (met)	38.9 (13.9-63.8)	0.916
Lung met	52.8 (38.9-66.7)	0.008
Liver met	18.4 (5.5-31.3)	0.001
Lung met, no liver met	62.2 (45.8-78.6)	0.001
Lung met and liver met	31.3 (5.7-56.8)	0.001
Liver mets, no lung mets	9.1 (4-22.1)	0.001

9032 Poster Session (Board #275), Mon, 1:15 PM-4:45 PM

A single-arm, open-label, phase II study to evaluate the safety of vemurafenib (VEM) followed by ipilimumab (IPI) in BRAF V600-mutated metastatic melanoma (MM). *First Author: Asim Amin, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC*

Background: There is much interest in determining how to incorporate BRAF inhibitors with immune checkpoint inhibitors in the treatment of patients (pts) with BRAF-mutant MM. A phase I study showed that concurrent administration of IPI, an antibody that blocks cytotoxic T-lymphocyte antigen-4, and VEM, an inhibitor of BRAF V600-mutated kinase, caused significant dose-limiting hepatotoxicity in BRAF-mutant MM pts. An alternate strategy is to use these agents sequentially in order to minimize toxicities observed with concurrent administration and to improve efficacy over either agent alone. **Methods:** This single-arm, open-label, phase II study evaluated the safety of VEM followed by IPI in treatment-naïve MM pts harboring a BRAF V600 mutation. Pts initially received VEM for 6 weeks (960 mg twice daily) followed by IPI at 10 mg/kg (Q3W x 4 doses, then Q12W beginning at week 24 until disease progression or unacceptable toxicity) [VEM1-IPI phase]; VEM was then restarted. The primary objective was to estimate the incidence of grade 3–4 drug-related skin adverse events (AEs) during the VEM1-IPI phase. **Results:** Among 46 pts treated in the VEM1-IPI phase, 80% were male, 52% had stage M1c, and 54% had ≥ 5 sites involved. Grade 3–4 drug-related skin AEs occurred in 15 (33%) pts during the VEM1-IPI phase, the most common of which was rash in 9 (20%) pts. Grade 3–4 drug-related gastrointestinal AEs occurred in 10 (22%) pts (diarrhea in 5 [11%]) and hepatobiliary AEs in 2 (4%) pts (hepatitis; hyperbilirubinemia). There were no deaths due to study drug toxicity. At a median follow-up of 10.5 mo, the objective response rate was 30% (95% CI, 18%–46%) during the VEM1-IPI phase. Median progression-free survival was 4.4 mo (95% CI, 4.2–5.9). Interim median overall survival was 20.3 mo (95% CI, 11.1–NE). **Conclusions:** VEM followed by IPI at 10 mg/kg has a manageable safety profile with no significant signals of hepatobiliary toxicity, as seen with concurrent VEM and IPI; the incidence of grade 3–4 skin AEs was higher than with either agent alone. The benefit/risk of this sequence needs to be evaluated further based on individual patient characteristics and new treatment options. Clinical trial information: NCT01673854.

9033 Poster Session (Board #276), Mon, 1:15 PM-4:45 PM

Clinical features of cobimetinib (COBI)–associated serous retinopathy (SR) in *BRAF*-mutated melanoma patients (pts) treated in the coBRIM study. *First Author: Luis De La Cruz-Merino, Hospital Universitario Virgen Macarena, Seville, Spain*

Background: Various ocular adverse events (AE) have been described with targeted agents. MEK inhibitors (MEKi) are associated with SR. We describe the clinical features of SR observed with COBI in the coBRIM study. **Methods:** coBRIM is a multicenter phase 3 study that evaluated the efficacy and safety of COBI + vemurafenib (VEM) in advanced $BRAF^{V600}$-mutated melanoma pts (Larkin et al. *N Engl J Med* 2014;371:1867-76). Ophthalmic examinations, including optical coherence tomography, were performed at baseline, day 28 and every 3 cycles thereafter (84 days). SR cases were identified in the study database using a group of relevant and synonymous AE terms. Corresponding clinical data were abstracted. **Results:** 495 advanced $BRAF^{V600}$-mutated melanoma pts were randomly assigned to receive COBI + VEM or placebo (PB) + VEM. No pt had retinal abnormalities at baseline. A total of 83 SR events were reported in 63 pts (26%) in the COBI + VEM arm (median age: 59 yr, male: 59%) and 7 SR events in 7 pts (3%) in the PB + VEM arm (median age: 62 yr, male: 29%). Highest severity grade of SR observed in the COBI + VEM arm were NCI-CTCAE grade 1 (asymptomatic/mild symptoms) – 33 pts (52%), 2 – 23 (37%), 3 – 6 (10%) and 4 – 1 (2%). All pts in the PB + VEM arm had grade 1 SR, except 1 pt with grade 2 SR. Median time to first onset of SR was 1 month in both arms. In the COBI + VEM arm, the majority of grade ≥ 2 SR (52%) occurred before study day 12 and most grade 1 SRs were identified during surveillance ophthalmic examination. No other concurrent ocular abnormalities (cornea, conjunctiva, anterior chamber or vitreous) were reported. Most (74%) grade 1 SR events were followed clinically without modification of COBI doses, while grade 2 and 3 SR events were commonly managed with interruption or reduction of COBI. After dose interruption, reduction, or permanent discontinuation of COBI, 75% of SR events resolved or were resolving. **Conclusions:** COBI-related SR occurred in 26% of COBI + VEM treated pts. The majority of SR observed with COBI was of low severity grade and was managed with dose modification of COBI. Surveillance ophthalmic examination identified mostly asymptomatic low severity grade SR, for which clinical significance is uncertain. Clinical trial information: NCT01689519.

9034 Poster Session (Board #277), Mon, 1:15 PM-4:45 PM

Prognostic relevance of baseline neutrophils and derived neutrophil to lymphocyte ratio for ipilimumab-treated advanced melanoma patients. *First Author: Pier Francesco Ferrucci, European Institute of Oncology, Milan, Italy*

Background: Clinical responses to ipilimumab are variable in terms of onset, magnitude and duration. Upfront identification of patients who are more likely to benefit from treatment is a major need. The prognostic value of baseline neutrophils and derived neutrophil to lymphocyte ratio (dNLR) has been addressed in different malignancies with interesting but contrasting data. **Methods:** Data from 720 metastatic melanoma patients treated with ipilimumab 3 mg/kg within the Italian expanded access programme were analyzed. Patients were stratified according to baseline neutrophilia (ANC ≥ 7500) and derived neutrophil to lymphocyte ratio (dNLR). The optimal cut-off value of baseline dNLR for survival was determined by the receiver operating characteristics curve analysis. Overall survival and progression free survival were estimated using the Kaplan-Meier method. The prognostic values of ANC and dNLR were assessed using multivariate Cox proportional hazard models. **Results:** The median follow-up was 16.5 months. Both baseline neutrophilia and dNLR were significantly associated with the outcome of melanoma patients treated with ipilimumab, in terms of disease progression and death ($P< 0.0001$ for all). When the two indexes were combined, we found that patients with both elevated ANC and dNLR had a significantly increased risk of death (HR = 6.25; 95%CI: 4.73-8.25) and of progression (HR = 4.60; 95%CI: 3.51-6.03) when compared to patients with both low ANC and dNLR. The 1-year and 2-years survival rates were 2% and 0%, respectively, for patients with both elevated ANC and dNLR, and 43% and 24%, respectively, for patients with both low ANC and dNLR. **Conclusions:** By analyzing a large cohort of ipilimumab-treated advanced melanoma patients, we identified a subpopulation of patients that is very unlikely to benefit from this treatment. Based on these data responders could be easily selected from general population, allowing for an upfront screening that could spare toxicity to non responder ones.

9035 Poster Session (Board #278), Mon, 1:15 PM-4:45 PM

An adjuvant clinical trial of SCIB1, a DNA vaccine that targets dendritic cells *in vivo*, in fully resected melanoma patients. *First Author: Poulam M. Patel, University of Nottingham, Nottingham, United Kingdom*

Background: SCIB1 is a DNA vaccine encoding a human IgG1 antibody, with T cell epitopes from gp100 and TRP-2 antigens engineered into its CDRs. It targets dendritic cells *in vivo* via the high affinity Fc receptor. A clinical trial in stage III/IV melanoma patients showed that doses of 2-8 mg could induce T cell responses in 7/9 patients with no associated toxicity. Overall median survival was 24 months. In this study SCIB1 is used as an adjuvant therapy. **Methods:** 16 patients with fully resected stage III (9) or stage IV (7) melanoma, were immunised with SCIB1 by Intramuscular electroporation at 0, 3, 6, 12 and 24 weeks. Patients tolerating treatment were allowed to continue treatment for up to 5 years. **Results:** Thirteen patients received 4mg doses of SCIB1 on 5 occasions and one received 4 doses of 4mg followed by one dose of 2mg. One patient only tolerated administration of three 2mg doses of SCIB1. One patient received three 2mg doses and then two 4mg doses. Seven patients received additional doses of SCIB1. One patient received 3 doses prior to withdrawal due to disease progression and one patient received 5 doses. The other six patients remain on continuation: three have received 5 doses and two have received 6 doses of SCIB1. Apart from soreness at the injection site, there have been no significant toxicities. All sixteen patients showed an epitope specific proliferation response *ex vivo* and an γIFN Elispot response *in-vitro*after T cell expansion. Eleven patients responded to all 4 epitopes, three patients to 3 epitopes, one patients to 2 epitopes and one patients to 1 epitope. All patients with continued treatment showed strong T cell memory responses. Currently patients have a median survival time from trial entry of 29.5 months and from diagnosis of metastases of 34 months. Progression free survival is 78% and 72% for stage III and IV respectively and overall survival is 100% for both groups. Only 4 patients have relapsed at 4, 14, 18 and 18 months, since the last relapse there have been no further recurrences for 23 months. **Conclusions:** These results suggest that SCIB1 may confer protection from recurrence of melanoma with little associated toxicity. This vaccine deserves further evaluation as an adjuvant therapy. Clinical trial information: 2009-017355-10.

9036 Poster Session (Board #279), Mon, 1:15 PM-4:45 PM

Updated overall survival (OS) results for BRF113220, a phase I–II study of dabrafenib alone versus combined dabrafenib and trametinib in patients with *BRAF* V600 metastatic melanoma (MM). *First Author: Adil Daud, UC San Francisco, San Francisco, CA*

Background: This Phase I—II study evaluated the safety and efficacy of the combination of dabrafenib and trametinib (the combination) compared with dabrafenib alone (monotherapy) in patients (pts) with *BRAF* V600 MM. **Methods:** *BRAF* V600E/K MM pts naive to BRAF and MEK inhibitors were enrolled. Part B (Ph I, n = 77 BRAFi-naive) pts enrolled into escalating dose (mg) cohorts of dabrafenib twice daily (BID)/trametinib once daily (QD) as follows: 75/1, 150/1, 150/1.5 and 150/2. Part C (Ph II, n=162) pts were randomized 1:1:1 to dabrafenib 150 mg monotherapy, 150/1 and 150/2. Crossover from monotherapy to 150/2 combination was allowed post-progression of disease. Primary endpoints were progression-free survival, response rate, duration of response, and safety; secondary endpoints were OS and pharmacokinetics. **Results:** Previously reported landmark 2-year OS results for pts in Parts B and C with median follow-up of 35 and 34 mo is presented in Table 1.In Part C, median OS rate for 150/2 combination pts was 25 mo (HR = 0.79 vs monotherapy; p = 0.3341). OS rate for monotherapy was confounded by crossover to the 150/2 arm; 45 (83%) pts crossed over at time of analysis. In the 150/2 arm, 16 (30%) pts continued to receive combination beyond progressive disease. Subsequent systemic therapies were similar across arms; 39 (24%) pts received ipilimumab, 17 (10%) received anti-PD-1/PD-L1 therapies, and 21 (13%) received vemurafenib. **Conclusions:** Landmark 2-year OS rate was 51% for Part C 150/2. Further follow-up is ongoing. Landmark 3-year OS rate and safety data with 12 mo additional follow-up will be presented. NCT01072175 Clinical trial information: NCT01072175.

Treatment	Deaths, n (%)	Med. OS, mo (95% CI)	HR (95% CI) p-value	12-mo OS rate (%)	24-mo OS rate (%)
Part B 150/2 combination (n = 24)	10 (42)	27.4 (12.9, NR)	NA	72	60
Part C dabrafenib monotherapy (n = 54)	36 (67)	20.2 (14.5, 27.1)	NA	70	44
Part C 150/2 combination (n = 54)	32 (59)	25.0 (17.5, NR)	0.79 (0.49, 1.27) 0.3341	80	51

NA: not applicable; NR: not reached

9037 Poster Session (Board #280), Mon, 1:15 PM-4:45 PM

Prognostic value of *BRAF^{V600}* mutations in American Joint Committee on Cancer (AJCC) stage 3 cutaneous melanoma patients in the MelanCohort prospective cohort. *First Author: Philippe Saiag, Hospital Ambroise Pare, Boulogne-Billancourt, France*

Background: Prognosis of AJCC stage 3 melanoma pts is heterogeneous. The prognostic value of *BRAF^{V600}* mutations in melanoma is debated. In a retrospective study of 105 stage 3 pts with a nodal deposit of > 2 mm, we showed that *BRAF^{V600}*mutation was an independent factor of decreased both overall and distant metastasis free survivals (DMFS). We aimed to validate this finding in an independent prospective data set and to expand it to the entire AJCC stage 3 spectrum. **Methods:** We selected all pts with AJCC stage 3 cutaneous melanoma at inclusion or during follow-up that were included in Melancohort (NCT00839410), which recruited prospectively during 2003-8. *BRAF^{V600}*mutations were detected by pyrosequencing of DNA in nodal or in transit met samples with > 60 %melanoma cells. Melanoma was considered mutated when > 10% of DNA was mutated. Endpoints were melanoma-specific survival (MSS) and DMFS. Kaplan-Meier curves and multivariate Cox PH regression model were used. 9 pts receiving targeted therapy were censored at first dose given. A sample of 155 pts gave 89% power to detect an HR of 2 for survival, with α risks set at 0.05. **Results:** Median follow-up for stage 3 pts was 56 months. *BRAF* status was assessed in 158 melanomas. *BRAF^{V600mut}* (V600E & V600K in 89 and 9 % of cases, respectively) were detected in 50.6 % of melanomas. The only significant differences according to BRAF at entry in AJCC stage 3 were histological subtypes and age (younger for *BRAF^{V600mut}*). The only characteristics associated with worst MSS in multivariate model were higher AJCC stage (P = 10^{-5}, HR: 2.74, 95%CI: 1.69-4.43), age > 50 (P = 0.02, HR: 1.86, 95%CI: 1.1-3.14), *BRAF^{V600mut}* (P = 0.02, HR: 1.9, 95%CI: 1.1-2.78), male sex (P = 0.02, HR 1.71, 95%CI 1.06-2.75), and mitosis in primary melanoma (P = 0.04, HR 1.6, 95%CI 1.01-2.54). Worst DMFS was associated with higher AJCC stage (P = 0.003, HR: 1.9, 95%CI: 1.27-2.85), age > 50 (P = 0.0007, HR: 2.11, 95%CI: 1.34-3.33), and *BRAF^{V600mut}* (P = 0.02, HR: 1.59, 95%CI: 1.05-2.38). **Conclusions:** *BRAF^{V600mut}* was an independent prognostic criteria in stage 3 pts. This may help to better characterize this stage. Results of adjuvant trials in *BRAF^{V600mut}* stage 3 pts are urgently needed. Clinical trial information: NCT00839410.

9038 Poster Session (Board #281), Mon, 1:15 PM-4:45 PM

***XPC, XPF, TP53* and *GSTP1* polymorphisms in prognosis of cutaneous melanoma patients.** *First Author: Carmen Silvia Passos Lima, Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil*

Background: *XPC*, *XPF*, *TP53* and *GSTP1* genes act on repair and detoxification of ultraviolet (UV) radiation-induced DNA damage, which are related to cutaneous melanoma (CM) development and progression. The DNA repair ability is variable in humans, since the genes enrolled in the process are polymorphic. This study aimed to evaluate whether *XPC* c.2815A > C, *XPF* c.2505T > C, *TP53* c.215G > C and *GSTP1* c.313A > G polymorphisms are associated with survival of CM patients. **Methods**: We analyzed 237 CM patients diagnosed from 2000 to 2014 at the University of Campinas. Genomic DNA of patients was analyzed by polymerase chain reaction and restriction fragment length polymorphism assays, for discrimination of pertinent genotypes. Relapse-free survival (RFS) and overall survival (OS) times were calculated using Kaplan-Meier estimate probabilities and differences between survival curves were analyzed by the log-rank test. The prognostic impact of genotypes was examined using univariate and multivariate Cox regression analyses. **Results**: The median follow-up time of all patients enrolled in this study was 52 months (range: 0.9-175.1 months). At 60 months of follow-up, patients with *XPC* CC genotype presented shorter RFS (59.6% vs. 74.0%, *P*= 0.03), and patients with *XPF* CC genotype presented a tendency for short RFS (48.0% vs. 73.5%, *P*= 0.06) and a shorter OS (71.8% vs. 85.6%, *P*< 0.001) than those with other genotypes (Kaplan-Meier estimates). Patients with *XPC* CC genotype (HR: 1.85, *P* = 0.03) and *XPF* CC genotype (HR: 3.59, *P*= 0.01) had more chance to recurrence than those with other genotypes in univariate and multivariate Cox regression analyses, respectively. Patients with *XPF* CC (HR: 3.52, *P*= 0.001) and *XPF* TC+CC (HR: 9.40, *P*= 0.02) genotypes were associated with greater risk of progressing to death than other genotypes in univariate and multivariate Cox regression analyses, respectively. **Conclusions**: The data suggest, for the first time, that inherited abnormality in DNA repair pathway related to *XPC* and *XPF* polymorphisms influence prognosis of CM patients. These findings, once validated in additional studies, will contribute to individualize high-risk patients, who deserve to receive a closer follow-up and/or adjuvant therapy.

9039 Poster Session (Board #282), Mon, 1:15 PM-4:45 PM

A global genomic and small molecule inhibitor interrogation of KIT mutant melanoma to reveal underlying biology and novel molecular targets. *First Author: Junna Oba, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Activating mutations in *KIT* are present in 15-20% of acral lentiginous (AL), mucosal (MM) and chronic sun-damaged melanomas. Functional studies in *KIT* mutant melanoma have been hampered by a paucity of cell lines with recurrent mutations, and limited information about the molecular context in which they occur. This study analyzes the co-mutation status of a large set of cancer-related genes that could influence cell signaling programs in *KIT* mutant melanomas. Further, we perform first-to-date functional studies on a melanoma cell line with a common (10%) recurrent *KIT* mutation at amino acid position 822. **Methods:** Results of a CLIA-certified clinical next-generation sequencing (NGS) platform that interrogates regions of recurrent mutations in 46 cancer-related genes for 1430 melanoma patients were reviewed to identify tumors with mutations in *KIT* (n = 116). Those tumors were analyzed for associated clinical and molecular characteristics. A novel *KIT* mutant (N822Y) melanoma cell line was generated from an AL tumor, upon which global copy number, protein activation and high-throughput small molecule inhibitor testing were performed. **Results:** Among patients with clinical NGS results, 116 tumors with *KIT* mutations were identified (46 non-acral cutaneous [CM], 26 AL and 44 MM). Unlike *KIT* mutant CMs, AL and MM tumors harbored few non-redundant *KIT* missense mutations or mutations in known oncogenes (*BRAF, N/H-RAS*), and when present, mutations in tumor suppressor genes were more frequent in CM tumors by the technique employed. Low frequency hotspot mutations in *CTNNB1* were present in all *KIT* mutant subtypes (2-12%). A bioactive 1,161 compound screen of an AL KIT N822Y cell line revealed a selective set of compound classes (KIT, RAF, PI3K-MTOR, CDK inhibitors) to meet threshold efficacy. **Conclusions:** AL and MM *KIT* mutant melanomas lack co-mutations frequently present in CMs. High-throughput compound screening test of KIT (N822Y) melanoma cell line suggests a small set of compound classes for combinatorial screening.

9040 Poster Session (Board #283), Mon, 1:15 PM-4:45 PM

Patient-reported outcomes (PROs) in KEYNOTE-002, a randomized study of pembrolizumab vs chemotherapy in patients (pts) with ipilimumab-refractory (IPI-R) metastatic melanoma (MEL). *First Author: Dirk Schadendorf, University Hospital Essen, Essen, Germany*

Background: Pembrolizumab is approved for treating advanced MEL that progressed following IPI and, if *BRAF*^{V600} mutant, a BRAF inhibitor. In KEYNOTE-002 (NCT01704287), pembrolizumab significantly prolonged PFS compared with chemotherapy in IPI-R advanced MEL ($P < .0001$) and was associated with a lower rate of grade 3-5 AEs. Herein, we present the PRO analysis. **Methods:** Pts with advanced MEL that progressed within 6 mo after ≥2 IPI doses and, if *BRAF*^{V600} mutant, following a BRAF/MEK inhibitor, were randomized 1:1:1 to pembrolizumab 2 or 10 mg/kg every 3 wk or investigator's choice of chemotherapy. Primary end points were PFS and OS. PROs were an exploratory end point with prespecified analysis. The EORTC QLQ-C30 was collected at baseline, wk 3, 6, 12, 24, 36, treatment discontinuation, and safety follow-up. The key PRO end points are the score change from baseline and the proportions of improvement/deterioration at wk 12 of the global health status score. A constrained longitudinal data analysis model assessed between-arm differences in all pts with ≥1 PRO assessment. **Results:** 520 of 540 enrolled pts were included in the PRO analysis. Baseline global health status scores were similar across treatment arms. Pembrolizumab-treated pts had significantly lesser decreases from baseline in the global health status scale score compared with control (Table). At wk 12, the proportion of pts with a ≥10-point decrease in global health status was 38% for control, 32% for pembrolizumab 2 mg/kg, and 27% for pembrolizumab 10 mg/kg. Pembrolizumab-treated pts had consistently lesser score changes from baseline for the different function and symptoms scales. **Conclusions:** In KEYNOTE-002, quality of life was maintained to a greater degree with pembrolizumab versus chemotherapy in IPI-R MEL. Clinical trial information: NCT01704287.

	Global Health Status Scale Score				
	Baseline		Wk 12		Change From Baseline, Least Squares Mean (95% CI)
	Mean	SD	Mean	SD	
Control (n = 167)	64.0	21.9	59.0	23.2	–9.1 (–12.9, –5.4)
Pembro 2 mg/kg (n = 176)	66.2	22.1	66.3	23.0	–2.6 (–6.2, 1.0)*
Pembro 10 mg/kg (n = 177)	63.0	23.6	64.3	22.9	–2.6 (–6.0, 0.9)*

*P = .01 versus control.

9041 Poster Session (Board #284), Mon, 1:15 PM-4:45 PM

Melanoma-specific MHC-II expression to predict response to α-PD-1 therapy. *First Author: Justin M. Balko, Vanderbilt Univ Medcl Ctr, Nashville, TN*

Background: αPD-1 therapy yields objective clinical responses in 30-40% of advanced melanoma (MEL) patients (pts). While promising, many pts do not benefit clinically. Predictive biomarkers to guide pt selection are needed. We hypothesized that tumor antigen presentation (MHC-I or MHC-II expression) is a requirement of αPD-1 benefit, and presence of these cell surface markers would predict benefit. **Methods:** We profiled MHC-I/II mRNA across 60 MEL cell lines. The transcriptional characteristics of MHC-II+ cell lines were analyzed by Gene Set Analysis. Cell surface expression of MHC-I and MHC-II was confirmed by flow cytometry (FC) in a subset of cell lines under basal and stimulated (IFNγ) conditions. In 26 tumor samples from αPD-1 treated MEL pts, immunohistochemistry (IHC) was performed for HLA-DR (MHC-II) or HLA-A (MHC-I), SOX10, CD4 and CD8. IHC results were correlated with response and progression-free survival (PFS). **Results:** MHC-I mRNA was expressed in all cell lines while MHC-II expression was bimodal (60% positive). MHC-II$^+$ cell lines had transcriptional signatures of the PD-1 signaling, allograft rejection, and T-cell receptor signaling. By FC, MHC-II$^+$ (mRNA) cell lines were constitutive and inducible (IFNγ stimulation) for HLA-DR while MHC-II$^-$ cells did not express or induce HLA-DR. In contrast, all tested cell lines significantly upregulated PD-L1 with IFNγ stimulation. Of 26 pts treated with αPD-1, 10 were MHC-II$^+$. All 10 MHC-II$^+$ (100%) pts had partial, complete, or mixed responses (MR), while only 7/16 (44%) of MHC-II$^-$ pts benefited (Fisher's exact p = 0.004). Excluding MR pts (n = 2), median PFS for MHC-II$^+$ was 728 days (d), while the median PFS for MHC-II$^-$ tumors was 98d (log-rank p = 0.01) . MHC-II$^+$tumors had enhanced CD4 and CD8 infiltrate (Pearson's correlation p = 0.000002 and p = 0.03, respectively). MHC-I positivity was ubiquitous and not associated with response. **Conclusions:** A subset of MEL demonstrates an MHC-II signature that correlates with αPD-1 response and enhanced CD4/CD8 T-cell infiltrate. MHC-II+ tumors can be robustly identified by routine melanoma-specific IHC for HLA-DR to guide pt selection. Combining HLA-DR IHC with other biomarkers, including PD-L1 expression may further improve pt selection.

9042 Poster Session (Board #285), Mon, 1:15 PM-4:45 PM

Multiplatform biomarker analysis on non-sun exposed mucosal melanoma. *First Author: Alan H. Bryce, Mayo Clinic, Scottsdale, AZ, Scottsdale, AZ*

Background: Mucosal melanoma is a rare malignancy, notoriously resistant to conventional chemotherapy, with few treatment options. Because of their origin, they do not receive screening and, hence, are detected in advanced stages where prognosis and curative rates are poor. The purpose of this study is to identify novel, potential targets and therapeutic options for this disease, utilizing a multiplatform approach. **Methods:** In total, 93 mucosal melanoma specimenswere tested via a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ) consisting of gene sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]) and/or gene amplification (CISH or FISH). Conjunctival melanoma was excluded. **Results:** Notable protein overexpression rates included co-expression of PD-1 and PD-L1 (71.4%, 5/7) and cKIT (42.4%, 14/33). Percent agreement between c-KIT by IHC and sequencing was 62% (16/26). Overall, sequencing revealed the highest mutation rates in TP53 (17%, 4/23), cKIT (18.2%, 14/77), BRAF (12.0%, 10/83), and NRAS (10.0%, 4/40). A sub-analysis of BRAF, cKIT, and NRAS (BRAF/cKIT/NRAS) based on the anatomic location of the melanoma revealed the following: sinonasal (5.3%, 0.0%, 27.0%), vulvovaginal (21.2%, 27.3%, 7.1%), and anorectal (5.0%, 18.0%, 0.0%). Details on the TP53-mutated specimens (n=4) are shown in the table below. **Conclusions:** Multiplatform tumor profiling identified multiple, potentially actionable targets. Given the high rate of PD-1 and PD-L1 co-expression, new immunotherapies should be strongly considered in advanced stages of this disease. In addition, mutations detected may provide further guidance in this rare malignancy. The highest rates of NRAS mutations occurred in the sinonasal melanomas. Meanwhile, cKIT mutations were highest in vulvovaginal and anorectal mucosal melanomas. This variability in mutation rates of BRAF, cKIT, and NRAS based on the primary site's location should be further elucidated in larger studies for potential diagnostic and theranostic purposes.

Specimen Primary Site	TP53 Mutation(s)
Sinonasal	H179R (c.536A>G)
Nasopharyngeal	V272L (c.814G>T), R248W (c.742C>T)
Vaginal	R337C (c.1009C>T), R273C (c.817C>T)
Rectal	N268fs

9043 Poster Session (Board #286), Mon, 1:15 PM-4:45 PM

Analysis of CTLA4 expression on T regulatory cells in patients with advanced stage melanoma in the setting of high dose IL-2 (HDIL-2). *First Author: Maggie L. Diller, Emory University, Atlanta, GA*

Background: HDIL-2 is associated with long-term remissions in stage IV melanoma, but in less than 10% of patients. Combination therapy with HDIL-2 and agents immunomodulating CTLA-4 have been undertaken. We investigated the effect of HDIL-2 on CTLA4 expression on T cell subsets in patients with melanoma. **Methods:** Peripheral blood was collected at baseline and serially post-treatment at 24, 48, 72, and 96 hours from 6 patients with advanced stage melanoma undergoing HDIL-2. All patients were treatment naïve with regard to anti-CTLA4 therapy. PBMCs were isolated and restimulated ex vivo for 4 hours using PMA/ionomycin. Fluorophore conjugated anti-CTLA4 antibody was added at time of restimulation and incubated with cells for 4 hours. Intracellular and extracellular cytokine staining was then performed and co-signaling molecule expression was quantified via flow cytometry and measured on a continuous scale. Statistical analysis was performed using paired *t* tests via Prism 6.0e software. **Results:** HDIL-2 resulted in increased frequencies of T regulatory cells ($T_{reg;}$ CD25+FoxP3+CD4+) on day 4 of therapy (24% +/- 12% on day 4 compared to 12% +/- 7% at baseline; p = 0.03; 95% CI [1.5,22]). Importantly, CTLA4 expression on T_{reg} cells was increased on day 4 post-treatment relative to baseline (51% +/- 19% on day 4 compared to 35% +/- 19% at baseline; p = 0.02; 95% CI [2.5,28]). CTLA4 expression was not statistically different within other CD4+ T cell compartments or within the CD8+ T cell compartments. **Conclusions:** These results demonstrate that HDIL-2 is associated with an increase in the expression of CTLA4 onT_{reg} cells in patients with advanced melanoma. HDIL-2 effect on the T_{reg} population provides a potential rationale for the lack of efficacy of HDIL-2 in most patients and implies potential synergy between HDIL-2 and CTLA4 blockade. Together, these findings provide justification for testing the combination of HDIL-2 and anti-CTLA4 therapy in patients with advanced melanoma and that timing of anti-CTLA4 therapy with HDIL2 will be crucial.

9044 Poster Session (Board #287), Mon, 1:15 PM-4:45 PM

Association of PD-L1 expression in melanoma with response and prognosis to ipilimumab. *First Author: Caroline Brueggemann, Department of Dermatology, University Hospital Erlangen, Erlangen, Germany*

Background: Immunotherapy with ipilimumab demonstrated a statistically significant survival benefit. In two large phase III trials responses were observed in 10-15% of patients. However, 64% of patients exhibited significant and 20% of the patients severe grade 3 and 4 side effects. Identifying predictive biomarker profiles could enable better treatment allocation. **Methods:** In this multicenter study 176 tumor samples from 125 patients with metastatic melanoma were analyzed for PD-L1 gene expression, thereof 78 patients had received ipilimumab (30 responders and 48 non-responders). mRNA was extracted from formalin-fixed paraffin embedded (FFPE) tumor tissue by a fully automated method and measured by quantitative RT-PCR. Differences of survival and PD-L1 expression between patient groups were assessed using the Mann-Whitney U test, the logrank test and the Kaplan-Meier technique. **Results:** Patients with low PD-L1 expression showed a significantly better survival than those with high expression of PD-L1 ($p = 0.002$) not considering the subsequent therapy. No statistical difference in PD-L1 expression between responders ($n = 30$) and non-responders ($n = 48$; $p = 0.458$) to ipilimumab was observed. **Conclusions:** Our results suggest that PD-L1 expression is not predictive for response to therapy with ipilimumab but is a positive prognostic marker for survival of melanoma patients.

9045 Poster Session (Board #288), Mon, 1:15 PM-4:45 PM

Evaluation of the impact of infliximab use for the treatment of ipilimumab related diarrhoea on the outcome of patients with advanced melanoma. *First Author: Edurne Arriola, University of Southampton, Southampton, United Kingdom*

Background: The use of immunosuppressants for the treatment of immune related (IR) toxicities from immunoregulatory antibodies, such as ipilimumab is intended to dampen harmful adaptive immune responses. It is uncertain whether this also results in reduction of anti-tumour immunity and adversely affects disease specific outcome. The aim of our study was to evaluate the impact on overall survival (OS) of infliximab use for the treatment of immune related diarrhoea from ipilimumab in patients with metastatic melanoma. **Methods:** We retrospectively evaluated 90 patients with advanced melanoma treated with ipilimumab (3mg/kg) with assessment of response during and following treatment. We recorded clinical characteristics, toxicity data and outcome. Kaplan Meier and Log rank tests were used to assess outcome differences. **Results:** Fifty-one percent of patients were male, the median age was 64 years; sixty-nine (77%) patients has cutaneous primaries, 11(12%) uveal and 2(2%) mucosal. Sixty-five patients (72%) had M1c disease. *BRAF*assessment was available in 77% of tumours and 32% cases harboured a V600E mutation. Ipilimumab was administered as second line treatment and 60% completed four cycles. Thirty percent ($n = 27$) of patients developed ipilimumab-related diarrhoea of any grade. Twenty-one (80%) required oral steroids for management, escalated to iv methylprednisolone (1-2mg/kg/24hrs) in 12 cases. In seven patients (25%) infliximab was required to control G3/4 colitis. Median follow up was 8 months for the whole population. M1c disease, poor performance status at treatment initiation and progression at the week 12 response assessment were associated with shorter survival (all p-values < 0.05). Patients who developed diarrhoea had improved OS when compared to those who did not (8.8m vs 5.4m; $p = 0.041$). Within patients with diarrhoea, the median OS of those treated with infliximab compared to those without was 8.8m vs 6.8 ($p = 0.16$), respectively. **Conclusions:** In our series infliximab does not negatively affect the outcome of patients with advanced melanoma treated with ipilimumab and early switch in order to spare steroid toxicity appears warranted and safe.

9046 Poster Session (Board #289), Mon, 1:15 PM-4:45 PM

Safety of infusing ipilimumab (ipi) over 30 minutes (min). *First Author: Parisa Momtaz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The approved dose of ipi is 3mg/kg infused over 90 min. In clinical trials, however, 10mg/kg has also been infused over 90 min. At 10mg/kg, patients (pts) receive 3mg/kg within the first 27 min of treatment. We sought to determine if the standard 3mg/kg dose could be safely infused over 30 min. **Methods:** We first retrospectively reviewed the incidence of infusion-related reactions (IRRs) to ipi at our institution in melanoma pts receiving either 3mg/kg or 10mg/kg doses infused over 90 min. Our findings led to a change in institutional guidelines for ipi infusion time from 90 min to 30 min. We then prospectively reviewed the 30 min infusion of ipi. **Results:** Between 4/1/08 and 6/30/13, 595 pts received ipi infused at either 3mg/kg ($n = 457$) or 10mg/kg ($n = 138$) over 90 min. There was no significant difference in the incidence of IRRs between pts receiving 10mg/kg (4.3%) vs. 3mg/kg (2.2%) of ipi over 90 min ($p = 0.22$). 120 pts were then treated prospectively with 3 mg/kg ipi infused over 30 min. 7 pts (5.8%) had an IRR ($p = 0.06$ compared to 10/457 (2.2%) in the 3 mg/kg 90 minute infusions). All IRRs occurred at dose 2; 6 were grade 2, one was grade 3. Five IRRs occurred during the infusion, two occurred after (one 30 min after and the second immediately after completion of infusion). All 7 pts received subsequent doses of ipi safely administered over a range of 30-90 min. 5/7 pts received subsequent doses with pre-medication (diphenhydramine, steroids) without incident. One of the 2 pts who did not receive pre-medication at dose 3, experienced an IRR at dose 3, received pre-medication for dose 4, and did not experience an IRR at dose 4. **Conclusions:** Ipi at 3mg/kg can be infused safely over 30 min with an acceptably low incidence of IRRs. Dose 2 is most commonly associated with an IRR. After an IRR, patients can safely receive additional doses of ipi with premedication. It is unclear from our data whether subsequent infusions need to be administered more slowly. It may be reasonable to observe patients for a short period of time after the infusion. A 30 min infusion time enhances patient convenience and allows more efficient use of outpatient infusion facilities.

9047 Poster Session (Board #290), Mon, 1:15 PM-4:45 PM

Efficacy of high-dose adjuvant interferon therapy in high-risk melanoma harboring gene mutations. *First Author: Xuan Wang, Peking University Cancer Hospital & Institute, Beijing, China*

Background: BRAF/NRAS mutations are predictors of poor prognosis in melanoma. High-dose interferon (HDI) is the only drug approved by FDA as adjuvant therapy in high risk resected melanomas. However, efficacy of HDI in high-risk melanomas harboring BRAF/NRAS mutations has not been evaluated systemically. This study aimed to clarify whether there is beneficial effect of HDI in these patients. **Methods:** Melanoma patients, after melanoma resection, with BRAF mutation (Exon 15) or NRAS mutation (Exon 2) in melanoma of high risk (Stage IIB to Stage IIIC) were enrolled in this study. Patients were randomized (ratio of 2:1) into 1-year adjuvant HDI therapy group ($n = 88$) and observation group ($n = 52$). The endpoint was disease-free survival (DFS). The median follow-up is 16 months till Dec. 2014. Somatic mutations were detected by DNA sequencing. All the statistical analyses were performed using SPSS 16.0 software. **Results:** The proportion of stage IIB/IIC and III disease were 55.0% and 45.0%, respectively. 53.6% patients were acral melanomas. Primary ulceration was found in 52.9% lesions. Of the 140 patients, 108 cases harbored BRAF mutation, and 32 cases with NRAS mutations. At the end of follow-up, 55% patients had metastatic or local recurrence. The overall median DFS was 19.0 months. DFS in HDI group was significantly longer than observation group (21.0 months vs. 10.0 months, $p = 0.002$). DFS of HDI vs. observation group were 19.0 vs. 9.0 months ($p = 0.021$) in BRAF-mutated patients. But stratified analysis did not show significantly DFS improvement of HDI in acral or stage IIB/IIC subgroups in BRAF-mutated patients. NRAS-mutated patients did not get significantly benefit from HDI therapy (DFS: 24.0 months vs. 20.0 months, $p = 0.21$). Stratified analysis did not show significantly different in DFS between two groups either in different stages (stage IIB/IIC vs. III) or in different subtypes (Non-CSD/CSD vs. acral). **Conclusions:** In the BRAF-mutated high-risk melanoma, HDI may provide beneficial effect in the resected patients. However, more powerful adjuvant therapy should be explored for NRAS-mutated melanoma patients.

9048 Poster Session (Board #291), Mon, 1:15 PM-4:45 PM

Evaluation of genetic heterogeneity in paired lymph node metastases from melanoma patients using next-generation sequencing (NGS) approaches. *First Author: Giuseppe Palmieri, ICB-CNR, Cancer Genetics Unit, Sassari, Italy*

Background: In our previous experience (*JCO 2012;30:2522-9*), we demonstrated a high consistency of *BRAF* and *NRAS* mutations between primary tumors and lymph node metastases in melanoma patients. A subset of paired samples of multiple asynchronous lymph node metastases from that series was here screened mainly using NGS technologies in order to better elucidate the existence of a real genetic homogeneity during clonal expansion to lymph node sites. **Methods:** Genomic DNA was isolated from frozen tissues of paired asynchronous lymph nodes, ascertained for presence of melanoma metastases (at least 80% of metastatic cells), using standard methods. Specimens from 12 patients were analyzed for mutations in 50 most common cancer genes with the Ion Torrent AmpliSeq Cancer Panel HotSpot.V2 (CHPv2) on the Ion PGM sequencer. All variants detected by NGS were confirmed through PCR-based Sanger sequencing. Paraffin-embedded tumor tissues from the same series were evaluated by fluorescence *in situ* hybridization (FISH) assays, using probes specific for *CyclinD1*/*EGFR* genes or 9p21 locus and correspondent control centromeres. **Results:** Overall, only one (8%) of the 12 analyzed patients presented discrepancies in mutation patterns between the two distinct lymph nodal metastases developed in different times. In particular, the differences were represented by the BRAF-V600E and the CDKN2A-R80X mutations, suggesting that changes, when occur (though in a limited fraction of cases), they affect the main genes controlling cell proliferation and survival involved in melanomagenesis. No discrepancy was observed by FISH analysis into the same series. Considering the total number of analyzed samples, we detected the following mutations: BRAF-V600E (54% of cases), KDR-Q472H (50%), TP53-P72R (42%), cKIT-M541L (25%), NRAS-Q61R/K (25%). **Conclusions:** Our findings indicated a very low genetic heterogeneity during lymph node dissemination in melanoma patients, confirming the previously published data. Mutations in *BRAF*, *NRAS*, and *cKIT* genes were further confirmed to play a predominant role in melanoma pathogenesis.

9049 Poster Session (Board #292), Mon, 1:15 PM-4:45 PM

Analysis of mTOR Mutations in Chinese Melanoma Patients and Evaluation of Their Sensitivity to PI3K-AKT-mTOR Pathway Inhibitors. *First Author: Yan Kong, Peking University Cancer Hospital & Institute, Beijing, China*

Background: mTOR is a validated target in cancer treatment. *mTOR* mutations are estimated to be 2.46% of all cancers and 5.76% of cutaneous melanoma. However, *mTOR* mutations in other types of melanoma have not been reported. **Methods:** This study involved tumor samples from 412 Chinese melanoma patients, including 210 acral melanomas, 105 mucosal melanomas, 30 melanomas on skin with chronic sun-induced damage and 58 melanomas on skin without chronic sun-induced damage. Tissue samples were analyzed for mutations in all exons of *mTOR* gene in genomic DNA by Sanger sequencing. Mutation status was confirmed using Agilent's sureselect target enrichment system. HEK293T cells stably expressing mutant mTOR were constructed by TALEN (Transcription Activator-like Effector Nucleases). Function of mTOR mutants in these cells and in vitro sensitivity of *mTOR* gain-of-function mutations to PI3K-AKT-mTOR pathway inhibitors were analyzed. **Results:** The overall incidence of somatic mutations within the *mTOR* gene was 10.4% (43/412). Increased *mTOR* mutations were relatively more frequent in acral (11.0%) and mucosal (14.4%) melanomas than in CSD (6.7%) and Non-CSD (3.4%) melanomas. Of the 43 cases with *mTOR* mutations, 41 different mutations were detected, affecting 25 different exons. Point mutations resulting in single amino acid substitutions (totaling 40 mutations detected in 43 patients) were the most common type of *mTOR* mutation. The median survival time for melanoma patients with *mTOR* mutation was significantly shorter than that for patients without *mTOR* mutation ($P = 0.028$). Transient expression of several mTOR mutants in HEK293 cells strongly activated the mTOR/p70S6K pathway. In HEK293 cells with stable expression of H1968Yor P2213S mTOR mutants, LY294002 and AZD5363 showed higher potency than Temsirolimus or BYL719 in inhibiting the mTOR/p70S6K pathway. **Conclusions:** These data demonstrate that *mTOR* mutations are more frequent in Chinese melanoma patients than in Caucasian melanoma patients. *mTOR* mutations is a worse prognostic factor in Chinese melanoma patients. Clinical trials with PI3K-AKT-mTOR pathway inhibitors may be beneficial for melanoma patients with *mTOR* mutations.

9050 Poster Session (Board #293), Mon, 1:15 PM-4:45 PM

Association of immune-related thyroid disorders with pembrolizumab (pembro, MK-3475) in patients (pts) with advanced melanoma treated in KEYNOTE-001. *First Author: Caroline Robert, Gustave Roussy, Villejuif, France*

Background: The anti–PD-1 antibody pembro is approved in the US for treating advanced MEL that progressed following IPI and, if $BRAF^{V600}$ mutant, a BRAF inhibitor. Immune-related AEs (irAEs) are of interest for immunotherapies such as pembro. Among the first 411 MEL pts treated with pembro in the phase 1 KEYNOTE-001 study (NCT01295827), 18% experienced irAEs (4% gr 3/4). We describe the incidence and treatment of thyroid disorders, the most common irAEs observed in KEYNOTE-001. **Methods:** AEs were monitored throughout treatment and for 30 d thereafter (serious AEs and potential irAEs for up to 90 d). AEs were graded per CTCAE v4.0. Thyroid disorders included hypothyroidism, hyperthyroidism, thyroiditis, and related terms. TSH and free T4 (FT4) levels were measured at baseline and once per treatment cycle. **Results:** Thyroid disorders occurred in 39 (9.5%) pts: hypothyroidism in 33 (8.0%), hyperthyroidism in 6 (1.5%), and thyroiditis in 3 (0.7%); 2 pts experienced both hypo- and hyperthyroidism, and 1 pt experienced hypothyroidism and thyroiditis. 2 events were of gr 3 severity: 1 hypo- and 1 hyperthyroidism. Hypothyroidism was managed with long-term hormone replacement therapy, with no permanent discontinuation required; only 4 pts required temporary pembro interruption. 2 pts with hyperthyroidism required corticosteroids, and 2 permanently discontinued pembro. Hyperthyroidism resolved in 83% of pts. Thyroiditis resolved in 67% of pts; no cases required treatment interruption, discontinuation, or corticosteroid use. Median time to onset and duration are shown in the Table. 111 (33.9%) pts had ≥1 abnormal postbaseline TSH or FT4 value, with subclinical hypo- and hyperthyroidism most common (20.5% and 19.3%, respectively). **Conclusions:** Thyroid disorders are the most frequent irAEs associated with pembro. Most events are of gr 1 or 2 severity and can be managed with supportive care and temporary treatment interruption. These findings support regular assessment of thyroid function in pembro recipients. Clinical trial information: NCT01295827.

	Median (range), d	
	Time to Onset	Duration
Hypothyroidism	106 (5-576)	385 (14-740)
Hyperthyroidism	47 (15-665)	84 (29-201)
Thyroiditis	29 (20-64)	57 (43-108)

9051 Poster Session (Board #294), Mon, 1:15 PM-4:45 PM

Utility of PET/CT for surveillance of asymptomatic patients with resected stage III or IV melanoma. *First Author: Roberto Antonio Leon-Ferre, Mayo Clinic, Rochester, MN*

Background: Evidence-based guidelines for the use of surveillance imaging in melanoma patients are lacking. Here, we present a retrospective review of the Mayo Clinic experience using PET/CT (PET) for surveillance of asymptomatic patients with resected stage III-IV melanoma. **Methods:** A search of our radiologic database identified 601 melanoma patients seen at Mayo Clinic who underwent PET between 1/1/2008 and 6/30/2009. 153 met the inclusion criteria of having a resected cutaneous or mucosal stage III-IV melanoma, and at least 2 PETs performed < 1 year apart for surveillance. **Results:** 95(62%) were male and 58(38%) were female. 120(78%) had resected stage III [IIIA: 49(32%), IIIB: 51(33%), IIIC: 20(13%)], while 33(22%) had resected stage IV. Primary was cutaneous in 128(84%), mucosal in 8(5%) and MUP in 17(11%). Mean age at diagnosis of stage III or IV was 54. Of all patients, 80(52%) developed a first recurrence. 39(49%) were asymptomatic, not apparent on exam and detected by PET, 7(9%) were asymptomatic and detected by other imaging techniques, while 27(33%) were symptomatic and 7(9%) were detected on exam. Treatment to no evidence of disease (NED) with resection, radiation or ablation was possible in 26(67%) recurrences detected by PET and in 25(74%) symptomatic or exam-detected recurrences ($p = 0.64$). Median survival was superior among patients whose first recurrence was successfully treated to NED compared to patients in whom treatment to NED was not possible (7.08 vs 2.92 years, $p = 0.0002$). However, median survival was similar regardless of method of detection of first recurrence (5.04 in the PET group vs 5.18 years in the symptomatic group, $p = 0.87$). Median time to detection of first recurrence was 12 months by PET vs 10.7 months by symptoms/exam ($p = 0.93$). Median number of PET per patient was 9. **Conclusions:** Survival was superior among patients with resected stage III or IV melanoma whose first recurrence was amenable treatment to NED. Use of PET, however, did not appear to increase the proportion of patients that benefited from treatment to NED of first recurrence. Survival did not appear to be different among asymptomatic recurrences detected by PET compared to recurrences that were symptomatic or detectable on exam.

9052 Poster Session (Board #295), Mon, 1:15 PM-4:45 PM

Identification of a predictive signature based on immunohistochemical (IHC), RNA-seq and epigenetic profiling of melanoma metastases for response to ipilimumab-based immunotherapy. *First Author: Teofila Seremet, Universitair Ziekenhuis Brussel, Brussels, Belgium*

Background: Ipilimumab (Ipi) improves the survival of patients (pts) with advanced melanoma. Combination of Ipi with an autologous monocyte-derived DC therapy (TriMixDC-MEL) may further improve patient outcome (Neyns et al., 2014 ASCO AM). A predictive melanoma tissue signature for the clinical efficacy of Ipi and TriMixDC is needed to optimize individualized treatment strategies. **Methods:** Between 01/2011 and 05/2013 freshly frozen melanoma metastases were collected from pts treated with Ipi (n: 9), TriMixDC-MEL (n: 2), or TriMixDC-MEL plus Ipi (n: 14). Samples were profiled by IHC (incl. CD3, CD8, PanMel, MCSP, CD20, CD163, DC-LAMP, Casp-3, Ki-67, PHH3, HLA class I, vWF), RNA-seq and MBD-seq (genome-wide DNA methylation profiling). Tumor response was assessed according to the irRC. **Results:** Five pts obtained a complete response (CR), 6 obtained a mixed response (MR), and there was no evidence of tumor response in 14 pts (NR). A total of 26 metastases (15 obtained prior to and 11 post therapy) were profiled by IHC and 18 were additionally profiled by RNA and MBD-seq. Intra-tumor CD3 and CD8 T cell infiltration was observed in 23/26 samples, with variable pattern and extent of infiltration. None of the 3 pts with absent CD3/CD8 infiltration in their tumor core regions responded to Ipi-based immunotherapy. The differential analysis of the RNA-seq data resulted in a list of 195 genes with a statistically significant difference in expression between CR and NR (false discovery rate < 0.05). A gene ontology enrichment analysis revealed that the differentially expressed genes were enriched for immune-related ontologies. The MR expression profiles clustered together with the NR group. MBD-seq revealed differences in methylation status between CR and NR pts. These differences in methylation status were not linked to the observed differences in RNA expression. **Conclusions:** Comprehensive analysis of melanoma metastases with gene expression and methylation status provides a distinct profile that identifies long-term responders to Ipi-based immunotherapy. Prospective validation is warranted.

9053 Poster Session (Board #296), Mon, 1:15 PM-4:45 PM

A multi-center phase II study of high dose IL-2 (HD IL-2) sequenced with vemurafenib in patients with BRAF-V600E mutation positive advanced melanoma. *First Author: Joseph Clark, Loyola Univ Medical Center, Maywood, IL*

Background: Durable unmaintained remissions are consistently observed in a small percentage of patients with metastatic melanoma (mM) treated with HD IL-2. Vemurafenib therapy gives rise to a high response rate in BRAF-V600 (BRAF) mutated melanoma patients, but these are relatively short-lived; thus using both drugs in sequence may complement the individual strengths of each therapy. We report the early efficacy and safety results for the PROCLIVITY01 clinical trial of sequenced vemurafenib and HD IL-2. **Methods:** The primary objective is to assess the CR rate at 10 wks $\pm$3 (assessment 1) and 26 wks $\pm$ 3 (assessment 2) from start of HD IL-2. Trial patients were IL-2 eligible and BRAF mutant positive. Cohort 1 patients were treatment naïve and on trial received vemurafenib 960 mg BID for 6 weeks prior to HD IL-2. Cohort 2 patients received vemurafenib for 7-18 weeks prior to enrollment. Both cohorts received HD IL-2 at 600,000 IU/kg every 8 hours for up to 14 doses on days 1-5 and days 15-19. Vemurafenib was held during HD IL-2 treatment. **Results:** A total of 53 patients received vemurafenib (cohort 1, N = 38); cohort 2 (N = 15). Of these, 40 had assessment 1 and 15 had assessment 2. The overall response rate is14.8% and disease control rate is 51.9% for cohort 1, assessment 1 (n = 27), and 15.4 and 69.2% for cohort 2 (n = 13), respectively. An independent safety committee did not raise safety concerns with the sequencing of these two drugs and patients experienced toxicities as anticipated for IL-2 or vemurafenib. There were no treatment-related deaths. A shift in the melanoma treatment landscape during this trial adversely affected accrual, and led to early trial closure. **Conclusions:** Vemurafenib given in sequence with HD IL-2 did not change the known toxicity profile for either drug. Early efficacy results reveal low response rates for vemurafenib. Durability of response and long term survival will be reported as patients continue to be followed in the PROCLAIM IL-2 database. Clinical trial information: NCT01683188.

9054 Poster Session (Board #297), Mon, 1:15 PM-4:45 PM

Triple wild type melanoma profiling in the Caris Molecular Intelligence registry. *First Author: Krisztian Homicsko, University Hospital Lausanne, CHUV, Lausanne, Switzerland*

Background: Malignant melanoma is a genetically diverse disease. The most frequent mutation is BRAF, followed by NRAS and cKIT mutations. While BRAF, NRAS and cKIT mutations represent the largest fraction of patients, there is also an important group of triple wild type patients (3xWT) in dire need for potential targeted therapies. We compared mutational and PD-L1 profiles of 3xWT tumors using the database of the Caris Molecular Intelligence. **Methods:** We analyzed 541 patient samples for immunohistochemistry (IHC) and next generation sequencing (NGS) data available from the Caris database. Out of the 541 samples 89 samples also had PD-L1 expression data available. Samples were grouped in 4 subtypes: $BRAF^{mut}$ (n = 169), $NRAS^{mut}$ (n = 151), $cKIT^{mut}$(n = 25) and 3xWT (n = 197). **Results:** The database is skewed with an underrepresentation of $BRAF^{mut}$ patients and enrichment of 3xWT tumors. $BRAF^{mut}$, $NRAS^{mut}$, $cKIT^{mut}$and 3xWT patient were 30%, 26%, 3.7% and 40% of the total population, respectively. $BRAF^{mut}$ and 3xWT subgroups have more frequent cMET expression (p = 0.002). While $NRAS^{mut}$ tumors show lack of ERCC1 expression, $cKIT^{mut}$ tumors lack PGP expression. All mutation subtypes present equally frequent expression of MGMT, SPARC, TOP2A, TOPO1, TS, TUBB3 and RRM1 suggestive of multiple chemoresistance pathways. TP53 mutations are recurrent (~15%) in all mutation subgroups. In 3xWT tumors a different spectrum of mutations arise with low frequency ($<$ 10%). Mutant KRAS, JAK3, cMET, GNA11, GNAQ, APC, KDR, BRCA1, ERBB4, represent actionable alterations in up to 40% of that subgroup. None of the 541 tumors presented mutation in Akt, BRCA2, IDH1, CSF1R, GNAS, Notch1, Smo, STK11, VHL, MLH1, MPL, MPM1 A PD-L1 subanalyzes showed an overall 75% positivity. 3xWT tumors were more frequently PD-L1 negative as compared to $BRAF^{mut}$(p = 0.077) **Conclusions:** To our knowledge,the Caris database provides one of the largest profiling of 3xWT. In contrast to $BRAF^{mut}$, $NRAS^{mut}$ and $cKIT^{mut}$ tumors, 3xWT melanoma harbor a more complex mutational landscape. Low frequency mutations can identify targets in up to 40% of these patients. 3xWT are less frequently PD-L1 positive. Overall 3xWT patients should be tested for multiple markers in order to identify low frequency mutations

9055 Poster Session (Board #298), Mon, 1:15 PM-4:45 PM

Survival, biomarker, and toxicity analysis of nivolumab (NIVO) in patients that progressed on ipilimumab (IPI). *First Author: Jeffrey S. Weber, Moffitt Cancer Center, Tampa, FL*

Background: PD-1 antibodynivolumab was administered with/without a multi-peptide vaccine to 126 patients (pts) with unresectable melanoma that failed at least one regimen and were IPI naïve (34), or progressed after IPI (92). We assess its toxicity especially in those with prior dose limiting immune related adverse events (irAEs) to IPI, update survival and response duration data, and characterize myeloid derived suppressor cell (MDSC) and T cell subsets in IPI refractory pts. **Methods:** Pts refractory to IPI received NIVO at 3 mg/kg: two cohorts of pts were A*0201 positive and had either grade 2 or less IPI-related irAE (10 pts), or grade 3-4 dose limiting irAE (21 pts); 61 pts had grade 2 or less irAE, were not HLA restricted and received NIVO alone. Pre- and 12 week post-treatment peripheral blood was analyzed. **Results:** Median follow-up for IPI refractory pts was 18.7 months (mos);the response ratewas 29% by mWHO; 44% had clinical benefit with confirmed partial and complete response or stable disease at 24 weeks (CR+PR+SD).Median duration of response was 14.3 mos. Median progression-free survival (PFS) was 5.4 mos, and estimated median overall survival (OS) was 20.1 mos (95% CI: 17.0, not reached) with 1 and 2 year OS of 69.2% (95% CI: 57.9-78.0%) and 39.1% (95% CI 26.0-52.0%). Of 14 pts that have completed all therapy or stopped due to toxicity while stable or in response, all remain in remission. Of 21 pts with prior IPI-induced grades 3-4 irAEs, only 2 had a subsequent dose limiting (and different) irAE with NIVO, with 8 PR and 5 SD seen; all 8 PR and 3 SD are without progression. Biomarker studies showed that circulating pre-treatment HLA-DR lo/CD14+/CD11b+ myeloid-derived suppressor cells (MDSC) were associated with progression and worse OS (p = 0.0001 and 0.0009). Pre-treatment, MDSC suppressed T cell reactivity (p = 0.006) which was overcome by PD-1 blockade ex vivo, and had high levels of VISTA, CD244 and BTLA. Low PD-L1 and Tim3 expression on MDSC was associated with response. **Conclusions:** This is the first survival assessment in IPI refractory NIVO treated melanoma pts, with median OS of 20.1 mos and PFS of 5.4 mos. Prior irAEs to IPI were not replicated with NIVO. Novel biomarkers of outcome were found on circulating MDSC. Clinical trial information: NCT01176461.

9056 Poster Session (Board #299), Mon, 1:15 PM-4:45 PM

A phase I study of vemurafenib and decitabine in metastatic melanoma. *First Author: Sneha Deepak Phadke, University of Iowa Hospitals and Clinics, Iowa City, IA*

Background: Targeted therapy in metastatic melanoma has shown unprecented response rates. However, this effect is usually short lived, with a median progression free survival of 5.3 months with the use of vemurafenib. This phase I study explored the novel combination of vemurafenib and decitabine. **Methods:** Patients with BRAF V600E mutated metastatic melanoma were eligible for participation. Dosing of decitabine was modified for each cohort, which is detailed in the Table. The primary objective was safety while the secondary objective was response rate. **Results:** There were 4 patients were enrolled in cohort 1, 3 in cohort 2, 4 in cohort 3, and 3 in cohort 4. Seven patients had previously been exposed to vemurafenib. The most common adverse events included hyperbilirubinemia, hypophosphatemia, leukopenia, arthralgia, and rash. Most were grade 1-2. Ten patients required a dose reduction of vemurafenib. Maximum tolerated dose of decitabine was not reached, and there were no dose limiting toxicities. Six patients (43%) had a response to therapy with three (21%) achieving a complete response (CR). Five patients (36%) achieved stable disease while 3 (21%) had progressive disease. Two of the 3 patients with partial response had previously progressed on single agent vemurafenib. Of the 6 patients that had a response, 3 were in cohort 1. **Conclusions:** This study demonstrated that the combination of vemurafenib and decitabine in BRAF V600E mutated metastatic melanoma is safe and resulted in an overall response rate of 43%. In comparison to the BRIM-3 trial, this trial had a significantly higher rate of patients achieving CR with the combined treatment (21% vs $< 1\%$, $p < 0.01$). As half the patients that responded were enrolled in cohort 1, a similar phase I trial is planned which explores the effect of decitabine given at a low dose for a longer duration to ensure maximal depletion of DNA methyltransferase, the enzyme to which decitabine binds. Table. Clinical trial information: NCT01876641.

Cohort	Dose of decitabine	Duration of decitabine treatment	Dose of vemurafenib
1	0.1 mg/kg SQ three times weekly	2 weeks	960 mg BID continuous
2	0.2 mg/kg SQ three times weekly	2 weeks	960 mg BID continuous
3	0.3 mg/kg SQ three times weekly	1 week	960 mg BID continuous
4	0.3 mg/kg SQ three times weekly	2 weeks	960 mg BID continuous

9057 Poster Session (Board #300), Mon, 1:15 PM-4:45 PM

Demographics, tumor characteristics, and clinical outcomes associated with somatic mutations in 201 cancer-related genes in advanced melanoma patients (pts). *First Author: Michael A. Davies, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cutaneous melanomas (CM) have a high rate of somatic mutations. We analyzed the prevalence and correlations of mutations in 201 cancer-related genes to identify clinically significant molecular events in a cohort of pts with advanced melanoma. **Methods:** Next generation sequencing (NGS) of all exons of 201 cancer-associated genes was performed on tumor and germline DNA from pts with a known primary non-acral CM enrolled in an IRB-approved research protocol. Demographics, primary tumor characteristics, date of diagnosis of stage IV disease, and overall survival (OS) were collected for all pts. The significance of associations between these characteristics and somatic mutations was analyzed by a variety of statistical methods. **Results:** NGS was performed on 106 advanced melanoma pts with a known non-acral primary CM. Genes with a mutation rate $> 10\%$ ($n = 74$) were assessed for clinical associations. NF1 (OR 12.9, $p = 0.002$) and PCLO (OR 3.1, $p = 0.01$) mutations were associated with male gender, while BRAF V600 mutations were more common in women (OR 0.38, $p = 0.03$). BRAF mutations were associated with younger age at diagnosis ($p < 0.0001$), and 12 genes were associated with older age. Mutations in 5 genes were associated with increased primary tumor Breslow thickness, most significantly MET (mean 8.3 vs 3.5 mm, $p = 0.005$). Among all pts with NGS data with distant metastases ($n = 88$), NRAS mutation was associated with significantly shorter OS from the diagnosis of stage IV (HR 3.2, $p = 0.007$), while mutations in BRAF (HR 0.35, $p = 0.02$) and 12 other genes were associated with significantly longer OS (HR 0.12 to 0.40). Among stage IV pts without BRAF V600 mutations ($n = 52$), NRAS mutation was again a significant predictor of shorter OS (HR 2.8, $p = 0.04$), and mutations in 12 other genes correlated with increased OS (HR 0.11 to 0.37). **Conclusions:** Somatic mutations in several genes in advanced non-acral CM pts were significantly associated with disease characteristics and clinical outcomes, and merit analysis in additional cohorts of pts. Analysis of copy number variations will be included in the final report for the cohort.

9058 Poster Session (Board #301), Mon, 1:15 PM-4:45 PM

Trends in demographics, incidence, and survival in children, adolescents and young adults (AYA) with melanoma: A Surveillance, Epidemiology and End Results (SEER) population-based analysis. *First Author: Demytra Krista Lee Mitsis, Roswell Park Cancer Institute, Buffalo, NY*

Background: Whilemelanoma incidence continues to rise in the United States, trends in children and AYA groups are poorly defined.Understanding the burden in these groups is critical in developing effective prevention strategies to ↓ risk. **Methods:** Data from 9 registries that have contributed to the SEER program since 1973 were used to assess descriptive epidemiology & time-trends in incidence & overall survival (OS) of melanoma in children (0-14 yrs) & AYA (15-39 yrs) from 1973-2011. 4 time quartiles (1973-80, 1981-90, 1991-2000 & 2001-11) were used. OS was compared using univariate & multivariate proportional hazards methods controlling for age, gender, race, ethnicity, stage, site & time period of diagnosis. Analyses were done using SAS v9.4. **Results:** 35,726 cases of melanoma in < 40 yrs old were reported from 1973-2011; median age 32 yrs; 98.9% cases in AYA. There were 13,616 males (38%) & 22,110 females (62%) with ↑ incidence in both genders over time ($p < 0.001$). The incidence rate per 100,000 ↑ from 13.26 to 46.79 ($p < 0.001$); similar significant trends were noted in both age groups across time quartiles (children: 0.45 → 1.51; AYA 22.28 →74.36; all $p < 0.001$). An ↑ female/male incidence rate ratio over time was noted; females comprised 57% of cases from 1973-80 but 65.2% of cases from 2001-11 ($p < 0.001$). The incidence was significantly higher in whites (94.8%) than other races. Most cases were cutaneous (98.6%) & localized; the incidence of in-situ melanoma rose from 4.1% to 30.4% over time ($p < 0.001$). OS has ↑ over all time quartiles (ref 1973-80; HR = 0.86, 0.65, 0.38; all $p < 0.001$) with 5 & 10-yr OS of 0.93 and 0.90 respectively. No difference in OS was seen between children & AYA (HR = 0.79; 95% CI, 0.6, 1.05; $p = 0.1$) or between blacks & whites (HR = 1.02; 0.70, 1.49; $p = 0.907$). Ocular melanoma was associated with ↓ OS (HR = 1.75; 1.48, 2.08; $p < 0.001$). **Conclusions:** Since 1973, the incidence of melanoma in children and AYA has increased by 253% with white female young adults at particular risk. There is a trend in diagnosis at earlier disease stage. Potential causes must be explored to devise intervention strategies.

9059 Poster Session (Board #302), Mon, 1:15 PM-4:45 PM

Efficacy and toxicity of treatment with the anti-CTLA-4 antibody Ipilimumab in patients with metastatic melanoma who have progressed on anti-PD-1 therapy. *First Author: Prashanth Prithviraj, Medical Oncology Unit, Austin Health, Heidelberg, Australia*

Background: Immunotherapy with anti-CTLA-4 and anti-PD-1 antibodies has demonstrated overall survival benefits in patients (pts) with metastatic melanoma (MM) compared to standard therapy. An early phase clinical trial suggests that combination therapy with an anti-CTLA-4 and anti-PD-1 antibody increases the response rate compared to single agent treatment however is associated with increased toxicity. Anti-PD-1 therapy demonstrated equal efficacy and toxicity in pts that progressed on or were naive to treatment with the anti-CTLA-4 antibody Ipilimumab. So far only very limited evidence exists regarding the efficacy and toxicity of Ipilimumab in pts that have progressed on treatment with an anti-PD-1 agent. **Methods:** We retrospectively identified ten pts with MM who received anti-PD-1 therapy (Nivolumab/Pembrolizumab) in a clinical trial and were subsequently treated with Ipilimumab. Ipilimumab was administered at a dose of 3mg/kg every three weeks for four cycles and response has been assessed by CT scan 4-6 weeks after the last dose. **Results:** The median time between the last dose of anti-PD-1 therapy and the commencement of Ipilimumab was 7 months. The median age of the patient cohort was 58 years with all pts having stage IV C disease and 4/10 pts had an elevated LDH on commencement of Ipilimumab therapy. 1/10 of pts achieved a partial remission as their best response to anti-PD-1 therapy with an additional 5/10 having stable disease. 4/10 of pts received all four doses of Ipilimumab. The follow up after the last dose of Ipilimumab has been more than three months. 1/10 of pts achieved a response to ipilimumab with another 1/10 having prolonged stable disease. 3/10 pts experienced grade3/4 immune related adverse events (irAE). **Conclusions:** Ipilimumab therapy can induce responses in pts who have failed treatment with an anti-PD-1 antibody. The response rate and clinical benefit rate appears similar compared to pts that have not received prior anti-PD-1 antibody therapy. Although cases of severe and unusual irAEs (eg pneumonitis) have been observed in our pts, an analysis of a larger patient cohort will be required to test the significance of these observations.

9060 Poster Session (Board #303), Mon, 1:15 PM-4:45 PM

Adoptive Cell Therapy for metastatic melanoma: A UK centre experience. *First Author: Manon Rhys Pillai, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Adoptive cell therapy (ACT) with tumour infiltrating lymphocytes (TIL) has consistently demonstrated impressive clinical results in several international studies in the management of metastatic melanoma. We describe our experience as the only UK cancer centre providing TIL therapy. **Methods:** TIL are cultured from resected tumour samples as previously described. Infusion is preceded by non-myeloablative lymphodepleting chemotherapy (high dose cyclophosphamide and fludarabine) and followed by intravenous high dose interleukin 2 (HD-IL2). **Results:** Eleven patients have been treated to date: eight with cutaneous melanoma, two with ocular melanoma and one patient with mucosal melanoma. All patients had metastatic disease and were heavily pre-treated with a combination of targeted agents and immunotherapies (anti-CTLA4 and anti-PD1 antibodies). In the ten patients currently evaluable, 60% achieved an objective clinical response according to the response evaluation criteria in solid tumours. Five of eight patients with cutaneous melanoma achieved a response, including one ongoing complete response (30+ months) and four partial responses. All other patients showed disease stabilisation. One patient with ocular melanoma achieved a short lived partial response. Of eight patients with significant symptomatic progressive disease, six obtained clear symptomatic benefit. Treatment is well tolerated. All patients experienced anticipated toxicities associated with pre-conditioning chemotherapy and HD-IL2, which were short lived and manageable on the medical ward. **Conclusions:** We show that at our centre lympho-depleting chemotherapy followed by transfer of TIL and HD-IL2 is feasible and clinically effective, demonstrating tumour regression in over 60% of patients with metastatic cutaneous melanoma. Short lived responses were additionally seen in patients with ocular melanoma, where treatment options are limited, suggesting a potential role for TIL therapy in this group of patients also. Significant toxicities are attributable to HD-IL2 and further evaluation of TIL followed by low dose IL2 should be conducted to decrease treatment related complications and expand clinical participation in ACT.

9061 Poster Session (Board #304), Mon, 1:15 PM-4:45 PM

The expression quantitative trait loci (eQTLs) and their association with melanoma clinical outcomes. *First Author: Matjaz Vogelsang, New York University School of Medicine, New York, NY*

Background: Prognosis of cutaneous melanoma (CM) is modulated by tumor immunogenicity, which varies on the individual level. While this suggests a contributing role of germline genetic factors, current approaches suffer from difficulties in identifying biologically relevant germline prognostic biomarkers. Recent whole-genome scans have established comprehensive maps of eQTLs (i.e. gene expression correlating germline genetic variants) across different populations and human tissues. We hypothesize that the interrogation of inherited eQTLs in cells of the immune system may reveal biologically important germline markers of CM immunogenicity and clinical outcomes. **Methods:** Based on our computational analyses of publicly available eQTL data, we selected 43 genetic variants most significantly correlating with expression of 41 immune-modulating genes in lymphoblastoid cell lines derived from 857 healthy female twins from Multiple Tissue Human Expression Resource. Variants were genotyped in a prospective cohort of 1022 CM patients and analysed for their association with overall and recurrence-free survival using Cox regression model, adjusted by demographic and clinical covariates. **Results:** We have discovered novel and highly significant association of rs6673928, an *IL19* eQTL variant, with favorable CM overall survival (OS)(HR 0.54, 95% CI 0.37 to 0.79; P= 0.00087). Associations with melanoma OS were also observed for other significant eQTLs: rs6695772 (HR 1.76, 95% CI 1.21 to 2.55; P= 0.002), rs11569345 (HR 0.35, 95% CI 0.14 to 0.91; P= 0.014) and rs841718 (HR 1.75, 95% CI 1.12 to 2.72; P= 0.018) strongly correlating with expression of *BATF3*, *CD40* and *STAT6*, respectively. **Conclusions:** Our unique approach of interrogating lymphocyte-specific eQTLs from healthy twins was notably powerful in identifying several immunomodulatory eQTL variants as novel biologically relevant predictors of CM prognosis. These data suggest that eQTL-based strategy proposed here will be highly efficient in discovering the missing germline genetic component associated with risk, outcome or therapy response in other human cancers driven by specific molecular pathways.

9062 Poster Session (Board #305), Mon, 1:15 PM-4:45 PM

One-year overall survival (OS) and biomarker correlates from a phase II study of ipilimumab (IPI) with carboplatin and paclitaxel (CP) in patients with unresectable stage III or IV metastatic melanoma (MM). *First Author: Rahima Jamal, Hopital Notre-Dame, Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada*

Background: Pivotal studies with IPI demonstrated increased OS both as single agent (10.1 months) and with DTIC (11.2 months). We've previously reported an encouraging safety profile with IPI plus CP and early efficacy results. We now report updated 1-year OS and biomarker correlates of patient response. **Methods:** 30 patients were randomized in a 1:2 ratio to arm A (C (AUC = 6) and P (175mg/m2) every 3 weeks x 5 and IPI (3mg/kg) every 3 weeks x 4 starting at week 4) or arm B (similar dosing to arm A except IPI was given on week after CP). Tumor biopsies were collected at screening and week 8, and immune monitoring bloods were collected throughout. **Results:** Median OS was 16.1 months, with a 1-year OS of 56.5% for all patients with no differences between arms. Overall median follow-up was 23.2 months. Best overall response rate (BORR) and disease control rate (DCR) were 26.7% and 56.7% by irRC. BORR in patients whose tumors were wild type for BRAF and NRAS was 44%, compared to 8% in patients with a mutation in BRAF or NRAS. Clinical responses correlated with the abundance of peri and intratumoral CD3+ inflammatory cells in the pretreatment biopsy, but not with CD4/CD8 ratios or CD20 infiltrate. Circulating levels of some chemokines were elevated in non-responders compared to responders. While IPI influenced B cells and monocyte differentiation, this did not correlate with clinical outcome. Although all patients had an increase in $ICOS^+$ T cells after IPI treatment, a pre-existing low proportion of $ICOS^+$ T cells before treatment was associated with a more favorable clinical outcome. Lower levels of PD-1 on CD4 and CD8 T cells were observed in responders compared to non-responders. **Conclusions:** Median OS and 1-year OS compared favorably to previous pivotal trials. Patients whose tumors were wild type for BRAF/NRAS had a higher rate of objective response. High baseline level of CD3 infiltrate was associated with a positive clinical response to IPI/CP. A low activation state (ICOS) before treatment and maintenance of low levels of PD-1 on T cells during treatment correlated to a favorable clinical response to IPI. Clinical trial information: NCT01676649.

9063 Poster Session (Board #306), Mon, 1:15 PM-4:45 PM

Survival, safety, and response patterns in a phase 1b multicenter trial of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. *First Author: Igor Puzanov, Vanderbilt University Medical Center, Nashville, TN*

Background: T-VEC is an HSV-derived oncolytic immunotherapy designed to induce systemic antitumor immunity. In a phase 3 melanoma study, T-VEC monotherapy significantly improved durable response rate (DRR, ≥ 6 month response) vs GM-CSF (16% vs 2%, $P < 0.0001$; Andtbacka et al. ASCO 2013), and median OS was 4.4 months longer for T-VEC vs GM-CSF (23.3 vs 18.9 months; HR = 0.79, 95% CI: 0.62-1.00; P= 0.051; Kaufman et al, ASCO 2014). Combining T-VEC to promote tumor-derived antigen release with an immune checkpoint inhibitor may enhance efficacy compared to either agent alone. The phase 1b portion of this phase 1b/2 combination study (NCT01740297) completed enrollment and met its primary objective with no dose-limiting toxicities (DLTs) and an objective response rate (ORR) of 56% (Puzanov et al. ASCO 2014). **Methods:** Key inclusion criteria included stage IIIB-IV melanoma; no prior systemic treatment; measurable disease; and ≥ 1 injectable cutaneous, subcutaneous, or nodal lesion. T-VEC was given intralesionally at ≤ 4 mL of 10^6 PFU/mL at week 1, then 10^8 PFU/mL at week 4, and then Q2W. Ipi 3 mg/kg Q3W was given as 4 infusions starting week 6. T-VEC continued until DLT, intolerance, all injectable tumors disappeared, or disease progression (PD) per immune-related response criteria (irRC). **Results:** The data cutoff was Dec 22, 2014 with all patients at least 17 months from start of treatment. 18 patients received T-VEC+ipi; grade 3/4 treatment-emergent AEs occurred in 32% and grade 3/4 immune-related AEs occurred in 2 patients with no treatment-related deaths. Per irRC, ORR was 56% (33% CR) and DRR was 44%. Median time to response was 5.3 months (range 2.6-5.7). Median progression-free survival (PFS) was 10.6 months (2.6-19.3+). Median overall survival (OS) was not reached; 12-month and 18-month survival were 72.2% and 67%. On a lesion level, 24 and 11 of 35 injected index lesions and 8 and 5 of 16 uninjected index lesions regressed ≥ 50% and 100%, respectively. **Conclusions:** At > 17 months, T-VEC+ipi continued to demonstrate durable responses with 2/3 of patients alive at 18 months and no new safety signals. Phase 2 (ipi vs T-VEC+ipi) is ongoing. Clinical trial information: NCT01740297.

9064 Poster Session (Board #307), Mon, 1:15 PM-4:45 PM

Identification of potentially actionable mutations in RTKs in melanoma detected by next generation sequencing (NGS). *First Author: Jan Kemnade, Baylor College of Medicine, Houston, TX*

Background: The success of personalized cancer therapies targeting patients with specific actionable mutations underscores the need to expand the search for relevant mutations with functional and/or clinical consequences. Cutaneous melanomas have a high mutation burden due to ultraviolet radiation exposure, thus necessitating approaches to distinguish driver versus passenger mutations. Here we report the analysis of the nature and location of somatic mutations in 16 receptor tyrosine kinases (RTKs) in a cutaneous melanoma cohort analyzed by next generation sequencing (NGS). **Methods:** NGS for all exons of 201 cancer-related genes was performed on tumor and germline DNA from pts with non-acral cutaneous melanoma (n = 108). Somatic mutations in RTKs (MET, PDGFRA, PDGFRB, KIT, EGFR, ERBB2, ERBB3, RET, IGF1R, EPHA3, DDR1, DDR2, ALK, JAK1, JAK2, JAK3) were mapped to the tyrosine kinase domain (TKD), other functional regions (i.e. transmembrane domains, binding domains) or conserved protein domains (ORD), or regions of unknown significance (RUS) in each gene. The COSMIC database was analyzed for presence of the same mutations in other tumors. **Results:** Missense mutations were detected in all 16 RTKs. The number of mutations identified in each RTK ranged from 2 (IGF1R) to 24 (EPHA3), with a median of 7.5 mutations per RTK. The average incidence of mutations found in the TKD region for each RTK was 29% and ranged from 0% (ERBB2, ERBB3) to 80% (JAK2). For the ORD regions the average was 34%, ranging from 0% (ERBB2, ERBB3, RET, DDR2) to 61.5% (MET). For the RUS regions the average was 37%, ranging from 0% (PDGFRB, DDR1) to 100% (ERRB2, ERRB3). Mutations detected in 11 of the RTKs were also identified in cancer sequencing datasets available on COSMIC. **Conclusions:** The prevalence of mutations in the TKD, ORD, and RUS regions varied significantly among the 16 RTKs in the cutaneous melanoma cohort. Overall ~62% of the mutations mapped to regions with potential functional significance, and ~16% have been reported previously in other cancers. Integration of these analyses with predicted structural and functional consequences may be used to prioritize candidate actionable mutations for in-depth characterization.

9065 Poster Session (Board #308), Mon, 1:15 PM-4:45 PM

The effect of ipilimumab on natural killer cells identifies the subset of advanced melanoma patients with clinical response. *First Author: Ines Esteves Domingues Pires Da Silva, New York Univ Langone Medcl Ctr, New York, NY*

Background: The concept of immune cell exhaustion in the context of metastatic melanoma has been reinforced by the success of immunotherapies targeting the exhaustion markers CTLA-4 and PD-1. Natural Killer (NK) cell exhaustion, characterized by an up-regulation of inhibitory receptors and loss of function, was described in the context of melanoma. Ipilimumab (IPI - anti-CTLA-4) improves the anti-tumor T cell activity and achieves response rates of 15-20%, however the effect of IPI on NK cells is unknown. In this project, we studied the effect of IPI on the phenotype of NK cells from melanoma patients and how it relates with clinical response. **Methods:** NK cells were purified from the peripheral blood of 10 advanced melanoma patients treated with IPI. Blood samples were collected at baseline, after the 2nd and 4th cycles of IPI. NK cells were characterized acccording to the expression of activating (NKG2D) and inhibitory (KIRB1) receptors, function (cytotoxicity, IFN-γ production), levels of the IL-2R α chain and response to IL-2 stimulation. We analyzed the effect of IPI on NK cells as it relates to clinical response. **Results:** IPI induces an upregulation of 50% in the IL-2R α chain levels on NK cells ($p = 0.03$). There was no significant difference in other receptors or function ($p > 0.05$). We then checked the phenotype and function of these NK cells after 48 hours of IL-2 stimulation and in 4 patients out of 10 there was an improvement of cytotoxicity and higher levels of IL-2R α chain. Remarkably, this better response to IL-2 was observed in patients with clinical response to IPI (partial/complete response) compared with non-responders, with higher cytotoxicity ($p = 0.05$) and levels of IL-2R α chain ($p = 0.02$). **Conclusions:** CTLA-4 is expressed mainly on T cells, including regulatory T cells, with no expression on NK cells. Nevertheless, we have shown an effect of IPI on the phenotype of NK cells, with an increase of IL-2R expression. More importantly, the effect of IPI on NK cells (better response to IL-2 stimulation and cytotoxicity) is associated with a good clinical response. The mechanism behind this effect is not clear yet, however this may be indirect through the action of IPI on other immune cells.

9066 Poster Session (Board #309), Mon, 1:15 PM-4:45 PM

Continued evaluation of a 31-gene expression profile test (GEP) for prediction of distant metastasis (DM) in cutaneous melanoma (CM). *First Author: David H. Lawson, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: A GEP has been validated as an independent predictor of DM, distant metastasis free survival (DMFS) and overall survival (OS) (Gerami, CCR 2015; Gerami JAAD, 2015). This abstract combines the third validation cohort study with the two prior studies for analysis by T factor subgroups.**Methods:** 555 patients (pts) were enrolled in a multi-center IRB approved archival tissue study with a primary endpoint of DMFS. 492 CMs had T-factors available for analysis. Quantitative RT-PCR and Radial Basis Machine modeling classified CM tumors as low risk Class 1 vs. high risk Class 2. Results are reported for thin (T1), intermediate (T2/T3) and thick (T4) lesions. Most patients were node negative clinically or by sentinel node biopsy.**Results:** GEP Class 1 vs 2 was found to be a significant predictor of DMFS and OS (log-Rank $p<0.0001$), and GEP, Breslow's thickness, and ulceration were independent predictors in Cox multivariate analysis (DMFS HR=2.7, p=0.0003; 2.2, p=0.03; 3.3, $p<0.0001$, respectively and OS HR=2.8, p=0.0002, 2.5, p=0.01, 1.7, p=0.01, respectively). In the T2/T3 N0 cohort (n=180) frequency of class 2 signature increases with depth [T2:35/78 (45%) Class 2; T3:75/102 (74%) Class 2] and ulceration [nonulcerated: 54/108 (50%) Class 2; ulcerated: 53/63 (84%) Class 2]. The table reflects survival analysis in this cohort. In the T1 group (median followup for non-DM group = 7.4 yrs) 14/173 (8%) reported DM. For T4 group: 42/80 (53%) developed DM. Data not considered adequate for further analysis of either group.**Conclusions:** GEP offers prognostic information that complements conventional staging at least in patients with T2/T3 CM. Ongoing studies will further define the role of GEP in evaluating these patients.

T2/T3 N0 group (n=180)

	DM	all cause deaths
Total events	51/180 (28%)	47/180 (26%)
Class 1	7/70 (10%)	7/70 (10%)
Class 2	44/110 (40%)	40/110 (36%)
Of ulcerated primaries		
Class 1	5/19 (26%)	5/19 (26%)
Class 2	28/53 (53%)	21/53 (40%)
K-M* analysis		
Class 1 5-yr rate	91%	90%
Class 2 5-yr rate	58%	63%
***p*-value**	<0.0001	<0.0001
Cox multivariate**	HR (*p*-value)	HR (*p*-value)
GEP	3.9 (0.003)	5.3 (0.0007)
ulceration	2.6 (0.002)	1.5 (0.203)

9067 Poster Session (Board #310), Mon, 1:15 PM-4:45 PM

Long-term results of ultrasound (US)-guided fine needle aspiration cytology (FNAC) in conjunction with sentinel node biopsy (SNB) to support step-wise approach in melanoma. *First Author: Alexander Christopher Jonathan Van Akkooi, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands*

Background: Ultrasound (US) guided Fine Needle Aspiration Cytology (FNAC) is a common diagnostic tool in the work-up of other cancers, i.e. breast and thyroid. The results in melanoma (mel) were poor (sensitivity 20-40%). Introduction of the Berlin Morphology criteria has recently shown potential improvements up to 65 – 80% in selected patients (pts). **Methods:** Between 2001 and 2010 over 1000 stage I/II consecutive mel pts prospectively underwent US-FNAC prior to Sentinel Node (SN). All pts underwent lymphoscintigraphy prior to US-FNAC. The Berlin US morphology criteria: Peripheral perfusion (PP), loss of central echoes (LCE) and balloon shaped (BS) were registered and FNAC was performed if any factor was present. SN tumor burden was measured according to the Rotterdam criteria. All pts underwent SN or lymph node dissection in case of positive FNAC. **Results:** Mean/median Breslow thickness was 2.58/1.57 mm. Mean/median follow-up was 69/63 months (IQR 42 - 98). SN positivity rate was 21%. US-FNAC Sensitivity was 71% (US only) and 51% (US-FNAC). Sensitivity of US-FNAC was highest for T4 (76%) and ulcerated melanomas (63%). PP, LCE and BS had sensitivity of 69%, 24% and 24% respectively. Sensitivity of US-FNAC increased with increasing SN tumor burden. PP was an early sign of metastasis (58% in < 0.1 mm metastases). Threshold size of a metastasis for FNAC was 0.3 mm. Survival analyses for different end-points (Melanoma Specific, Disease-Free, Distant-Metastasis-Free) demonstrated that pts with pos FNAC and/or BS/LCE had poor survival. Pts with PP and with neg FNAC had a slightly worse survival (HR 1.61 (P = 0.025), 1.45 (P = 0.034) and 1.72 (P = 0.007) compared to completely neg pts (regardless of SN result). **Conclusions:** The long-term results support the step-wise approach to melanoma patients. In case of positive FNAC and/or clearly malignant US (BS and/or LCE) patients have larger amounts of SN tumor burden and poor survival, they can be spared a SNB. In case of PP and negative FNAC, patients should proceed to undergo a SNB to detect microscopic occult disease. Completely US-FNAC negative patients might only require follow-up and no SN staging.

9068 Poster Session (Board #311), Mon, 1:15 PM-4:45 PM

Phase II trial of trametinib in combination with the AKT inhibitor GSK 2141795 in BRAF wild-type melanoma. *First Author: Alain Patrick Algazi, University of California, San Francisco, San Francisco, CA*

Background: There is currently a lack of effective targeted therapies for BRAF wild type (WT) melanoma. We explored the combination of the MEK inhibitor trametinib with the AKT inhibitor GSK2141795 in BRAF/NRAS WT and BRAF WT/NRAS mutant (MT) melanoma. **Methods:** Study accrual goal was 24 patients (pts) with metastatic BRAF WT/NRAS WT melanoma and 24 pts with BRAF WT/NRAS MT melanoma. Eligibility criteria included: unresectable stage III or IV disease, ECOG status 0-2, stable CNS disease, and adequate cardiac function (LVEF $\geq$ 50%, QTc $>$ 480). For each cohort, an interim analysis was pre-specified after 10 pts. If no responses were seen, the cohort would be closed. If one or more responses were seen, an additional 14 pts would be accrued. Pts received trametinib (1.5 mg) and GSK 2141795 (50 mg) orally, once daily for each cycle lasting 28 days. ORR was assessed by RECIST 1.1 with restaging performed every 8 weeks (2 cycles). **Results:** Twenty pts were enrolled from October 2013 to October 2014: 10 pts in each NRAS cohort. Rash (70%) and diarrhea (50%) were the most common drug-related adverse events (AE's) for all grades; mucositis occurred in 40% of pts. The best overall response was stable disease in 65%: 80% of BRAF WT/NRAS WT patients and 50% of BRAF WT/NRAS MT patients. No RECIST-confirmed partial or complete responses were observed. As a result, both cohorts were closed to further accrual. Median progression-free survival was 2.75 months (IQR: 1.7 to 3.7 mos), with no difference between the NRAS cohorts ($p = 0.46$). **Conclusions:** The combination of trametinib and GSK2141795 is safe, but at these doses and schedules, is ineffective in the BRAF WT population, regardless of NRAS status. Clinically significant adverse events were common at the doses tested. Pharmacodynamic studies are ongoing to determine the extent of pathway inhibition achieved. Clinical trial information: NCT01941927.

9069 Poster Session (Board #312), Mon, 1:15 PM-4:45 PM

Changes in blood eosinophilia during anti-PD1 therapy as a predictor of long term disease control in metastatic melanoma. *First Author: Lydia Gaba, Hospital Clinic de Barcelona, Barcelona, Spain*

Background: The anti-PD1 antibody (Ab) Nivolumab (Nivo) has demonstrated to improve the overall survival (OS) in patients (pts) with metastatic melanoma (MM) compared to DTIC. Pembrolizumab (Pembro), another anti-PD1, showed durable antitumor activity in pts with MM and has been approved in the US for the treatment (tmt) of MM that progressed on ipilimumab and, if *BRAF*V600 mutant, a BRAF inhibitor. To date, no lab test has been identified to predict clinical benefit (CB) to anti-PD1 Abs. **Methods:** This retrospective observational study included pts with MM who received anti-PD1 tmt in a single institution. The objective was to identify whether an increase of at least 100/mm3 at 3 weeks over the baseline or increase $>$ 400/mm3 at 12 weeks in the absolute eosinophil counts (AEC) could predict CB. Blood tests were performed before every administration. Response to tmt according immune-related response criteria, progression free survival (PFS) and OS were evaluated. Descriptive statistics were used to analyze patient baseline characteristics. Response rates (RR) were compared by exact Fisher test. PFS and OS were estimated by the Kaplan-Meier method. **Results:** From March 2013 to December 2014, 29 pts were treated with anti-PD1 Abs (3 pts with Nivo and 26 pts with Pembro). Median age was 57 years (range 30-83) with 10.3% stage M1a, 24.1% M1b and 65.5% M1c, and 51.7% had elevated LDH. Pts who experienced an increase in AEC over the baseline $>$ 100/mm3 at 3 weeks demonstrated better outcomes in terms of RR (55.6% vs 9.1%, $p = 0.190$), PFS (9.9 [95% CI: 5.8-14.0] vs 2.6 [95% CI: 1.0-4.2] months, $p = 0.008$) and OS (18.8 [95% CI: 15.5-22.1] vs 6.9 [95% CI: 3.5-10.3] months, $p = 0.001$) compared with those who did not. Moreover, pts with an AEC $>$ 400/mm3 at 12 weeks responded to tmt (100% vs 18.2%, $p = 0.002$) and showed more benefit regarding PFS (18.6 vs 3.6 months, $p < 0.0001$) and OS (not reached vs 11.4 months, $p = 0.017$) compared to those who did not. **Conclusions:** An increase in AEC of 100/mm3 over baseline at week 3 and an absolute AEC $>$ 400/mm3 at week 12 during anti-PD1 tmt might identify pts with MM most likely to experience long-term disease control with anti-PD1 Abs.

9070 Poster Session (Board #313), Mon, 1:15 PM-4:45 PM

Immunologic profile of melanoma brain metastases (MBM) in patients (pts) with prolonged survival. *First Author: Kevin P. Lui, Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY*

Background: Median survival of MBM pts is significantly shorter than pts with extra-cranial metastases. However, a subset of MBM pts exhibit extended survival. Radiation therapy (RT - radiosurgery and whole-brain radiation) is used to treat MBM pts and recent data by several groups including ours demonstrate that RT may potentiate response to immunotherapies by inducing an immunological tumor cell death. In this study, we investigate the immunomodulator effect of RT on MBM tissue and attempt to identify an immunological profile associated with improved post-MBM survival. **Methods:** Expression of 560 immunoregulatory genes was assessed in 32 MBM tissues (10 post radiation and 22 no radiation) using a customized NCounter GX Human Immunology Kit (Nanostring) comprising of 24 immunology-related gene networks compiled from the Gene Ontology Consortium List of immunologically important genes. We also compared expression of the immunoregulatory genes in long term survivors ($>$ 1 year) compared to short term survivors ($<$ 1 year). We then verified the data using RT-PCR and IHC in an expanded cohort of 47 MBM tissues. **Results:** Irradiated MBM had higher expression of genes involved in: (1) autophagy/apoptosis (ATG12, BCL2L11 and CASP8); (2) adhesion (CD209, ICAM2; ITGA4 , ITGB1 and PECAM-1); (3) immune cell development and activation (IFNAR2, IKZF2, MAP4K2, NFATC3, POU2F2 and TCF4) ($p < 0.05$). In addition, RT induced upregulation of PD-L1 (transmembrane protein involved in immunoinhibitory signals) and TGF-b (immunosuppressive cytokine and cell cycle regulator) at the gene expression level, as determined by Nanostring and confirmed by RT-PCR, and protein level of PD-L1 by IHC. Genes involved in lymphocyte activation such as CD44, CD81 and IL16 were significantly overexpressed in long term survivors ($p < 0.05$). **Conclusions:** Our data demonstrate that RT induces both lymphocyte activation and upregulation of immunosuppressive signals. Our data also suggest that MBM pts with prolonged survival host an immunologically distinct subset of tumors with upregulated lymphocyte activating genes. Identification of MBM pts with enhanced immunogenicity may aid in prognostication and prediction of response to immunotherapy.

9071 Poster Session (Board #314), Mon, 1:15 PM-4:45 PM

A novel algorithm applicable to cancer next-generation sequencing panels to predict total tumor mutation load and correlation with clinical outcomes in melanoma. *First Author: Jason Roszik, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Next-generation sequencing (NGS) panels of cancer-related genes are increasingly utilized in oncology. We developed an algorithm to estimate total tumor mutation burden in melanoma using genes present in local and commercial NGS panels. The algorithm was validated using independent datasets and analyzed for clinical significance in two cohorts of advanced melanoma patients (pts). **Methods:** Overlapping genes ($n = 170$) from two NGS panels were used for algorithm development. Publicly available whole exome sequencing (WES) data ($n = 345$) from the cutaneous melanoma TCGA was employed to develop a mutation score for each gene in the panel. The summation of the mutation scores yields the Predicted Total Mutation Load (PTML) of the tumor. The algorithm was applied to 3 independent melanoma WES datasets to test the correlation of predicted with actual mutation burden. The PTML was then determined for cohorts of melanoma pts treated with immune-therapy regimens (e.g., adoptive cell transfer (ACT)), and associations with clinical outcomes were determined. **Results:** The PTML correlated strongly with the actual WES mutation load of each tumor in all 3 tested melanoma WES datasets (Set 1, $n = 121$, $r2 = 0.58$; Set 2, $n = 64$, $r2 = 0.84$; Set 3, $n = 127$, $r2 = 0.93$). For subsequent analyses low PTML was defined as $\leq$ 100, and high as $>$ 100 based on observed distributions. High PTML predicted both increased PFS ($n = 36$, $p < 0.05$) and OS ($n = 35$, $p < 0.05$) among pts treated with ACT. Pts with high PTML also had a longer interval from stage III to stage IV ($n = 55$, $p < 0.05$) and improved OS from stage IV ($n = 62$, $p < 0.01$) in a large cohort of MDACC patients with NGS data. Further testing demonstrated that accurate disease-specific PTML algorithms for other cancers (e.g., lung) are feasible. **Conclusions:** In this proof of concept study, a novel algorithm applied to NGS panels accurately predicted total mutation burden in cutaneous melanoma pts. High PTML ($>$ 100 mutations) correlated with improved OS in two cohorts of melanoma pts, including pts treated with immunotherapy. These results support further testing of the PTML algorithm in risk assessment and management of melanoma pts.

9072 Poster Session (Board #315), Mon, 1:15 PM-4:45 PM

Low vemurafenib plasma exposure as a short-term predictive parameter of progression disease in metastatic *BRAFV600^{mut}* melanoma. *First Author: Lauriane Goldwirt, AP-HP, Hôpital Saint-Louis, Department of Pharmacology, Paris, France*

Background: The BRAF inhibitor Vemurafenib (V) improves survival in *BRAFV600* mutated metastatic melanoma patients, with a 59% response rate (BRIM-3). The aim of this retrospective study is to explore the potential relationship between V plasma concentration ($_{pl}$VC) and progression disease (PD). **Methods:** Patients with AJCC stage IIIb/c (n = 9) or IV (n = 39) *BRAFV600^{E}* melanoma treated with V in monotherapy were retrospectively included according a signed informed consent. Blood samples were collected monthly. Response evaluation (RECIST 1.1) and toxicity evaluation were performed monthly after V initiation. $_{pl}$VC were quantified using a routine HPLC-UV method. All samples were included in the response-concentration analysis. Regression analysis was performed with R- software. $_{pl}$VC cut-off to predict progression was determined with ROC curve analysis (pROC R Package). Progression-free survival (PFS) was assessed with multivariate Cox analysis (survival R package). **Results:** $_{pl}$VC obtained in 48 patients (148 blood collections) displayed a wide inter- and intra-individual variability (5.3 to 135.2μg/mL, median 66.8). All patients declared high compliance to treatment. Eleven patients (23%) experienced PD during V treatment. With a median follow-up of 12 months (1 to 50), progression on V occurred after a median 5 months treatment duration (14$\pm$9). Median $_{pl}$VC tended to be lower in patients experiencing PD (51$\pm$22μg/mL) compared to complete, partial or stable responders (67$\pm$24 μg/mL, p = 0.06). Maximal concentrations were higher in responding patients (67 vs 51 μg/mL, p = 0.01). Patients with at least one value reaching 65 μg/mL tended to have a lower risk of disease progression than other patients (p = 0.11). This threshold value of 65 μg/mL predicted progression with 78% specificity and 82% sensibility. Interestingly, this effect appeared to be more significant before 6 month (PFS6). **Conclusions:** $_{pl}$VC was confirmed highly variable at steady state. As low exposure was associated to higher progression risk and lower PFS6, therapeutic drug monitoring should be performed at least for 6 months from treatment initiation of V that is now used in combination to the MEK inhibitor cobimetinib.

9073 Poster Session (Board #316), Mon, 1:15 PM-4:45 PM

Patterns of response to anti-PD1 treatment: Comparison of three radiological response criteria and effect on overall survival (OS) in metastatic melanoma patients (MM). *First Author: Minnie Kibiro, Princess Margaret Hospital, Toronto, ON, Canada*

Background: Radiological assessment of patterns of response (R) to checkpoint inhibitors remain imperfect. irRC accounts for pseudoprogression but does not evaluate change in density. We aimed to evaluate individual lesion and inter patient R by RECIST 1.1, irRC, CHOI and modified CHOI (mCHOI) and correlate R with OS. **Methods:** 37 patients (pts) with 567 measurable lesions treated with pembrolizumab in a phase 1 trial were studied. Bidimensional tumor diameter and density measurements were obtained at baseline and serial assessment CT scans. Overall R was assigned as per final CT scan assessment. Association of each criterion with OS was determined. **Results:** R varied according to site of metastases; lung lesions had the highest rate of complete response (CR) compared to other sites (69/163 (42%) lesions vs 71/404 (18%) p < .0001) and R varied at first assessment by RECIST compared to irRC (table). Delayed R post first scan were seen in 2/37 (5%) deemed PD by RECIST and 2/14 (14%) pts deemed PD by irRC at 1st assessment. 1/6 pts deemed to have PD by irRC at second assessment also had delayed R. 24 (65%) pts met CHOI density and size criteria for R at first follow-up. mCHOI criteria (> 15% density decrease and decrease in tumor size > 10%) showed R of 38% (14/37). Change in tumor size and density on 1st follow-up assessment was associated with OS with each 1000 mm^2 increase in tumor size from baseline increasing the hazard of dying by 25.9% (HR = 1.259, [95% CI = 1.116-1.420], p = 0.0002). Similarly each 100HU increase in density increased the HR by 99% (HR = 1.99, [95% CI 1.246-3.176], p = 0.0039). R defined by any criteria had superior OS (CHOI, p = 0.0084; mCHOI, p = 0.0183; irRC, p < 0.0001 and RECIST, p = 0.0003). **Conclusions:** R by any criteria was prognostic and pseudoprogression was seen. The novel patterns of R and changes on treatment in tumor density suggest complex anti-tumor R of immunotherapy and require further validation.

		CR (%)	PR/SD/PD (%)
Site of Metastases	Lung	42	58
	Liver	24	76
	Other solid organ	22	78
	Peritoneal	37	63
	Node	7	93
	Subcutaneous	21	79
	Other	11	89
R at first assessment scan	RECIST 1.1		9/12/16 (24/32/44)
	irRC		10/13/14 (27/35/38)

9074 Poster Session (Board #317), Mon, 1:15 PM-4:45 PM

Tumor size and clinical outcomes in melanoma patients (MEL pts) treated with talimogene laherparepvec (T-VEC). *First Author: Howard Kaufman, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: T-VEC is an HSV-1 derived oncolytic immunotherapy designed to selectively replicate in tumors, produce GM-CSF, and enhance systemic antitumor immune responses. We describe factors associated with clinical outcomes in 436 pts with previously treated or untreated, unresected stage IIIB-IV MEL in OPTiM, a randomized (2:1) phase 3 trial of intralesional T-VEC vs subcutaneous GM-CSF. **Methods:** Multivariate analyses (MVAs) and Cox regression were used to evaluate association of BTB (sum of products of 2 largest perpendicular diameters [per investigator] of measurable lesions at baseline), stage (IIIB/C/IVM1a vs IVM1b/c), treatment (tx) line (TL; 1st vs ≥ 2nd), and ECOG PS (0 vs 1), previously reported to be associated with clinical outcomes, with overall response rate (ORR), durable response rate (DRR; continuous PR or CR ≥ 6 months), and overall survival (OS). **Results:** 288 T-VEC and 126 GM-CSF pts had available BTB; all received tx as randomized. Median BTB: 14.8 cm^2 (interquartile range, 5.8-39.3) for T-VEC, 14.1 cm^2 (5.7-31.0) for GM-CSF (P = 0.50). Median BTB was higher with advanced stage (IVM1b/c: 23.6 [11.5-53.1]; IIIB/C/IVM1a: 8.6 [3.2-23.2], P < 0.001) and later TLs (≥ 2nd: 18.0 [7.0-45.9]; 1st: 12.9 [5.3-25.6], P < 0.001). In MVA of T-VEC pts (Table), BTB < median, stages IIIB/C/IVM1a, and 1st TL were associated with improved ORR and DRR; BTB < median and stages IIIB/C/IVM1a were associated with better OS. In MVA of all OPTiM pts, T-VEC tx (vs GM-CSF; HR 0.74, 95% CI 0.58-0.96, P = 0.023), BTB < median (HR 0.42, 95% CI 0.32-0.54, P < 0.001), stages IIIB/C/IVM1a (HR 0.54, 95% CI 0.42-0.69, P < 0.001), and ECOG 0 (HR 0.63, 95% CI 0.49-0.82, P < 0.001) were associated with better OS. **Conclusions:** Based on these exploratory analyses, BTB was prognostic for OS and achieving a DR and OR with T-VEC in OPTiM. BTB should be further evaluated as a prognostic factor in future MEL trials.

	ORR		DRR		OS	
	OR (95% CI)	P	OR (95% CI)	P	HR (95% CI)	P
BTB < median vs ≥ median	4.51 (2.47, 8.23)	< 0.001	4.40 (2.11, 9.17)	< 0.001	0.33 (0.24, 0.45)	< 0.001
IIIB/C/IVM1a vs IVM1b/c	3.71 (1.96, 7.01)	< 0.001	2.97 (1.38, 6.43)	0.006	0.49 (0.36, 0.68)	< 0.001
TL 1st vs ≥ 2nd	2.41 (1.35, 4.28)	0.003	2.38 (1.23, 4.60)	0.01	0.75 (0.55, 1.01)	0.06

OR: odds ratio.

9075 Poster Session (Board #318), Mon, 1:15 PM-4:45 PM

Investigation of intrapatient heterogeneity in the tumor infiltrating T cell repertoire in patients with metastatic melanoma treated with pembrolizumab. *First Author: Rodrigo Ramella Munhoz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Blockade of the programmed death-1 (PD-1) receptor results in impressive activity in patients (pts) with metastatic melanoma (MM). Mechanisms of antitumor effect are not fully understood but may be associated with the degree of T cell receptor (TCR) repertoire clonality in tumor infiltrating lymphocytes (TIL). We hypothesized that differences among multiple tumors in the same patient may be reflected in heterogeneity of TCR repertoire clonality in TIL. We tested this hypothesis using TCR sequencing in pts with MM treated with pembrolizumab. **Methods:** Post-treatment samples were obtained from different lesions at the same time points. TCR repertoire quantification was performed using high-throughput sequencing of the rearranged TCR β-chain genes; these were amplified and sequenced using the survey ImmunoSeq assay in a multiplexed PCR method using primers to TCR Vβ and Jβ gene segments. Productive TCR sequences were used to obtain a clonality metric, and frequency of each T cell clone was obtained by comparing the number of reads generated by each unique CDR3 sequence. The proportion of TIL was determined using quantitative immunohistochemistry. Variations in proportion of TIL and clonality between samples were analyzed using ANOVA test. Tests were performed in duplicate. **Results:** Eight tumors from two pts receiving pembrolizumab (Four from pt A and four from pt B, obtained 2 and 4 months after treatment initiation, respectively) were analyzed. Significant intrapatient intertumoral heterogeneity in TCR repertoire was observed (pt A: p = 0.000153 and p = 0.013/pt B: p = 0.00083 and p = 9.01E-07 for differences in proportion of TIL and clonality, respectively). There was a high correlation between duplicates (r^2 = 0.86- > 0.99), suggesting these findings were not the result of experimental variation. **Conclusions:** Our data suggest significant intrapatient intertumoral heterogeneity in the proportion of TIL and clonality of the TCR repertoire at the same post-treatment timepoint. Caution should be exercised in interpreting the results of TCR analyses from single tumor biopsies in patients treated with checkpoint blockade.

9076 Poster Session (Board #319), Mon, 1:15 PM-4:45 PM

Phase I trial of the CDK 4/6 inhibitor, P1446A-05 (voruciclib) in combination with the BRAF inhibitor (BRAFi), vemurafenib in advanced, BRAF-mutant melanoma. *First Author: Adi Diab, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: P1446A-05 is a potent, selective CDK 4/6 inhibitor with activity in multiple BRAF-mutant and wild type cell lines. The BRAFi have been transformative in the therapy of BRAF-mutant melanoma. However, resistance does develop frequently, often in only a few months. The addition of a CDK 4/6 inhibitor to BRAF inhibitors is supported by extensive preclinical data. **Methods:** A prospective, multicenter Phase I trial was conducted to determine the safety, maximum tolerated dose (MTD) and dose limiting toxicity of P1446A-05 in combination with Vemurafenib. The Phase I, "dose escalation" part of the trial is reported here. A total of 4 cohorts were planned in the Vemurafenib-arm of this phase in the trial. Vemurafenib was escalated from 720 mg PO BID to 960 mg PO BID and P1446A-05 was planned to be escalated from 150 mg up to 350 mg PO QD. In each cohort, 3 to 6 patients were planned to be enrolled. Extensive PK analysis was conducted. Eligible patients could be BRAFi-naïve or resistant, ECOG PS 0-1, and QTc $<$ 480 at baseline. **Results:** A total of 9 patients have been accrued to date. The combination has been well tolerated and no significant drug-drug interactions have been seen. Adverse events include fatigue (n = 3), headache (n = 3) and constipation (n = 3); no DLTs have been observed. C_{max} for P1446A-05 in combination was observed to be 796 ng/ml on D1 and $AUC_{0\text{-}24}$was 14451 ng.hr/ml, similar to that achieved with the single agent, P1446A-05. Nine patients were assessable for clinical response (3 BRAFi-naïve, 6 refractory). Responses were seen in 3/3 BRAFi-naive patients [1 complete response (CR) and 2 partial responses (PR)]. **Conclusions:** The combination of P1446A-05 and Vemurafenib is well tolerated. This trial was stopped by the Sponsor after accrual of 9 patients (2 dose escalation cohorts) for non-medical reasons. The MTD was not reached in the trial. Based on the available data, the recommended dose for further testing of this combination is Vemurafenib 960 mg PO BID with 150 mg PO QD of P1446A-05. No drug-drug interactions were observed and the PK parameters for the combination were acceptable. Preliminary evidence of efficacy in the treatment-naïve patients was seen. Clinical trial information: NCT01841463.

9077 Poster Session (Board #320), Mon, 1:15 PM-4:45 PM

Next generation sequencing of solid tumor and circulating tumor DNA (ctDNA) in metastatic melanoma. *First Author: Erica L. Carpenter, Division of Hematology/Oncology University of Pennsylvania School of Medicine, Philadelphia, PA*

Background: Capture and molecular analysis of ctDNA represents a promising strategy for noninvasive detection of circulating tumor material. This approach is particularly promising for melanoma, in which detection of intact circulating tumor cells has low sensitivity. We conducted a pilot study using ultra-deep sequencing ctDNA in melanoma patients. **Methods:** Plasma samples ranging from 1-5ml were obtained from 9 metastatic melanoma patients. DNA was extracted using Qiagen Circulating Nucleic Acid Kit. Ultra-deep sequencing of ctDNA was conducted using the Illumina Melanoma Gene Panel to detect variants in a panel of 38 genes. Matched tumor tissue samples were obtained for 5 of these patients; next generation sequencing in the tumor tissue DNA was conducted using a separate assay, the Illumina TrueSeq Cancer Amplicon panel of 47 genes. **Results:** Nonsynonymous variants of known significance were detected in ctDNA from 8 of 9 patients. 13 mutations were detected in 6 genes, including *BRAF, KIT, TSC2, MET, FGFR3, and AKT3*. More than one mutation was detected in 5/9 patients. *BRAF* mutations were detected in 5 of 9 patient ctDNA samples. For 5 patients with matched solid tumor data, 11 variants were detected by either the ctDNA panel, the solid tumor panel, or both panels. Among these 11 variants, 7 were covered by both panels, 2 by the ctDNA panel only, and 2 by the solid tumor panel only. Among the 7 covered by both panels, 3/7 variants were identified identically on both panels and were therefore deemed concordant, while 2/7 variants were only detected on the ctDNA panel and not the solid tumor panel, and the remaining 2/7 variants were only detected on the solid tumor panel and not the ctDNA panel. Possible reasons for these 4/7 discordant calls include tumor heterogeneity over time, with solid tumor tissue collected earlier in the disease course and/or the higher sensitivity of the ctDNA panel. **Conclusions:** Non-invasive monitoring for ctDNA via plasma detection of mutational variants is feasible in metastatic melanoma. Comparison of tumor DNA and plasma ctDNA yields a discordance that underscores the need to validate ctDNA assays in clinical trials, while accounting for assay sensitivity and tumor heterogeneity.

9078 Poster Session (Board #321), Mon, 1:15 PM-4:45 PM

Factors associated with worse outcome for patients with AJCC stage IIC relative to stage IIIA melanoma. *First Author: Caroline C. Kim, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

Background: Sentinel lymph node (SLN) status is used in melanoma AJCC staging to distinguish between stage I or II and stage III disease. However patients (pts) with stage IIC (Breslow $>$ 4 mm, ulcerated, SLN -, T4bN0) have worse survival than pts with stage IIIA (any Breslow, nonulcerated, SLN +, Txa,N1a or N2a) disease. We sought to identify factors beyond stage criteria associated with worse outcomes for Stage IIC pts and to compare a matched IIIB population (T4bN1a or N2a). **Methods:** We performed a retrospective chart review of pts diagnosed with T4b (stage IIC and IIIB) or IIIA melanoma in the BIDMC Cutaneous Oncology Program between 1998-2011. Demographics, risk factors, tumor characteristics and outcomes were collected. Groups were compared using a Wilcoxon rank sum test or Fisher's exact test. Log-rank testing and Cox regression modeling were performed. **Results:** 162 pts with stage IIC (56), IIIA (80) and matched Stage IIIB (26) melanoma were identified. Median follow-up time was 5.6 years. The estimated 5-year survival rate for pts with IIC vs IIIA disease was 56% (38-70, 95% CI) vs. 79% (67-87, 95% CI). Besides stage criteria, significant differences between IIC vs. IIIA cohorts included: age at diagnosis (62 vs. 51, $p < 0.001$), amelanotic tumors (45% vs. 22%, $p = 0.03$), mitotic rate (10 mits/mm^2 vs. 2 mits/mm^2, $p < 0.001$), nodular subtype (71% vs. 24%, $p < 0.001$), radial growth (23% vs. 55%, $p < 0.001$) and presence of precursor lesion (6% vs. 22%, $p = 0.02$). Regression modeling revealed that older age at diagnosis ($>$ 55, $p < 0.001$) and higher mitotic rate ($>$ 5 mits/mm^2, $p = 0.001$) were associated with worse survival in pts with stage IIC disease. Of note, pts with matched stage IIIB disease had similar 5-yr survival (52% [29-74, 95% CI])) to pts with IIC disease. **Conclusions:** Our study suggests that aside from stage criteria, there are inherent differences between the IIC and IIIA melanoma population, and older age and higher mitotic rates are associated with worse prognosis for IIC vs. IIIA pts. Further, the similar survival for IIC pts with matched IIIB (T4bN1a or N2a) pts calls into question the value of SLN biopsy as a staging tool in this population. These factors merit consideration in the management of pts with T4b primary lesions.

TPS9079 Poster Session (Board #322a), Mon, 1:15 PM-4:45 PM

A randomized phase II study of ipilimumab induction in patients with melanoma brain metastases receiving stereotactic radiosurgery. *First Author: Ann W. Silk, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Despite recent advances in the treatment of metastatic melanoma, survival remains poor in patients who develop brain metastases. Radiation therapy continues to be the backbone of treatment of brain metastases. Stereotactic radiosurgery (SRS) is a type of external radiation therapy that uses multiple beams to deliver a large dose of radiation to a tumor in a single session. The use of immunotherapy may complement radiation therapy because the latter damages the blood brain barrier (BBB), alters the tumor microenvironment, and increases immunogenicity of tumors. Ipilimumab, an immune checkpoint inhibitor, improves survival in patients with metastatic melanoma. The time to best response after ipilimumab is often several months, emphasizing the need for early initiation of treatment. Ipilimumab has a 16% response rate in patients with brain metastases who are neurologically asymptomatic. Previous studies have suggested that treatment with SRS and ipilimumab was associated with a 16-month prolongation in overall survival as compared to SRS alone. The optimal combination schedule to induce effective antitumor immunity is unknown. We hypothesize that "induction" with ipilimumab prior to SRS will improve control of the irradiated metastases. The trial will explore the use of dynamic contrast-enhanced (DCE) MRI as a potential imaging biomarker for predicting tumor response. DCE MRI is a functional imaging technique that can quantitatively map the spatial distribution of physiologic vascular parameters in the brain, such as regional cerebral blood volume and gadolinium-DTPA transfer constant, which is a measure of "leakiness" across the BBB. **Methods**: This is a randomized phase II "pick the winner" selection study. Forty subjects with 1-4 asymptomatic brain metastases will be randomized to one of two sequences of therapy: either ipilimumab (3 mg/kg IV every 3 weeks x 2 doses) bracketing SRS (Induction arm), or SRS followed by ipilimumab (3 mg/kg IV every 3 weeks x 4 doses; No Induction arm). The primary endpoint is the rate of control of the irradiated metastases at 6 months assessed by MRI. DCE-MRI and various immune parameters will be explored as potential biomarkers. Clinical trial information: NCT02097732.

TPS9080 **Poster Session (Board #322b), Mon, 1:15 PM-4:45 PM**

A multi-center phase II open-label study (CheckMate 204) to evaluate safety and efficacy of nivolumab (NIVO) in combination with ipilimumab (IPI) followed by NIVO monotherapy in patients (pts) with melanoma (MEL) metastatic to the brain. *First Author: Kim Allyson Margolin, Stanford University Medical Center and the Cytokine Working Group (CWG), Stanford, CA*

Background: Brain metastasis develops in approximately 50% of pts with metastatic MEL. In these pts, progressive brain disease is the major cause of tumor-related death (median overall survival [OS] after diagnosis, 4 months). NIVO (a fully human IgG4 PD-1 immune checkpoint inhibitor antibody) and IPI (a fully human IgG1 CTLA-4 immune checkpoint inhibitor antibody) are each approved as monotherapy for advanced MEL. In a phase II study, IPI showed activity in some pts with advanced MEL and brain metastases. Building upon the success of that study, this open-label, multi-site, US, phase II study is the first to evaluate NIVO combined with IPI followed by NIVO monotherapy for pts with MEL metastatic to the brain. It is anticipated that approximately 50% of enrolled pts will have had prior stereotactic radiotherapy (SRT). **Methods:** Pts ≥ 18 years of age with MEL measurable in extracranial sites and with asymptomatic brain metastases are eligible. Pts with a history of leptomeningeal involvement, a history of whole brain irradiation, autoimmune disease or corticosteroid use will be excluded. Pts will receive NIVO 1 mg/kg combined with IPI 3 mg/kg every three weeks (Q3W; 4 doses), followed by NIVO monotherapy 3 mg/kg Q2W until progression or unacceptable toxicity. SRT for progression of a single central nervous system (CNS) lesion will be permitted. The primary objective is to assess the CNS clinical benefit rate (CBR; complete response + partial response + stable disease [SD] ≥ 6 months) per protocol-defined response criteria; this endpoint was selected based on its relevance in this population and ability to capture both objective response and durable SD. Secondary objectives are to assess extracranial CBR per RECIST v1.1; global CBR (CNS plus extracranial) per RECIST v1.1 with modifications; CNS, extracranial and global CBR per immune-related response criteria; OS and safety. Exploratory correlates are also planned. An estimated 110 pts will be enrolled. Clinical trial registration number: NCT02320058. Clinical trial information: NCT02320058.

TPS9081 **Poster Session (Board #323a), Mon, 1:15 PM-4:45 PM**

A multicenter, open-label trial of talimogene laherparepvec (T-VEC) plus pembrolizumab vs pembrolizumab monotherapy in previously untreated, unresected, stage IIIB-IV melanoma. *First Author: Antoni Ribas, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA*

Background: T-VEC is a herpes simplex virus-1-based oncolytic immunotherapy designed to preferentially replicate in tumors, produce GM-CSF and stimulate an anti-tumor immune response. OPTiM, a phase III trial of T-VEC vs GM-CSF in unresected stage IIIB-IV melanoma (n = 436), met the primary endpoint of improved durable response rate (DRR) in the T-VEC arm (16 vs 2%; Andtbacka et al ASCO 2013). Pembrolizumab is a human programmed death receptor-1 (PD-1)-blocking antibody indicated in the U.S. for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Combining T-VEC with pembrolizumab may enhance the anti-tumor immune response vs either therapy alone. Here, we describe a study (NCT02263508) assessing safety and efficacy of T-VEC + pembrolizumab in previously untreated, unresected stage IIIB-IV melanoma. Phase 1b enrolment began 12/2014. **Methods: 1º objectives:** Phase 1b: assess dose-limiting toxicities of T-VEC + pembrolizumab. Phase 2: compare confirmed ORR by immune-related response criteria (irRC) at Wk 24 for T-VEC + pembrolizumab vs pembrolizumab alone **2º objectives:** Best OR, DRR, duration of response (DOR), PFS, OS, treatment-emergent/related AEs **Treatment:** T-VEC is injected into cutaneous, subcutaneous or nodal lesions at up to 4 mL of 10^6 plaque forming units (PFU)/mL Day 1, then at up to 4 mL of 10^8 PFU/mL Day 22 and Q2W (phases 1b and 2). Pembrolizumab is given at 200 mg IV Q2W from Day 36 in phase 1b (n = 20) and Day 1 in phase 2 (n = 90). Treatment with both therapies will continue until (whichever comes first): CR or PD per irRC, intolerance, for up to 2 yrs or, for T-VEC only, when there are no longer injectable lesions. Pts in phase 2 will be randomized 1:1 to T-VEC + pembrolizumab vs pembrolizumab alone. **Key eligibility:** Stage IIIB-IV melanoma naïve to systemic treatment (except adjuvant), injectable lesions, ECOG PS 0-1, no active cerebral metastases, no autoimmunity/immunosuppression, no active herpetic infection. Clinical trial information: NCT02263508.

TPS9082 **Poster Session (Board #323b), Mon, 1:15 PM-4:45 PM**

Phase III multicenter trial of eltrapuldencel-T: Autologous dendritic cells loaded with irradiated autologous tumor cells (DC-TC) in granulocyte-macrophage colony stimulating factor (GM-CSF) in patients with metastatic melanoma (INTUS trial). *First Author: Robert O. Dillman, NeoStem, Newport Beach, CA*

Background: Melanomas harbor non-synonymous mutations that can result in unique, immunogenic tumor associated antigens (TAA). Recognition of TAA can be induced or enhanced by vaccination. The best source of TAA for this purpose may be proliferating, self-renewing, autologous tumor cells (patient-specific tumor stem cells). Patients with stage IV and recurrent stage III melanoma were treated with repeated s.c. injections of autologous dendritic cells loaded with antigens from irradiated tumor cells derived from autologous melanoma cell lines (DC-TC), and suspended in GM-CSF. In a single arm Phase II trial (n = 54) 5-year survival was 50%. In a randomized Phase II trial (n = 42), 2-year survival was 72% for DC-TC vs. 31% for control patients (HR = 0.27, p = 0.007). Toxicities associated with DC-TC were minimal (n = 72). Improvements in manufacturing have increased the probability of establishing a tumor cell line and decreased the time needed to manufacture DC-TC. Eltrapuldencel-T (DC-TC) was granted special protocol assessment (SPA) and fast track designation by the U.S. Food and Drug Administration in association with approval of this pivotal trial. **Methods:** INTUS is a Phase III, double-blind, randomized, placebo-controlled trial. Eligible patients have stage IV or recurrent stage III melanoma with at least one lesion amenable to surgical resection. Resected tumor is transferred to a manufacturing facility to grow the cell line. After successful establishment of a cell line and referral for treatment, 250 patients with good performance status (ECOG 0-1) will be stratified by whether they have no evidence of disease, non-measurable disease by RECIST, or measureable disease with elevated LDH or without elevated LDH, then randomized 2:1 to receive either DC-TC or autologous mononuclear cells. Patients undergo leukapheresis to obtain mononuclear cells for each arm. Both products are suspended in 500 micrograms of GM-CSF and injected weekly for 3 weeks, and then monthly for 5 months. The endpoint is overall survival (death from any cause) [NCT01875653]. Clinical trial information: NCT01875653.

TPS9083 **Poster Session (Board #324a), Mon, 1:15 PM-4:45 PM**

A single-arm, open-label, multicenter phase II trial (CheckMate 172) of nivolumab (NIVO) safety in European patients (pts) with advanced melanoma (MEL) who have progressed after ipilimumab therapy (IPI). *First Author: Dirk Schadendorf, University Hospital Essen, Essen, Germany*

Background: In recent years, the treatment landscape for advanced MEL has evolved with approval of an anti-CTLA-4 antibody (IPI), BRAF/MEK inhibitors and anti-programmed death-1 (PD-1) antibodies (NIVO and pembrolizumab). In a phase III study with pts previously treated with IPI, NIVO had an objective response rate of 32% (vs 11% with chemotherapy) and a manageable safety profile. Anti-PD-1 antibodies have been associated with select adverse events (AEs; i.e., those with a potential immunologic etiology), most of which resolve using established safety management guidelines. However, further safety information would be desirable in pts who progressed after prior IPI, particularly in pt subgroups that were under-represented in previous studies. Consequently, this phase II trial will assess the safety of NIVO in a large population of European pts with stage III or IV MEL progressing after prior IPI treatment, including a separate prospective cohort of pts with ECOG performance status (PS) 2. **Methods:** Eligible pts are ≥ 18 years of age, have histologically confirmed malignant stage III (unresectable) or stage IV MEL, have ECOG PS 0–1 (Cohort 1) or 2 (Cohort 2), were previously treated regardless of BRAF mutation status and have evaluable RECIST v1.1-defined disease progression. Pts will be treated with NIVO 3 mg/kg every 2 weeks (Q2W) until progression or unacceptable toxicities for a maximum of 24 months. Safety assessments will be performed Q2W in Cohort 1 and Q1W in Cohort 2. Tumor assessments will begin at week 12. The primary objectives are to determine the rate and frequency of high-grade (CTCAE v4.0 grade 3 or higher), treatment-related, select AEs. Secondary objectives are to characterize the outcome (grade of resolution; duration of AE-specific treatment) of high-grade, select AEs and to estimate overall survival and investigator-assessed best overall response. Approximately 1,800 pts will be enrolled across Europe, including a maximum of 300 pts with ECOG PS 2. Clinical trial registration number: NCT02156804. Clinical trial information: NCT02156804.

TPS9084 Poster Session (Board #324b), Mon, 1:15 PM-4:45 PM

Phase 1 dose escalation and expansion safety study of BLZ-100 in subjects with skin cancer. *First Author: Dennis Michael Miller, Blaze Bioscience Inc, Seattle, WA*

Background: BLZ-100 is an intraoperative, fluorescent imaging agent designed to specifically label malignant tissue and enable more complete surgical resection of tumor tissue. BLZ-100 achieves tumor targeting through the peptide portion of the molecule, a modified chlorotoxin (CTX) peptide, and its imaging properties from the coupled near-infrared fluorescent dye, indocyanine green. Tumor-specific uptake of BLZ-100 has been shown in multiple mouse tumor models and in dogs with spontaneous cancers. **Methods:** In order to characterize the safety of BLZ-100, a first-in-human, phase 1 dose escalation and expansion study in subjects with suspected skin cancer is being conducted. BLZ-100 is administered via a 15-minute IV infusion to subjects approximately 2 days before planned excision of their skin tumor. Subjects with known or suspected non-melanotic skin cancer (e.g., basal cell carcinoma) are included in the dose escalation. Subjects with known or suspected melanoma are included in the dose expansion. Subjects must have adequate bone marrow, liver and kidney function to participate. Dose escalation is being conducted according to a traditional "3+3" design. Dose limiting toxicity is defined as any related adverse event (AE) of ≥ Grade 3 severity occurring within 7 days of BLZ-100 administration. Measures of safety include patient or physician reported adverse events, laboratory measures of hematology, liver and kidney function, and coagulation parameters and changes in vital signs and electrocardiograms (ECG). Blood samples are collected over the 7-day DLT period to measure BLZ-100 serum concentrations via a LC/MS method. Serial fluorescence imaging of suspected skin tumors in situ is conducted over 48 hours using the Fluobeam 800 device. Portions of the excised skin specimens from the dose escalation were also subjected to fluorescent image analysis using an Odyssey scanner and immunohistochemistry analysis for the presence of Annexin A2 (presumed target of BLZ-100). Dose escalation in the 5 pre-specified dose levels has been completed without DLT. Enrollment of the expansion cohorts is on-going as of December 16, 2014. Clinical trial information: NCT02097875.

TPS9085 Poster Session (Board #325a), Mon, 1:15 PM-4:45 PM

SWOG S1404: A phase III randomized trial comparing high dose interferon to pembrolizumab in patients with high risk resected melanoma. *First Author: Kenneth F. Grossmann, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Current adjuvant treatment for patients with a surgically resected stage III-IV melanoma is limited to high dose Interferon (HDI) and pegylated interferon (pegIFN), which have shown limited but consistent benefits in RFS (HDI and pegIFN) and OS (HDI) in high-risk melanoma, while no other agents have been proven superior in randomized trials. Anti-PD-1 antibodies such as pembrolizumab (MK-3475) have shown unprecedented rates of durable tumor response in patients with metastatic melanoma with low rates of adverse events. S1404 is a Phase III randomized trial comparing the standard of care HDI to pembrolizumab in patients at high risk for recurrence and death after surgery. **Methods:** Patients age 15 or greater with Stages IIIA(N2), IIIB, IIIC and IV (M1a, b and c) are eligible. Patients with brain metastasis will be excluded. At entry, patients must have had complete staging and adequate surgery to render them free of melanoma including completion lymph node dissection for those with sentinel lymph node positive disease. Prior therapy with PD-1 blockade or interferon are not allowed. Two treatment arms are assigned based on stratification by stage and PD-L1 staining status (positive vs negative vs unknown). Patients (n = 1,378) will be randomized 1:1 to either 1) interferon Alfa-2b 20 MU/m2/days 1-5 weeks 1-4, followed by Interferon Alfa-2b 10 MU/m2/d SC days 1,3,5weeks 5 -52, or 2) pembrolizumab 200 mg day 1, q 3 weeks for 52 weeks. Efficacy will be measured in terms of both overall survival and relapse free survival, with interim analyses planned for both endpoints at 50% OS information. Safety, pharmacokinetics, and quality of life data will also be studied.

TPS9086 Poster Session (Board #325b), Mon, 1:15 PM-4:45 PM

A phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in patients with metastatic Merkel cell carcinoma. *First Author: Howard Kaufman, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: The programmed death-1 receptor (PD-1) and its ligand (PD-L1) are key therapeutic targets in the reactivation of the immune response against multiple cancers. Avelumab* (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in clinical trials. Merkel cell carcinoma (MCC) is a rare, aggressive, Merkel cell polyomavirus (MCPyV)-induced skin cancer with suboptimal therapeutic options. Cytotoxic chemotherapy is commonly used to treat metastatic MCC, although responses are seldom durable. There is a strong rationale for investigating PD-1/PD-L1 blockade in MCC. Despite their immunogenicity, MCC tumors are able to evade the host immune system through multiple mechanisms that include exhaustion of tumor virus-specific T cells via expression of PD-L1 on the tumor cells and adjacent immune-cell infiltrates. **Methods**: This is a multicenter, international, single-arm, open-label, phase II trial to evaluate the efficacy and safety of avelumab in patients (pts) with metastatic MCC who have received ≥ 1 prior line of chemotherapy. Up to 84 eligible pts will receive avelumab at a dose of 10 mg/kg as a 1h intravenous (IV) infusion Q2W. Treatment will continue until disease progression, unacceptable toxicity, or if criterion for treatment withdrawal is met. Primary objective is to assess the clinical activity of avelumab as determined by the objective response rate (ORR) according to RECIST 1.1 by an Independent Endpoint Review Committee. Secondary objectives include assessment of the duration of response, progression-free survival time (PFS), overall survival (OS), and safety. The pharmacokinetic (PK) profile of avelumab will also be evaluated. Exploratory objectives include assessment of immune-related responses and evaluation of PD-L1 expression and its potential association with response rate. This study will also explore the quality of life of pts with MCC who have been treated with avelumab. The trial is in progress: 19 of a planned 84 patients have been recruited (trial start June 2014, estimate end January 2017). NCT02155647. *Proposed INN. Clinical trial information: NCT02155647.

TPS9087 Poster Session (Board #326a), Mon, 1:15 PM-4:45 PM

Randomized phase II study comparing the MET inhibitor cabozantinib to temozolomide (TMZ) or dacarbazine (DTIC) in ocular melanoma: A091201. *First Author: Jason John Luke, University of Chicago, Chicago, IL*

Background: Ocular melanoma has been described to express the receptor tyrosine kinase MET in up to 80% of specimens and preclinical data suggests that MET inhibitors reduce proliferation and metastatic potential in cell lines and murine xenografts. Cabozantinib is a receptor tyrosine kinase inhibitor with significant inhibitory activity against MET and VEGFR2 (among other targets). Cabozantinib was associated with a median progression-free survival (mPFS) of 4.8 months in final follow up of the ocular melanoma cohort of the cabozantinib randomized discontinuation clinical trial. Notably, the MEK inhibitor selumetinib was determined to deliver mPFS of 3.9 months in a randomized phase II study. **Methods:** This is a national (Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group, NCIC Clinical Trials Group) open-label phase II study comparing cabozantinib with TMZ/DTIC in advanced ocular melanoma (clinicaltrials.gov: NCT01835145). The study randomizes patients 2:1 to cabozantinib and facilitates cross-over from the chemotherapy arm to cabozantinib at progression of disease. Eligibility is for any line of therapy and allows for prior treatment with MEK inhibitor or immunotherapy. Other eligibility includes biopsy proven metastatic ocular melanoma, ECOG 0-1 and adequate organ function (modified for elevated liver function tests related to hepatic metastases). The primary endpoint is PFS at 4 months with secondary endpoints evaluating RECIST response rate, PFS, overall survival and correlation of the primary endpoint with pre-treatment tumor tissue MET expression by IHC. The study is open to accrual via the Cancer Trials Support Unit (CTSU) of NCI to any cooperative group member site. Recruitment is on-going (target 69 patients). Clinical trial information: NCT01835145 or Alliance for Clinical Trials in Oncology # A091201. Clinical trial information: NCT01835145.

TPS9088 Poster Session (Board #326b), Mon, 1:15 PM-4:45 PM

Phase 2 study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (coBRIM-B). *First Author: Melissa K. Yee, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: Significant advances in the management of melanoma have improved the prognosis and overall survival of patients (pts) with metastatic disease. However, pts with active melanoma brain metastases (MBM) have been excluded from large Phase III trials and overall prognosis remains poor. Resistance to BRAF inhibitors (BRAFi) has been associated with reactivation of MAPK pathway and combination with MEK inhibitors (MEKi) has shown synergy and delays resistance. Cobimetinib is a potent MEK 1/2 inhibitor. In pts without MBM, the combination of vemurafenib + cobimetinib has improved response rates and PFS as compared to vemurafenib. Single agents BRAFi are safe to administer in pts with MBM resulting in objective intracranial responses. We aim to improve the outcomes of pts with MBM by assessing the clinical benefit of combination BRAFi/MEKi (vemurafenib + cobimetinib) in this population. **Methods:** This is a multi-center single arm, open label, Simon 2-stage Phase 2 study to determine the safety and efficacy of the combination of cobimetinib and vemurafenib in patients with BRAF-mutated melanoma with active MBM. Pts must have histologically confirmed BRAF V600-mutated metastatic melanoma and $>$ 1 measurable intracranial target lesion. Prior BRAFi or MEKi is not allowed. Subjects will be given vemurafenib 960 mg PO BID and cobimetinib 60 mg PO QD for 21 days (28-day cycle). The primary objective is to determine the investigator-assessed objective intracranial response rate (OIRR) as measured by modified RECIST. The primary efficacy analysis is based on pts with BRAF V600E mutations and the study will accrue 29 pts in the 1st stage. If $>$ 6 pts experience an OIRR, acrrual to the 2nd stage will proceed to a total of 72 pts. Pts with non-V600E mutation are allowed but will not enter into the primary efficacy analysis. Secondary objectives include safety/tolerability, ORR (intracranial + extracranial), PFS, OS, duration of response, changes in relative apparent diffusion coefficient by MRI, volumetric response using 3D-MRI in a subset of pts, immune modulation and early markers of progression in peripheral blood, and health-related quality of life (by FACT-Br). The trial is open for enrollement. NCT02230306 Clinical trial information: NCT02230306.

TPS9089 Poster Session (Board #327a), Mon, 1:15 PM-4:45 PM

A Phase 2 biomarker-enriched study of evofosfamide (TH-302) in patients with advanced melanoma. *First Author: Elaine McWhirter, Juravinski Cancer Centre, Hamilton, ON, Canada*

Background: In melanoma, tumor hypoxia is associated with invasion, angiogenesis, and metastasis formation, as well as treatment resistance such as immune evasion. Evofosfamide (EVO, TH-302) is a hypoxia-activated prodrug designed to release the bis-alkylating DNA crosslinker bromo-isophosphoramide mustard (Br-IPM) when reduced in severe hypoxia. In the Phase 1 study (NCT00495144) of EVO monotherapy, 7 of 36 (19%) patients with advanced melanoma had partial responses and 12 of 36 (33%) stable disease. Dose limiting adverse events included skin and mucosal toxicities. A Phase 2 biomarker-enriched trial was initiated to further evaluate the efficacy of EVO in melanoma, and identify hypoxia and other biomarkers predictive of response. **Methods:** This Phase 2 trial is a single-arm, multi-center, study investigating the efficacy and safety of EVO monotherapy (NCT01864538). The primary endpoint is 3-mo PFS. The study incorporates a Simon two-stage design (alpha = 0.15; beta = 0.15) based on 3-mo PFS with level of disinterest of 20% and level of interest of 35%. Secondary endpoints include response rate, overall survival, pharmacokinetics, safety, and evaluation of imaging, serum, and tissue biomarkers that may be associated with tumor response and predict for efficacy and safety of EVO. EVO (480 mg/m^2) is given by IV infusion over 30 - 60 minutes on Days 1, 8 and 15 of a 28-day cycle. Hypoxia PET imaging using [^{18}F]HX4 or [^{18}F]FAZA, *in vivo* hypoxia detection using pimonidazole, hypoxia biomarkers such as CA-IX, HIF1-alpha, OPN, and VEGF; DNA damage markers such as gamma-H2AX, as well as tumor immune monitoring are included. Up to 40 patients will be enrolled with histologically confirmed recurrent or metastatic melanoma, measureable disease by RECIST 1.1, and ECOG 0-1. There are no limits on the number of prior targeted therapies or immunotherapies; however, patients may not have received more than one prior chemotherapy. Patients with brain metastases are eligible, if treated and stable for 2 months. Eligible patients must also have adequate tumor tissue available for pre-therapy and post-therapy biopsies. The first patient was treated in August 2013; recruitment is ongoing. Clinical trial information: NCT01864538.

TPS9090 Poster Session (Board #327b), Mon, 1:15 PM-4:45 PM

A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with metastatic melanoma with brain metastasis: the NIBIT-M2 trial. *First Author: Anna Maria Di Giacomo, Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy*

Background: The anti-CTLA-4 monoclonal antibody (mAb), ipilimumab (Ipi) significantly improves the survival of metastatic melanoma (MM) patients (pts). In spite of their poor prognosis, initial studies have evaluated the therapeutic potential of Ipi also in MM pts with brain metastasis (BM), providing preliminary evidences of efficacy. Among these, the multicentric, phase 2, Italian Network for Tumor Biotherapy (NIBIT)-M1 trial, combining Ipi with fotemustine, showed initial signs of activity in a subset of 20 MM subjects with active BM, regardless of prior radiotherapy. Though limited by the number of pts enrolled, disease control in the brain was long lasting achieving a 3-year survival rate of 28% (Di Giacomo et al, *Annals Oncol*, 2014). Based these results and on the highly promising efficacy of Ipi in combination with nivolumab (Nivo) in MM patients without BM, the NIBIT-M2 study will further explore the efficacy of immunotherapy with check-point blocking mAb in MM pts with BM. **Methods:** The NIBIT-M2 is a randomized, phase 3, open-label, study that will enroll 168 MM pts with untreated, asymptomatic BM, ECOG performance status of 0 or 1, BRAF W/T or mutant disease. Pts will be randomized to receive fotemustine i.v. at 100 mg/m2 weekly for 3 weeks (wk), and q3 wk from week 9 (ARM A) or Ipi i.v. at 10 mg/kg q3 wk for 4 doses and once q12 wk from week 24 in combination with fotemustine (ARM B) or Ipi i.v. at 3 mg/kg q3 wk for 4 doses in combination with Nivo at 1 mg/kg q3 wk for 4 doses and then Nivo at 3 mg/kg q2 wk (ARM C). Primary objective is Overall Survival; secondary are safety, Disease Control Rate in and outside the brain, Objective Response Rate and Duration of Response evaluated using both the modified-WHO response criteria and the immune-related response criteria; progression Free Survival (PFS), 3- and 6-months Brain-PFS rate and Quality of Life will also be evaluated. Phenotypic and functional cellular and humoral translational studies will correlate the immunomodulatory activity of treatment with clinical outcomes. Seventeen pts have been enrolled to date. (EUDRACT # 2012-004301-27) Clinical trial information: 2012-004301-27.

TPS9091 Poster Session (Board #328a), Mon, 1:15 PM-4:45 PM

Neoadjuvant BRAF (dabrafenib) and MEK (trametinib) inhibition for high-risk resectable stage III and IV melanoma. *First Author: Jennifer Ann Wargo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Significant advances have been made in the treatment of melanoma through the use of mitogen -activated protein kinase pathway (MAPK)-targeted therapies, with several agents now FDA-approved for patients (pts) with BRAF V600 mutations with stage IV or unresectable stage III disease. Based on the efficacy of BRAF inhibitors and combined BRAF/MEK inhibitors in patients with stage IV melanoma, these agents are being investigated as adjuvant therapy in patients with resectable stage III melanoma as part of multi-national phase 3 trials, where the current standard of care is upfront surgery. Mature results from these trials, however, will not be available for some time. A critical question to consider is whether neoadjuvant treatment with MAPK-targeted therapy will improve outcomes in a subset of these patients with significant burden of disease. **Methods:** Here we report 2 current phase II trials -- at MD Anderson Cancer Center (MD Anderson) and Melanoma Institute Australia (MIA) -- of neoadjuvant combined BRAF inhibition (dabrafenib, at 150 mg by mouth twice a day) and MEK inhibition (trametinib, at 2 mg by mouth once a day) for high risk resectable metastatic melanoma (stage IIIB-C; MIA and MD Anderson) and oligometastatic stage IV (MD Anderson)). Both trials incorporate serial biopsies during the course of treatment for translational research on molecular and immune biomarkers. At MD Anderson, eligible patients are randomized in a 2:1 fashion to neoadjuvant BRAF/MEK x 8 weeks with adjuvant BRAF/MEK x 44 weeks versus upfront surgery and SOC adjuvant therapy (target accrual 84 patients). Endpoints include RECIST response (RR), relapse-free survival (RFS), overall survival (OS), pathologic CR rate, and toxicity. At MIA, all patients receive neoadjuvant BRAF/MEK x 12 weeks, followed by adjuvant BRAF/MEK for 40 weeks (target accrual 35 patients). The primary endpoint is pathologic CR rate, secondary endpoints include RFS, OS, toxicity, and translational endpoints correlated with outcome. This neoadjuvant approach has the potential to establish a new treatment paradigm for patients with high-risk resectable metastatic melanoma harboring a BRAF mutation. Clinical trial information: NCT01972347, NCT02231775.

TPS9092 Poster Session (Board #328b), Mon, 1:15 PM-4:45 PM

A pilot study of neoadjuvant cetuximab in locally advanced squamous cell carcinomas of skin (SCCS). *First Author: Kristen Renee Spencer, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

Background: The incidence of SCCS has increased over the past two decades, including a high risk subset with aggressive behavior. Due to a lack of high-quality clinical trials in this population, there is no standard systemic therapy for advanced SCCS. The epidermal growth factor receptor (EGFR), often highly expressed in SCCS, is implicated in UV-induced skin carcinogenesis and SCCS development. Cetuximab, a monoclonal antibody that competitively inhibits EGFR, improved disease control as first line therapy in unresectable SCCS in a single arm phase II trial. Despite impressive responses with cetuximab in some, most treated SCCS patients do not respond, and there is a need for predictive biomarkers. We hypothesize that the use of cetuximab will improve clinical outcomes in patients with advanced SCCS in the neoadjuvant setting, and that measures of antibody dependent cytotoxicity (ADCC) in tumor and/or specific genomic features of the tumor may predict response to therapy. **Methods:** In this pilot trial (NCT 02324608), we will enroll 20 patients with relapsed locally advanced SCCS or SCCS unamenable to definitive local therapy. The primary endpoint will measure response rate to cetuximab by RECIST criteria with secondary endpoints of progression free and overall survival, and conversion to resectability. Molecular tumor correlates include analyzing DNA mutations and measuring downstream activation of EGFR signaling and ADCC, correlating these with clinical benefit. Patients will receive cetuximab at 400mg/m^2 X 1 followed by weekly doses of 250mg/m^2 for 8 weeks prior to surgery. Patients will be evaluated for subsequent definitive surgical resection, or definitive radiotherapy if surgical resection is not possible. Postoperative adjuvant radiotherapy will be permitted. Patients will undergo pretreatment biopsies, and post-treatment tissue will be harvested at surgery or through a biopsy at the conclusion of cetuximab. Paired skin and tumor samples will be evaluated through partial DNA (FoundationOne™) and RNA sequencing, IHC analysis of EGFR signaling components, and measurement of ADCC. The trial is currently screening eligible subjects. Clinical trial information: 02324608.

TPS9093 Poster Session (Board #329a), Mon, 1:15 PM-4:45 PM

SWOG S1320: A randomized phase II trial of intermittent versus continuous dosing of dabrafenib and trametinib in BRAF$^{V600E/k}$ mutant melanoma. *First Author: Alain Patrick Algazi, University of California, San Francisco, San Francisco, CA*

Background: Combined BRAF and MEK inhibition yields improved response rates and overall survival compared with BRAF inhibitor monotherapy in BRAF mutant melanoma patients(Robert et al., 2015), but the median progression-free survival is less than one year. Recent preclinical data suggest that resistant BRAF mutant melanoma cells adapt to the presence of BRAF inhibitors, but these adaptations may be disadvantageous in the absence of drug(Das Thakur et al., 2013; Moriceau et al., 2015). Further *in vitro* and *in vivo* studies suggest that intermittent dosing of BRAF inhibitors and especially BRAF + MEK inhibitor combinations may extend disease control in BRAF mutant melanoma. Based on these findings, S1320, an intergroup SWOG/ECOG randomized phase 2 clinical trial, was designed to determine whether an intermittent dosing schedule of dabrafenib and trametinib improves progression-free survival (PFS) in BRAF mutant melanoma patients treated with a standard, continuous dosing regimen. **Methods:** ELIGIBILITY: Patients with unresectable or metastatic BRAF$^{V600E/K}$ melanoma who have not been treated previously with BRAF or MEK inhibitors are eligible. Patients must have adequate end organ function and any known brain metastases must be treated prior to enrollment. DESIGN: Patients will be treated with dabrafenib at 150 mg twice daily and trametinib 2 mg twice daily during an 8 week lead in period. Patients without disease progression at the end of the lead in period will be randomized 1:1 to either continuous dosing or intermittent dosing according to a 5 weeks on, 3 weeks off schedule. Reimaging will be performed once every 8 weeks. ENDPOINTS: The primary endpoint of this study is the PFS in the continuous versus intermittent dosing arms. Secondary endpoints include the toxicity, best overall response rate, and overall survival. Early and late molecular events associated with disease progression will also be assessed using serial biopsies in a subset of patients in each arm. Support: NIH/NCI/NCTN grants CA180888, CA180819, CA180820 Clinical trial information: NCT02196181.

TPS9094 Poster Session (Board #329b), Mon, 1:15 PM-4:45 PM

Phase 2, multicenter, randomized, open-label trial assessing efficacy and safety of talimogene laherparepvec (T-VEC) neoadjuvant treatment (tx) plus surgery vs surgery for resectable stage IIIB/C and IVM1a melanoma (MEL). *First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Risk of recurrence and death after resection of stage IIIB/C and IVM1a MEL is high. T-VEC is an HSV-1-derived oncolytic immunotherapy designed to selectively replicate in tumors, produce GM-CSF, and enhance systemic antitumor immune responses. In OPTiM, a randomized phase 3 trial of T-VEC vs GM-CSF in patients (pts) with unresected stage IIIB/C and IVM1a MEL, T-VEC improved the primary endpoint (EP) of durable response rate (continuous PR/CR for $\geq$ 6 mos) from 2% to 16%, $P <$ 0.0001. Median overall survival (OS, secondary EP) was 23.3 mos with T-VEC vs 18.9 mos with GM-CSF; HR = 0.79, 95% CI: 0.62-1.00; $P =$ 0.051. We hypothesize that neoadjuvant T-VEC will improve local control rates and decrease distant metastases (DM) in pts with resectable stage IIIB/C and IVM1a MEL. **Methods:** 150 pts with resectable stage IIIB/C and IVM1a cutaneous MEL with $\geq$ 1 injectable cutaneous, subcutaneous, or nodal lesion will be randomized 1:1 to immediate surgical resection vs 6 doses of neoadjuvant T-VEC for up to 12 wks, followed by surgical resection. T-VEC is administered as $\leq$ 4 mL x 10^6 pfu/mL, then after 3 wks $\leq$ 4 mL x 10^8 pfu/mL q2w until all injectable tumors have disappeared, intolerance to tx, or alternative tx initiated. Eligible pts are $\geq$ 18 y old, ECOG PS 0-1, with adequate hematologic, hepatic, and renal function; prior systemic, regional, radiation therapies for MEL were completed $\geq$ 3 mos before randomization; history or evidence of symptomatic autoimmune disease, immunodeficiency, active herpes, prior HSV-1 complications, systemic tx with antiherpetic drugs, and prior tumor vaccines are not allowed. Primary EP is recurrence-free survival (RFS); key secondary EPs are 2 y, 3 y, and 5 y RFS, OS, overall tumor response, R0 resection, pathological CR, local RFS, DM-free survival, and safety. Blood and tumor biomarkers for response to T-VEC will be explored. Primary analysis of RFS will be at the later of 2 y after the end of randomization (EOR) or 64 events. Additional analyses will occur 3 and 5 y after EOR. The trial is planned at ~50 sites in Australia, Brazil, Europe, and USA. Accrual began in February 2015. Clinical trial information: NCT02211131.

9500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase III trials of anamorelin in patients with advanced non-small cell lung cancer (NSCLC) and cachexia (ROMANA 1 and 2). *First Author: Jennifer S. Temel, Massachusetts General Hospital, Boston, MA*

Background: Patients with advanced cancers frequently experience anorexia and cachexia, which is associated with decreased functional status and poor tolerance of chemotherapy. ROMANA 1 and 2 were two randomized, double blind trials evaluating the effect of anamorelin, a ghrelin receptor agonist, on cachexia in patients with advanced NSCLC. **Methods:** We randomly assigned 484 patients (ROMANA 1) and 495 patients (ROMANA 2) with inoperable stage III or stage IV NSCLC and cachexia ($\geq$ 5% weight loss within prior 6 months or BMI $<$ 20 kg/m^2) to placebo or anamorelin 100 mg orally once daily. Co-primary efficacy endpoints were the change in lean body mass and handgrip strength from baseline over 12 weeks. Secondary endpoints included change in body weight and symptom burden over 12 weeks and pooled survival from ROMANA 1 and ROMANA 2. Exploratory analyses evaluated change in total body mass and fat mass from baseline to 12 weeks. **Results:** Patients assigned to anamorelin experienced an increase in lean body mass compared to those assigned to placebo in ROMANA 1 (1.10 vs -0.44 kg, $p < 0.001$) and ROMANA 2 (0.75 vs -0.96 kg, $p < 0.001$), but no difference in handgrip strength. Patients assigned to anamorelin also had a significant increase in body weight (2.2 vs 0.14 kg, $p < 0.001$) and (0.95 vs -0.57 kg, $p < 0.001$) and improvement in their anorexia/cachexia symptoms (4.12 vs 1.92, $p < 0.001$) and (3.48 vs 1.34, $p = 0.002$) in ROMANA 1 and 2, respectively. Exploratory analysis demonstrated an increase in total body mass (2.87 vs 0.07 kg, $p < 0.001$) and (2.04 vs -0.59 kg, $p < 0.001$), and fat mass (1.21 vs -0.13 kg, $p < 0.001$) and (0.77 vs 0.09 kg, $p = 0.012$) for anamorelin versus placebo in the two studies, respectively. Anamorelin was well tolerated with hyperglycemia and diabetes as the most frequent drug-related adverse events ($\leq$ 5%). Median 1-year survival was not different between study arms. **Conclusions:** Anamorelin increased lean body mass, body weight, total body mass and fat mass indicating anabolic activity and restoration of energy balance in patients with advanced NSCLC. Patients also experienced significant improvement in anorexia/cachexia symptoms. Anamorelin was well tolerated, with similar pooled survival between study arms. Clinical trial information: NCT01387269 and NCT01387282.

9501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

CALGB 70604 (Alliance): A randomized phase III study of standard dosing vs. longer interval dosing of zoledronic acid in metastatic cancer. *First Author: Andrew Louis Himelstein, Helen F. Graham Cancer Center & Research Institute, Newark, DE*

Background: Zoledronic acid (ZA) given monthly for 24 months (mo) reduces bone pain and skeletal-related events (SRE) in patients (pts) with bone metastases. We tested whether ZA every 3 mo would be non-inferior to monthly for 24 mo, with less toxicity, in a randomized trial in 1822 pts: breast (n = 833), prostate (n = 674), myeloma (n = 270), and other (n = 45). **Methods:** SRE were defined as radiation therapy (RT) to bone, fractures, spinal cord compression or surgery to bone within 24 mo. ZA doses were adjusted for creatinine clearance. The primary endpoint was the proportion of pts in each group who had $\geq$ 1 SRE; secondary endpoints included skeletal morbidity rates, performance status, pain using the Brief Pain Inventory, and incidences of jaw osteonecrosis and renal dysfunction. The trial design was non-inferiority (NI) with stratification and pre-planned analyses by disease. The NI margin was 7% absolute difference. With 1,230 pts (planned sample size 1758 with 30% allowance for inevaluable pts), the power was $>$ 82% when the NI margin was $<$ 0 using a 1-sided test at a 5% significance level. **Results:** Between May 1, 2009 and April 13, 2012, 1822 pts were randomized. Baseline characteristics of the 2 groups were comparable. Dose delays were more common with ZA monthly. The 2-year cumulative incidences of SRE and selected toxicities are presented in the Table. The proportions of SRE were 29.5% vs 28.6% (95% CI for margin: -3.3% to 5.1%, Cochran-Maentel-Hanzel p = 0.79) for monthly and every 3 mo, respectively. **Conclusions:** ZA administered every 3 mo is non-inferior to ZA administered monthly for 24 mo in breast cancer, prostate cancer and multiple myeloma. Bone turnover markers in a subset of pts and a cost analysis will be presented. Clinical trial information: NCT00869206.

	Q Month N = 911	Q 3 Months N = 911	HR (P-value)
Total ZA dose (median)	56 mg	24 mg	— ($<$ 0.01)
Dose delays	62%	37%	— ($<$ 0.01)
Any SRE	260	253	1.05 (0.60)
Any SRE – breast pts (N = 820)	113	119	0.90 (0.43)
Any SRE – prostate pts (N = 660)	107	101	1.15 (0.31)
Any SRE – myeloma pts (N = 265)	35	30	1.30 (0.29)
Bone RT	185	163	1.16 (0.18)
Bone fractures	62	79	0.78 (0.13)
Spinal cord compression	23	30	0.75 (0.30)
Bone surgery	22	42	0.51 (0.01)
Jaw osteonecrosis	18	9	— (0.08)
Grade 2-4 creatinine increase	11	5	— (0.46)

9502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Olanzapine versus fosaprepitant for the prevention of nausea and vomiting in patients receiving concurrent chemoradiation treatment. *First Author: Rudolph M. Navari, Indiana Univ School of Medcn South Bend, Mishawaka, IN*

Background: The purpose of the study was to compare the effectiveness of olanzapine (OLN) and fosaprepitant (FOS) for the prevention of nausea and vomiting in patients receiving concurrent highly emetogenic chemotherapy (HEC) and radiation therapy for head and neck and esophageal cancer. **Methods:** A randomized, double-blind, phase III trial was performed in chemo and radiation therapy naïve patients receiving concurrent local radiation and cisplatin, $>$ 70 mg/m^2, based chemotherapy comparing OLN to FOS in combination with palonosetron (PAL) and dexamethasone (DEX). The OLN, PAL, DEX (OPD) regimen was 10 mg of oral OLN, 0.25 mg of intravenous PAL, and DEX 20 mg intravenous pre-chemotherapy, day 1, and 10 mg/day of oral OLN alone on days 2-4 post-chemotherapy. The FOS, PAL, DEX (FPD) regimen was 150 mg of intravenous FOS, 0.25 mg intravenous PAL, and 12 mg intravenous DEX, day 1, and 4 mg DEX twice a day, days 2 and 3. Distribution of patients to different groups were similar in gender, types of cancer, and radiotherapy regimens. **Results:** One hundred and nine patients consented to the protocol and were randomized. One hundred patients were evaluable. Complete response (CR) (no emesis, no rescue) was 88% for the acute period (24 hours post-chemotherapy), 76% for the delayed period (days 2-5 post-chemotherapy), and 76% for the overall period (0-120 hours) for 51 patients receiving the OPD regimen. CR was 84% for the acute period, 73% for the delayed period, and 73% for the overall period in 49 patients receiving the FPD regimen. Patients without nausea (0, scale 0-10, visual analogue scale) were: OPD: 86%, acute; 71%, delayed; and 71%, overall; FPD: 77%, acute; 41%, delayed; and 41%, overall. There were no grade 3 or 4 toxicities. CR and control of nausea in subsequent chemotherapy cycles were equal to or greater than cycle one for both regimens. **Conclusions:** For the overall period, OPD was comparable to FPD in the control of emesis; nausea was significantly ($p < 0.01$) improved with OPD compared to FPD.

9503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Chemotherapy-related cognitive impairment (CRCI), and neurotransmitter signaling, longevity, and inflammation pathways in 366 breast cancer (BC) patients and 366 age-matched cancer-free controls: A prospective, nationwide, longitudinal URCC NCORP study. *First Author: Michelle Christine Janelsins, Department of Surgery, University of Rochester Medical Center, Rochester, NY*

Background: CRCI is a burdensome clinical problem for many BC patients. Large studies are needed to definitively assess CRCI and elucidate its' biological underpinnings. We conducted the largest longitudinal, observational study to date assessing CRCI in BC patients and controls, and assessed whether neurotransmitter signaling, longevity, and inflammation pathways are involved in CRCI. **Methods:** We recruited non-metastatic BC patients (n = 366) without previous chemotherapy (CT) and age-matched controls (n = 366). Cognitive function was assessed within 1 wk pre-CT and within 4 wks post-CT using the FACT-Cog to assess self-reported function and neuropsychological assessment (computerized CANTAB Verbal Memory (VM), paper-based Controlled Oral Word Association (COWA), phone-based word recall (RAVLT) and backward counting) to assess executive function. Controls were assessed at the same time intervals as patients. SNPs involved in neurotransmitter signaling (*COMT*) and longevity (*FOXO3*), and pre- and post-CT cytokines (IL-1β, MCP-1, sTNFR1) were measured in patients. **Results:** BC patients (89% white, mean age = 53) reported more CRCI on the FACT-Cog (total score and all 4 domains) from pre- to post-CT and performed worse on all 4 executive function tests over time via t-tests (all $p < 0.05$).Using ANCOVA, adjusting for age, education, WRAT-4 reading, anxiety (STAI), and pre-CT cognitive score, BC patients performed worse on all measures post-CT compared to controls: FACT-Cog Effect Size (ES) = 0.74, VM ES = 0.27, COWA ES = 0.33, RAVLT ES = 0.27, Backward Count ES = 0.19; all $p < 0.05$. *FOXO3* and *COMT* SNPs predicted level of CRCI on the FACT-Cog (both $p = 0.07$). Decreases in executive function were associated with increases in IL-1β, MCP-1 (both $p < 0.05$) and sTNFR1 ($p = 0.08$). **Conclusions:** This is the largest longitudinal study showing significant CRCI amongBC patients receiving CT compared to cancer-free controls. CRCI in BC patients is influenced by neurotransmitter signaling and longevity genes and leads to increased inflammation. NCI UG1CA18996, K07CA168886.

9504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

EXCAP exercise effects on cognitive impairment and inflammation: A URCC NCORP RCT in 479 cancer patients. *First Author: Karen Michelle Mustian, University of Rochester Medical Center, Rochester, NY*

Background: Cognitive impairment (CI) is one of the most troublesome side effects experienced by patients, arises due to chronic inflammation, and impairs quality of life (QOL). We conducted a nationwide, multi-site, phase III RCT examining the efficacy of exercise for improving CI and inflammation through the URCC NCORP Research Base. **Methods:** Non-metastatic cancer patients receiving chemotherapy were randomized into 2 arms: 1) chemotherapy and 2) chemotherapy plus a 6-week (wk) exercise intervention--Exercise for Cancer Patients (EXCAP): a home-based, personalized prescription of aerobic walking and anaerobic resistance band training. CI and inflammation were assessed via the FACT-Cog and standard serum Luminex assays, respectively, at pre- and post-intervention. **Results:** 479 patients beginning chemotherapy were accrued (94% female, 84% breast cancer, mean age = 54). ANCOVAs controlling for baseline CI and chemotherapy cycle (1 wk, 2 wk, 3 wk) revealed significant differences in CI total score, perceived CI, impact of CI on QOL, and perceived CI by others (all $p < 0.05$) with a trend for differences in perceived cognitive ability ($p < 0.10$) between groups at post-intervention. Follow-up analyses showed exercise participants receiving 2 wk cycles of chemotherapy demonstrated less CI overall and across all domains (all $p < 0.05$) except perceived cognitive ability ($p < 0.10$) than controls at post-intervention. T-tests revealed an exercise-induced anti-inflammatory response with down-regulation of pro-inflammatory cytokines (IFNg, IL-8, IL-1b) and up-regulation of anti-inflammatory cytokines (IL-6, IL-10, sTNFra) in exercisers (all $p < 0.05$). Conversely, t-tests revealed down-regulation of IL-10 and less up-regulation of sTNFra in controls (all $p < 0.05$). Canonical correlations revealed a trend where changes in inflammation predicted changes in CI in exercisers ($r = 0.33$; $p = .06$), but not controls. **Conclusions:** EXCAP exercise improves CI and inflammation in patients receiving chemotherapy, and exercise-induced anti-inflammatory responses may elicit improvements in CI. Clinicians should consider prescribing EXCAP to reduce CI and inflammation. NCI UGCA189961 & K07CA120025. Clinical trial information: NCT00924651.

9505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Randomized trial of exercise on quality of life and fatigue in women diagnosed with ovarian cancer: The Women's Activity and Lifestyle Study in Connecticut (WALC). *First Author: Yang Zhou, Yale Cancer Center, New Haven, CT*

Background: Ovarian cancer survivors experience a wide range of treatment side effects that can affect health-related quality of life (HRQOL). Physical activity has been shown to improve HRQOL for other cancer survivors; however, prior to our study, no large randomized exercise trial (RCT) has been conducted in ovarian cancer. We examined the effect of exercise vs. attention control on HRQOL and fatigue in ovarian cancer survivors. **Methods:** We randomized 144 physically inactive ovarian cancer survivors who had completed initial chemotherapy into a 6 month RCT of exercise vs. attention control. Women in the exercise arm received weekly phone calls from a certified exercise trainer and were counseled on increasing their physical activity to 150 min/wk of aerobic exercise. Women in the attention control arm also received weekly phone calls to discuss a relevant health topic. HRQOL and fatigue were measured via SF-36 and FACT-F questionnaires. Generalized linear models were used to compare baseline to 6-month changes in HRQOL and fatigue between the two arms. **Results:** At baseline, participants were, on average (mean + SD), 1.7 ± 1.0 years post-diagnosis, 54% stage III-IV, 57.3 ± 8.6 years of age, and exercised 31.0 ± 45.8 mins/wk. Baseline physical HRQOL (Physical component summary (PCS) score of the SF-36) (mean = 46.0 ± 9.0) and fatigue scores (mean = 36.3 ± 10.9) were similar for both arms.At 6 months, women in the exercise arm increased exercise by 132.8 ± 108.8 min/wk compared to 59.0 ± 90.4 min/wk in the attention control arm ($P < 0.001$). Women in the exercise arm improved physical HRQOL compared to a decreased physical HRQOL in women in the attention control arm (SF-36 PCS change score of 1.7 ± 1.1 vs. -1.9 ± 1.2, mean ± SE, $P = 0.02$). Borderline significant improvements in fatigue were observed for women randomized to exercise (FACT-F change score of 4.0 ± 1.1) vs. a 1.2 ± 1.2 increase for controls at six months, $P = 0.06$). **Conclusions:** Our results show that ovarian cancer survivors are interested in and able to exercise at recommended levels, with exercise improving physical HRQOL. Exercise programs for ovarian cancer survivors should be implemented in an effort to improve HRQOL. Clinical trial information: NCT02107066.

9506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Results of the exercise and nutrition to enhance recovery and good health for you (ENERGY) trial: A behavioral weight loss intervention in overweight or obese breast cancer survivors. *First Author: Cheryl L Rock, UC San Diego, La Jolla, CA*

Background: Obesity increases risk for all-cause and breast cancer mortality and co-morbidities in women who have been diagnosed and treated for breast cancer. The Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Study is the largest weight loss intervention trial among breast cancer survivors to date. **Methods:** In this multi-center randomized trial, 692 overweight/obese women, who were on average 2 years post-primary treatment for early stage breast cancer, were randomized to a group-based cognitive-behavioral intervention with telephone counseling and tailored newsletters to support weight loss or a less intensive (control) intervention and followed for 2 years. The primary endpoint for this randomized controlled trial was weight loss measured at both 1- and 2-year follow-up. Secondary aims included the exploration of effect modifiers (such as time since diagnosis and type of tumor and therapy) on weight loss at 24 months. Weight and blood pressure were measured at 6, 12, 18, and 24 months. Longitudinal mixed models were used to analyze change over time. **Results:** At 12 months, mean weight loss was 6.0% of initial weight in the intervention group and 1.5% in the control group ($P < .0001$). At 24 months, mean weight loss in the intervention and control groups was 3.7% and 1.3%, respectively ($P < .0001$). Physical activity increased significantly in intervention vs. control women at 6 and 12 months ($P < .0001$). Blood pressure (diastolic and systolic) was lower in the intervention vs. control groups at follow-up clinic visits ($P < .05$). The weight loss intervention was more effective among women older than 55 years than among younger women. **Conclusions:** A behavioral weight loss intervention can lead to clinically meaningful weight loss in overweight/obese breast cancer survivors. These findings support the need to conduct additional studies to test methods to support sustained weight loss. They also underscore the need for larger, longer-term trials to test the effects of intentional weight loss on breast cancer recurrence and survival. Clinical trial information: NCT01112839.

9507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

The impact of physical activity on fatigue and quality of life in lung cancer patients: A randomised controlled trial (RCT). *First Author: Janette L. Vardy, Concord Cancer Centre, University of Sydney, Sydney, Australia*

Background: Physical activity (PA) has been shown to improve fatigue and quality of life (QOL) in a range of cancer populations. Little research has been done in the advanced lung cancer setting. This RCT evaluated a 2-month PA intervention in patients with unresectable lung cancer. **Methods:** Participants were stratified (disease stage, performance status [PS] 0-1 vs 2, center) and randomized (1:1) to usual care (UC) (general nutrition and PA education materials) or UC plus 2-month program of supervised weekly PA and behaviour change sessions and home-based PA. Assessments were completed at baseline, 2, 4 and 6 months. The primary endpoint was fatigue (FACT-F subscale) at 2-months. Secondary endpoints included: QOL, functional abilities, physical fitness, activity (accelerometers), mood, dyspnea, survival and blood results. Intention-to-treat analysis using linear mixed models was done. **Results:** 111 patients were randomized: male 55%, median age 62 (35-80); 95% NSCLC, 5% SCLC; 95% Stage IV. At baseline 77% were on active treatment. Baseline characteristics, including PA levels, comorbidities and Glasgow Prognostic Score (GPS) were well balanced between groups. Attrition was 22, 36 and 50% at 2, 4 and 6 months respectively; no difference between groups. Adherence to intervention sessions: behavioral 77%, PA 69%. There were no significant differences in fatigue, QOL, symptoms, mood, distress, sleep, dyspnea, activities of daily living, GPS between groups at 2, 4 or 6 months. Patients over report PA levels compared to accelerometer data. Using accelerometer data, PA increased only in the PA group from 0 – 2 months, but the difference in PA between groups was not significant. Median survival (months): PA 13.7 vs UC 12.6 (p= 0.76): 38 participants remain alive. **Conclusion:** Adherence to the 8-week intervention was good but did not increase PA levels compared to education materials alone. No difference was seen in fatigue, QOL, symptom control or functional status. Clinical trial information: ACTRN12609000971235.

	PA n=55	UC n=56	P-value
FACT-F Fatigue:			
0	38.4	36.3	
2	37.5	36.3	0.61
4	39.6	35.4	0.10
6	36.6	34.5	0.44
EORTC Global QOL			
0	63.8	58.9	
2	63.2	64.3	0.81
4	64.2	60.2	0.45
6	60.8	54.2	0.26
Performance Status			
0	0.8	0.9	
2	0.8	1.0	0.30
4	0.8	1.0	0.16
6	0.7	1.2	0.01

9508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Impact of the LIVESTRONG at the YMCA Program on physical activity, fitness, and quality of life in cancer survivors. *First Author: Melinda L Irwin, Yale School of Public Health, New Haven, CT*

Background: Physical activity (PA) has been linke d to cancer risk and outcomes, yet many survivors are inactive. We evaluated the impact of the LIVESTRONG at the YMCA program, an exercise program available for cancer survivors at YMCA's across the USA, on PA, fitness, and quality of life (QOL). **Methods:** Participants were recruited through Yale Cancer Center/Smilow Cancer Hospital and Dana-Farber Cancer Institute. Key eligibility criteria included having a cancer diagnosis and being able to walk. Participants were randomized to immediate participation in a 12-week LIVESTRONG at the YMCA program at a participating YMCA in CT or MA, or to a wait-list control group. Study measures were collected at baseline and 12-weeks. Intervention effects were evaluated using chi-square tests and generalized linear models, with change at 12-weeks in PA and fitness (assessed through the 6-Minute Walk Test [6MWT]) as primary endpoints. **Results:** A total of 186 participants were randomized (95 to the LIVESTRONG Program and 91 to control). The majority of patients had stage I-II disease and 50% had breast cancer. A majority of participants were inactive at baseline, with only 34% reporting 150+ min/wk of PA. Participants randomized to the LIVESTRONG Program attended on average 83% of scheduled sessions over the 3-month program and experienced significant increases in physical activity (75% exercising at 150+ min/wk vs. 25% of controls, $p < .05$), and improvements in fitness and QOL compared to controls (Table). **Conclusions:** The LIVESTRONG program was effective in increasing PA, fitness and QOL in cancer survivors. Additional work is needed to evaluate sustainability of these effects, but this program could provide a platform to increase physical activity in thousands of cancer survivors across the USA. Clinical trial information: NCT02112149.

Baseline to 12-week changes in PA, fitness, and QOL, means (SD).

	Baseline			Changes over 12 weeks		
	Exercisers	Control	p-value	Exercisers	Control	p-value
Physical Activity (min/wk)	158.5 (215.0)	119.9 (169.8)	0.18	71.0 (243.4)	-23.6 (180.2)	0.004
6MWT (ft)	1592 (254)	1578 (335)	0.50	111 (204)	15 (220)	0.007
FACT-G	90.5 (14.4)	88.7 (12.3)	0.35	2.5 (1.1)	-0.3 (1.1)	0.024

9509 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Association between renal function and chemotherapy-related toxicity in older adults with cancer. *First Author: Lindsay Leuthen Peterson, Med Univ of South Carolina, Charleston, SC*

Background: Older adults with cancer are at increased risk for chemotherapy-related toxicity (CRT). Tools are needed to better define their risk and aid in treatment planning. Renal function declines with age and can be calculated with various formulas, although the ideal formula for such calculations is unclear. We therefore evaluated the association between renal function and CRT in older adults and compared the effect of different renal function formulas and body weight measurements on this association. **Methods:** This is a secondary analysis of data from a prospective multicenter study of 500 patients age 65 and older who were starting a new chemotherapy regimen. Renal function was estimated with four formulas (modified Jelliffe [Jelliffe], Cockcroft-Gault [CG], Wright, and Modification of Diet in Renal Disease [MDRD]), using actual, ideal and adjusted body weights. The association between baseline renal function and grade 3-5 CRT was evaluated by unconditional logistic regression. **Results:** Mean age of the 492 evaluable patients was 73 (range 65-91); 40% were aged ≥ 75 years (18% age 80-91); 61% had stage IV disease; 56% were female. Mean estimated renal function ranged from 56 to 78 mL/min, depending on the formula. One or more grade 3-5 toxicities occurred in 53% of patients (26% hematologic; 43% non-hematologic). Decreased creatinine clearance [CrCl] calculated by CG (actual body weight) was associated with increased odds of CRT (OR 1.12, $P < 0.01$ 95% CI 1.04-1.20); for every 10 mL/min decrease in CrCl, the odds of CRT increased 12%. This association is independent of the type of chemotherapy received (renally cleared vs not). Neither primary dose reduction nor chemotherapy duration was associated with CRT. There were no statistically significant associations between decreased renal function with non-CG formulas (Jelliffe, Wright and MDRD) and odds for CRT. Serum creatinine alone was not associated with toxicity risk (OR 0.67, $P = 0.15$ 95% CI 0.37-1.14). **Conclusions:** Decreased CrCl (as measured by CG with actual body weight) is associated with increased odds of chemotherapy-related toxicity and should be considered when treating older adults with cancer. Serum creatinine alone is not adequate for risk assessment.

9510 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Evaluation of a web-based cognitive rehabilitation programme (CRP) in cancer survivors reporting cognitive symptoms following chemotherapy. *First Author: Victoria J Bray, Liverpool Cancer Centre, Liverpool, Australia*

Background: Self-reported cognitive impairment is frequently seen in cancer survivors. We evaluated a CRP in cancer patients with cognitive symptoms. **Methods:** 243 adult cancer patients who had completed adjuvant chemotherapy within 6-60 months and reported changes in memory and/or concentration on EORTC-QLQ-CF, received a 30 minute phone consultation and were randomized to a 15-week, home-based CRP (Insight) or usual care (UC). Primary endpoint was self-reported cognitive function (FACT-COG Perceived Cognitive Impairment [PCI] subscale). Secondary endpoints included: neuropsychological (NP) testing (CogState), quality of life (QOL) and fatigue (FACT-F), anxiety/depression (GHQ), and stress (PSS). Primary analysis used linear mixed models comparing the difference in FACT-COG PCI between the 2 arms at each post baseline timepoint: post intervention (T2) and 6 months later (T3). **Results:** A total of 243 patients were randomized: median age 53 (range 23-74); 95% female; 89% breast cancer, 5% colorectal cancer. There were no significant differences between the groups at baseline. The CRP group had improvement in all FACT-COG domains including PCI at T2, which were sustained at T3. Individual NP test results were not significantly different at T2 or T3. Anxiety/depression was improved at T2 and T3, and stress at T3, in the CRP group. There were no differences between the groups in fatigue or QOL (global or in domains) at any timepoint. **Conclusions:** The web-based CRP Insight led to improvements in cognitive symptoms that were sustained at 6 months compared to phone consultation alone. Clinical trial information: ACTRN12609000683235.

	CRP (n=122)	UC (n=121)	p-value
FACT-COG: PCI			
T2	23.8	33.6	<.0001
T3	23.5	32.6	<.0001
Impact on QOL			
T2	4.5	5.8	0.0241
T3	4.4	5.7	0.0385
Perceived cognitive abilities			
T2	17.1	14.0	<.0001
T3	16.8	14.2	0.0010
Comments from others			
T2	1.5	2.4	0.0010
T3	1.8	2.3	0.0578
GHQ:			
T2	22.5	24.4	0.0222
T3	23.1	24.7	0.0638
FACT-G:			
T2	82.5	81.2	0.5096
T3	82.9	79.8	0.1131
FACT-F subscale:			
T2	36.9	35.3	0.2809
T3	37.2	35.9	0.3687
PSS:			
T2	22.5	23.5	0.1332
T3	22.3	23.9	0.0246

9511 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

A clinical score to predict early death at 100 days after a comprehensive geriatric assessment (CGA) in elderly cancer patients: A prospective study with 815 patients. *First Author: Rabia Boulahssass, UCOG PACA EST CHU de Nice, Nice, France*

Background: Trying to predict very early death after a CGA is very difficult in clinical practice. Last year, we presented predictors of early death (Boulahssass et al, 9511, *ASCO 2014*).The aim of this new study was the next step by developing a score to estimate the risk of death at 100 days in order to illuminate the clinical decision-making. **Methods:** This is a multicentric and prospective cohort study approved by an ethics committee. A standardized CGA has been done before the treatment decision at the baseline (MMSE, MNA, Grip strength, ADL, IADL, CIRSg, Charlson, Lee, PS, Gait speed, QLQc30, G8, Balducci score). During the follow up of 100 days, the events (death), the treatments made, and the targeted geriatric interventions were collected. A multivariate logistic regression permits the selection of risk factors. The calibration was assessed with the Hosmer-Lemeshow goodness of fit test. The internal validation of the model was performed by a bootstrap method with 1000 randomized samples. Score points were assigned to each risk factors by using the β coefficient. The accuracy of the score was assessed with the mean c-statistic (0.813). **Results:** 815 patients with a mean age of 82 years joined the study. The predictors were: metastatic cancer (OR 2.5 CI 1.6-3.6 $p < 0,0001$), gait speed < 0.8m/s (OR 1.7 CI 1.1-2.9 $p = 0,025$), MNA <17 (OR 8.8 CI 3.5-22.9 $p < 0.0001$), MNA ≤ 23.5 and ≥ 17 (OR 5.1 CI 2.1-12.2 $p < 0.0001$), PS > 2 (OR 1.9 CI 1.1-3.2 $p = 0.01$), cancers other than breast cancers (OR 2.1 CI 1.3-3.2 $P = 0.001$). We assigned in the score 5 points for MNA < 17, 3 points for MNA ≤ 23.5 and ≥ 17, 2 points for metastatic cancers, 1 point for: lower gait speed, PS > 2, and for cancers other than breast cancers. The risk of death at 100 days after a CGA was 5% for 0 to 5 points, 20% for 6 to 7 points,40% for 8 to 9 points and 60% for 10 points. **Conclusions:** This is the first score that estimates very early death in elderly cancer patients. This score could be useful in treatment decisions in clinical practice in order to choose the best treatment for the patient.

9512 Poster Discussion Session; Displayed in Poster Session (Board #171), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Pilot study of family caregiver burden in home hospice: Stress-induced immune changes. *First Author: Abdullah Ladha, Mayo Clinic Health System Eau Claire, Eau Claire, WI*

Background: In 2012, 1.5-1.6 million patients received hospice care in United States. The majority received care at home. Unfortunately caregiving has been reported as an independent risk factor for mortality. Caregivers of hospice patients comprise a special group, as most patients die within short time span and have diverse trajectories. Therefore, this group deserves study to confirm or negate immune dysregulation as seen in dementia caregivers. **Methods:** Family caregivers were enrolled after providing informed consent. Caregivers were included if they provided minimum of eight hours cares each day, for at least two weeks and had no active inflammation or infection. Participants filled a questionnaire and provided a blood sample. Samples from age and sex matched healthy control subjects were acquired from the Mayo Clinic Biobank. ELISA and flow cytometry were used to run lab tests. Paired t-tests were used to compare biomarker values in two groups. **Results:** Blood samples from 39 caregivers were compared with controls. The following markers were significantly higher in caregivers: IL-1 beta, IL-2, IL-12, CRP, IL-8, CXCL1, CXCL2 and CXCL3. Cell markers with higher values in caregivers were: CD4+, CD8+, CD56+16+, CD69 and CD62L. Regulatory markers like regulatory T cells and TIM-3 were also higher in caregivers. Cytokines and chemokines significantly lower in caregivers were: IL-4, CCL-7, CCL-22, CCL-4, Eotaxin (CCL-11, CCL-24, CCL-26), CX3CL1 and CXCL10. **Conclusions:** Hospice caregivers demonstrated an increased inflammatory state and enhanced cell mediated immune changes as compared to age-matched controls. These changes may reflect immune dysregulation and proliferation, either due to loss of regulatory markers like Eotaxins or inefficient regulatory machinery including TIM-3 and regulatory T-Cells, which is unable to suppress inflammation and potentially result in adverse caregiver health.

Biomarker	Paired Difference Median	P-value
CD16+56+	5.5 (-1.6 , 10.6)	0.003
CD3+CD4+	9.1 (-1.1 , 18.5)	0.001
CD3+CD8+	8.0 (-0.2 , 15.6)	0.003
CD4+TIM3+	3.1 (0.6 , 4.5)	< 0.001
Treg	6.3 (-1.7 , 15.3)	0.005
CRP	1.2 (-0.1 , 4.3)	< 0.001
Eotaxin	-148.3 (-246.3 , -94.5)	< 0.001
IL-2	0.3 (-1.1 , 5.8)	0.010
IL-12	5.5 (-0.6 , 17.4)	0.003

9513 Poster Discussion Session; Displayed in Poster Session (Board #172), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Quality of life and satisfaction with care in caregivers of patients with advanced cancer: Results from a trial of early palliative care. *First Author: Julie Clare McDonald, Department of Psychosocial Oncology and Palliative Care, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Early palliative care has been shown to improve the quality of life (QOL) and satisfaction with care of patients with advanced cancer, but little is known about its effects on family caregivers. Here we report secondary outcomes of caregiver QOL and satisfaction with care from a cluster-randomized controlled trial of early palliative care. **Methods:** 461 patients with advanced cancer were recruited from 24 medical oncology clinics at Princess Margaret Cancer Center between December 2006 and February 2011 to participate in a cluster-RCT of early palliative care versus standard care (Zimmermann, C et al. Early palliative care for patients with advanced cancer: a cluster-randomized controlled trial. Lancet 2014;383: 1721-30). The primary caregivers identified by these patients were approached for participation if they were ≥ 18 years of age and had sufficient English proficiency. Consenting caregivers (N = 182) completed validated measures at baseline and monthly for 4 months, assessing QOL (Caregiver QOL-Cancer [CQOLC] and Medical Outcomes Study Short Form [SF-36v2]), and satisfaction with care (FAMCARE). A random effect mixed-model was used to evaluate change of QOL and satisfaction with care over time; all analyses were by intention to treat. **Results:** 182 caregivers completed baseline measures (94 intervention, 88 control); 151 completed at least one follow-up assessment. Over the 4-month period of the study, there was no significant improvement in QOL scores in the intervention group compared to the control group for the CQOLC ($p = 0.53$), SF-36 physical component summary ($p = 0.27$), or SF-36 mental component summary ($p = 0.58$). Satisfaction with care improved significantly in the intervention compared to the control group ($p = 0.01$). **Conclusions:** In this study, early palliative care involvement increased caregivers' satisfaction with care but not their QOL. An intervention tailored specifically for caregivers may be required to have a substantial impact on caregiver QOL. Clinical trial information: NCT01248624.

9514 Poster Discussion Session; Displayed in Poster Session (Board #173), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Depression and anxiety among family caregivers of patients with advanced cancer. *First Author: Joel Nathan Fishbein, Massachusetts General Hospital, Boston, MA*

Background: Despite the important role family caregivers (CGs) play in the care of patients with cancer, little is known about their psychological distress. We sought to describe rates and correlates of depression and anxiety in CGs of patients with advanced cancer to determine those at greatest risk for psychological distress. **Methods:** As part of an ongoing trial of early palliative care, we are assessing baseline depression and anxiety in patients within 8 weeks of advanced lung or gastrointestinal cancer diagnosis and their CGs. We are administering the Hospital Anxiety and Depression Scale (HADS), subscale scores >7 denoting clinically significant depression or anxiety. We are assessing patient coping styles with the Brief COPE. We used multiple logistic regression with purposeful selection of covariates to identify correlates of CG depression and anxiety. **Results:** Of 240 CGs (mean age=57 years), 156 (65%) were spouses/partners, 167 (70%) were female, and 131 (55%) were working. 37 (15%) and 102 (43%) CGs reported significant depression and anxiety, respectively. CG age, gender and employment status, as well as patients' anxiety and lack of acceptance coping, were associated with higher rates of CG depression. CG age, gender, marital status and education level, as well as patients' anxiety and presence of brain metastases were associated with higher rates of CG anxiety. **Conclusions:** Younger, female CGs were at greatest risk of both depression and anxiety. Thus, this CG population should be monitored closely and referred for cancer center support services for distress management. We also found that patients' anxiety was associated with higher rates of both CG depression and anxiety, underscoring the importance of interventions that address both patient and CG psychological distress.

CG Depression			CG Anxiety		
Covariates	OR	P	Covariates	OR	P
CG			CG		
Age	0.94	0.02	Age	0.97	0.02
Female	4.60	0.03	Female	2.36	0.01
Working	0.21	0.01	Married to patient	5.74	<0.01
Patient			College education	0.53	0.04
Income > 50k	2.02	0.21	Lives with patient	1.60	0.40
Children	3.00	0.07	Patient		
Cancer type	0.47	0.14	Cancer type	1.60	0.17
Reports goal of care is cure	2.14	0.14	Brain metastases	2.30	0.05
Anxiety	3.32	0.02	Anxiety	2.81	<0.01
Acceptance coping	0.66	<0.01			

9515 Poster Discussion Session; Displayed in Poster Session (Board #174), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Intended and unintended consequences: Ethics, communication, and prognostic disclosure in pediatric oncology. *First Author: Jonathan Michael Marron, Dana-Farber/Boston Children's Cancer and Blood Disorder Center, Boston, MA*

Background: Most patients wish for all available information about their prognosis, but physicians can be hesitant to discuss prognostic information with patients, particularly those with poor prognoses. For some, concerns that this will cause anxiety, depression, or decreased hope outweigh the ethical obligation to provide such information. **Methods:** We surveyed 353 parents of children with newly diagnosed cancer at the Dana-Farber/Boston Children's Cancer and Blood Disorders Center and the Children's Hospital of Philadelphia. We used multivariable logistic regression to assess associations between parental report of elements of discussions of prognosis with the child's oncologist (quality of information, quality of communication, prognostic disclosure) and the intended/unintended outcomes of these discussions (trust, hope, peace of mind, depression, anxiety). Analyses were stratified by the child's prognosis: favorable (≥ 75% likelihood of cure) or less favorable (< 75% likelihood) as reported by the oncologist. **Results:** Among parents of children with less favorable prognoses (n = 140), those who reported receiving high quality information from the oncologist expressed greater peace of mind (odds ratio [OR] 4.44, 95% confidence interval [1.53, 12.90], $p < 0.01$), and those who reported their oncologist to have provided high quality communication endorsed greater trust in the oncologist (OR 3.25 [1.22, 8.70], $p = 0.02$) and feelings of hope (OR 2.96 [1.24, 7.03], $p = 0.01$). Parents who received more information about prognosis were not significantly more anxious ($p = 0.82$), depressed ($p = 0.55$) or less hopeful ($p = 0.86$) than those who received less prognostic information. Similar findings were seen in the more favorable prognosis subset and the overall cohort. **Conclusions:** We find no evidence that greater prognostic disclosure leads to the unintended consequences of increased anxiety, depression, or decreased hope, even in parents of children with less favorable prognoses. Rather, communication processes may increase the intended consequences of peace of mind, trust, and hope, supporting the discussion of prognosis with all parents, even those of children with a lower likelihood of cure.

9516 Poster Discussion Session; Displayed in Poster Session (Board #175), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A randomized, controlled trial of a cardiopulmonary resuscitation (CPR) video decision support tool for seriously ill hospitalized patients with advanced cancer. *First Author: Areej El-Jawahri, Massachusetts General Hospital, Boston, MA*

Background: Discussing CPR preferences with patients with advanced cancer who are hospitalized is a critical component of end-of-life decision making. However, these discussions are challenging and often avoided by clinicians. We examined the impact of a CPR video decision tool on patients' choices and knowledge about CPR, and their comfort with watching the video. **Methods:** We conducted a multi-center randomized controlled trial of 116 patients with advanced cancer hospitalized at two academic oncology centers. We randomized patients to either a 3-minute video describing CPR (n = 52) or standard-oncology care (n = 64). The primary outcome was participants' preferences for CPR (immediately after viewing the video in the intervention arm). Secondary outcomes included patients' knowledge (using 5-item questionnaire with higher score reflects greater knowledge), and intervention participants' comfort with watching the video. **Results:** The mean age was 66 years (SD = 12); 50% were women, 84% were white, and 48% had lung or gastrointestinal cancer. Only 47% of study participants reported having a discussion about their CPR preferences at the time of admission to the hospital. At baseline, there were no differences in patients' preferences for not wanting CPR between the intervention and control arms (63% vs. 58%, P = 0.79). After the intervention, participants randomized to the video were more likely not to want CPR (81% vs. 58%, P = 0.03) and were more knowledgeable (mean knowledge score 4.3 vs. 3.2, P < 0.0001) versus control participants. In the intervention arm, 81% of participants found the video helpful, and 94% felt comfortable watching it and would recommend it to others. **Conclusions:** Seriously ill hospitalized patients with advanced cancer who watched a CPR video decision support tool were more likely not to want CPR and were better informed about their options. Participants reported feeling comfortable watching the video and would recommend it to others facing similar decisions. Video decision support tools can facilitate end-of-life decision-making for hospitalized patients with advanced cancer. Clinical trial information: NCT01527331.

9517 Poster Discussion Session; Displayed in Poster Session (Board #176), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Quality of life and mood in patients with advanced cancer: Associations with prognostic understanding and coping style. *First Author: Ryan David Nipp, Dana-Farber / Harvard Cancer Center, Boston, MA*

Background: Patients' prognostic understanding and coping styles influence their treatment decisions, but how these factors relate to their quality of life (QOL) and mood has not been well described. We sought to examine the associations of patients' prognostic understanding and coping style with their QOL and mood. **Methods:** As part of an ongoing trial of early palliative care, we are assessing baseline QOL (Functional Assessment of Cancer Therapy-General), mood (Hospital Anxiety and Depression Scale), coping (Brief Cope), and prognostic understanding in patients within 8 weeks of diagnosis of advanced lung or gastrointestinal (GI) cancer. To determine associations, we used linear and logistic regression, adjusting for patients' age, sex, cancer type, and marital status. **Results:** Of 300 participants (mean age=64.7 years; 138 (46%) female), 132 (44%) had GI cancer and 168 (56%) had lung cancer. Using cutoff score >7 for the HADS, 61 (20%) and 85 (28%) reported depression and anxiety. 138 (49%) reported their prognosis as terminal. A terminal perception of prognosis was associated with lower QOL and higher rates of anxiety. Emotional support, acceptance, and active coping styles were associated with better QOL and mood. Denial and self blame were associated with worse QOL and mood. **Conclusions:** These data demonstrate that acknowledging a terminal prognosis may be associated with greater physical and psychological distress, or conversely, patients with worse QOL and mood may better appreciate the gravity of their illness. Certain coping styles (self blame and denial) are associated with lower QOL and higher distress. Understanding the relationships among patients' prognostic awareness, coping styles, QOL and mood will allow us to develop more effective supportive care interventions.

	QOL		Depression		Anxiety	
Variable	Beta	P	OR	P	OR	P
Prognosis terminal	-0.19	<0.01	1.53	0.29	2.19	0.02
Coping style						
Active	0.05	0.38	0.70	0.01	1.15	0.30
Denial	-0.18	<0.01	1.15	0.26	1.32	0.01
Emotional support	0.18	<0.01	0.73	0.09	0.80	0.21
Behavioral disengagement	-0.09	0.13	1.49	0.08	1.41	0.12
Positive reframing	0.09	0.14	0.85	0.19	0.97	0.76
Self blame	-0.12	0.04	1.35	0.03	1.34	0.02
Acceptance	0.19	<0.01	0.76	0.03	0.78	0.04

9518 Poster Discussion Session; Displayed in Poster Session (Board #177), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Clinical performance of the DigniCap system, a scalp hypothermia system, in preventing chemotherapy-induced alopecia. *First Author: Hope S. Rugo, University of California, San Francisco, San Francisco, CA*

Background: Alopecia is an emotionally traumatic side effect for breast cancer (BC) patients (pts) undergoing adjuvant chemotherapy (CTX). The DigniCap System is the first scalp cooling system studied under a clinical trial approved by the Food and Drug Administration (FDA) to minimize alopecia. **Methods:** This prospective trial evaluated the clinical performance of the DigniCap System in women with early stage BC receiving adjuvant CTX. The primary endpoint was efficacy evaluated by pt self-assessment of 5 photographs of the head using the Dean scale to estimate hair loss one month after the end of chemotherapy. A score of 0-2 (≤ 50% hair loss) was defined as treatment success. Tolerability was defined as the percentage of patients who completed all planned CTX cycles using the DigniCap System and by the Patient Symptoms Survey. Eligibility included women with stage I/II BC scheduled to receive adjuvant CTX, excluding sequential anthracycline/taxane regimens. With 100 pts enrolled, there was 90% power to detect the difference between the null hypothesis treatment success proportion of less than 40% versus an alternative proportion of 56%. Pts who chose not to undergo scalp cooling were enrolled in a control group. **Results:** 101 pts used the DigniCap System and were evaluable for the primary endpoint. CTX regimens included docetaxel (D)/ cyclophosphamide (76%), D/carboplatin (12%) & weekly paclitaxel (12%); trastuzumab and pertuzumab were allowed. Treatment success was seen in 71 (70.3%; 95% CI, 60.4 - 79.0%; p < 0.001), compared to 0/16 in the control group. Minimal or no hair loss (Dean score 0-1) was seen in 39 pts (39%). Toxicity included grade 1/2 headache (4), pruritus (1), pain of skin (1) and head discomfort (1). Three pts discontinued cooling, primarily from feeling cold. **Conclusions:** Use of the DigniCap System prevented significant hair loss in 70.3% of pts with breast cancer receiving adjuvant CTX, compared to control where 94% had > 75% hair loss. Treatment was well tolerated and there has been no evidence of scalp metastases. Pts will be followed for long-term safety. The DigniCap System is highly effective in reducing chemotherapy-induced alopecia with a clinically meaningful benefit. Clinical trial information: NCT01831024.

9519 Poster Discussion Session; Displayed in Poster Session (Board #178), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Chronic health conditions (CHCs) following cisplatin-based chemotherapy (CHEM): A multi-institutional study of 680 testicular cancer survivors (TCS). *First Author: Mohammad Issam Abu Zaid, Indiana University School of Medicine, Indianapolis, IN*

Background: Platinating agents are among the most commonly used group of cytotoxic drugs worldwide. Few studies, however, have comprehensively examined the number and range of co-morbidities following CHEM in uniformly treated patients. Given the limited number of CHEM regimens used to cure TC and high long-term survival rates, TCS represent a unique population to provide new knowledge. We examined CHCs in an ongoing North American multi-center study of TCS given CHEM (NCI 1R01 CA157823-02). **Methods:** Eligible TCS were aged < 50 y at diagnosis and treated with only first line cisplatin CHEM after 1990. Questionnaires regarding co-morbidities and prescription drugs were completed. Evaluated CHCs included tinnitus, hearing loss, peripheral neuropathy (PN), balance/vertigo, renal disease, hypertension (HTN), Raynaud's syndrome, diabetes (DM), thyroid disease, hypogonadism, erectile dysfunction (ED), anxiety/depression, pain, and others. For PN, responses of "a little", "quite a bit", or "very much" regarding tingling, numbness or shooting/burning pain were scored as 'yes'. Yes/no variables assessed ototoxicity (i.e., tinnitus, "problems hearing words, sounds, or language in crowds", hearing aid use, and deafness). **Results:** We evaluated 680 consecutively enrolled TCS. Median age at diagnosis was 31 (range, 15-49 y); median time since CHEM completion was 52 mos. (range, 1-30 y). Only 15% of patients reported no CHCs, with 21%, 23%, 17%, and 24% reporting 1, 2, 3, or 4+ CHCs, respectively. 47% reported any ototoxicity including tinnitus in 36% of all TCS. Ten patients reported hearing aid use. 55% reported PN, while 29% had both PN and ototoxicity. Medication use for HTN, hypercholesterolemia, DM, ED, pain, or anxiety/depression was reported by 8%, 11%, 4%, 4%, 7%, and 13% of patients respectively. **Conclusions:** Several years after CHEM, nearly a quarter of TCS in this study reported 4 or more CHCs. We may have overestimated the number of CHCs, since PN included "a little" symptomatology, and ototoxicity was based on limited binary variables without finer gradation of symptoms. Future studies will continue to identify important CHCs following CHEM in TCS.

9520 Poster Discussion Session; Displayed in Poster Session (Board #179), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Comparison between clinician- and patient-reporting of baseline (BL) and post-BL symptomatic toxicities in cancer cooperative group clinical trials (NCCTG N0591 [Alliance]). *First Author: Thomas Michael Atkinson, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Reporting of clinician-based toxicity assessment via the Common Terminology Criteria for Adverse Events (CTCAE) commonly does not distinguish between symptoms already present at BL versus those that develop during a trial. Therefore, current estimation of toxicities may include symptoms that predate trial entry. We hypothesize that patient (pts) provide more complete BL symptom reports than clinicians, and that these BL symptoms can be "subtracted" from those reported during a trial at the pt level to better understand which toxicities actually developed during the trial. **Methods:** Data were pooled from Alliance trials where at BL and throughout the trial, (1) clinician-reported symptomatic toxicities were documented with the CTCAE and (2) analogous pt self-reported symptoms were documented via a questionnaire. McNemar's test was used to compare between clinician- and pt-reporting of: 1) BL prevalence, 2) maximum post-BL, and 3) worsening (i.e., BL subtracted) scores. **Results:** Across 26 trials, 24 clinician- and analogous pt-reported symptoms were captured for 2608 pts (median age 60, 62% female, 93% Caucasian, 97% non-Hispanic). For 20/24 (83%) symptoms at BL, pts reported a significantly higher prevalence (grade or score $\geq$ 1) than did clinicians. Prevalence using maximum post-BL was significantly different between clinicians and pts for 21 (88%) symptoms with 16/21 (76%) having a higher prevalence by the pt report. When subtracting BL, a significant difference between clinicians and pts was observed in 16/24 (67%) symptoms, with a lesser number (9/16, 56%) having a higher incidence by pt report. **Conclusions:** Clinicians consistently under-reported prevalence of BL symptoms compared to pts. Change from pt-reported BL assessment appears to more closely match clinician-graded AEs. This method should be considered for future pt-based toxicity assessments in clinical trials as a more accurate appraisal of symptoms attributable to study treatments rather than to pre-existing etiologies.

9521 Poster Discussion Session; Displayed in Poster Session (Board #180), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Long-term safety of fertility preservation by ovarian stimulation and concurrent aromatase inhibitor treatment in women with breast cancer. *First Author: Kutluk Oktay, Institute for Fertility Preservation and New York Medical College, New York, NY*

Background: Cryopreservation of embryos and oocytes after ovarian stimulation (OS) is an established method of fertility preservation (FP). To minimize the elevation of serum estrogen levels, an aromatase inhibitor, letrozole, has been used concurrently with OS. However, long-term safety of this approach is unknown. The objective of this trial was to determine the long-term safety of controlled OS with letrozole supplementation (COSTLES) in women with breast cancer. The impact of BRCA mutations, estrogen-receptor (ER) and operative status on recurrence after COSTLES were also evaluated. **Methods:** A total of 337 women aged 24-45 with a diagnosis of stage $\leq$ 3 breast cancer were enrolled during FP consultations. Of those, 120 elected to undergo COSTLES for FP prior to chemotherapy; the remaining 217 served as controls. **Results:** The baseline characteristics were similar between FP and control groups except for the younger age ($P = 0.03$) and less frequent lymph node involvement ($P = 0.02$) in the former. The mean follow-up after diagnosis was 4.9 years (range 1-13) in the FP and 6.2 years (1-14) in the control group. In the FP group, the hazard ratio for recurrence was 0.77 (95% CI: 0.28, 2.13) and the survival was not compromised compared with controls ($P = 0.61$). Neither BRCA gene mutation status ($P = 0.18$), nor undergoing FP before breast surgery ($P = 0.56$) affected survival . Likewise, none of the tumor characteristics including the receptor status affected the survival following COSTLES. Thirty-three women attempted pregnancy with frozen embryos; 15 using a gestational carrier. Seventeen of those 33 had at least one child (FP rate: 51.5%; livebirth/embryo transfer rate: 45.0%). The livebirth rate was similar to an age-matched control group from a national IVF database. There were no recurrences among women who conceived. **Conclusions:** COSTLES is unlikely to cause substantially increased recurrence risk in breast cancer even in the presence of BRCA gene mutations, and it results in the preservation of fertility in a majority of women. Our data strongly support that FP via COSTLES should be made more widely available for young women with breast cancer even before undergoing breast surgery. Clinical trial information: NCT00504699.

9522 Poster Discussion Session; Displayed in Poster Session (Board #181), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

The impact of adjuvant breast cancer (BC) chemotherapy on ovarian reserve and menses. *First Author: Shari Beth Goldfarb, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In prior studies, menses was used as a surrogate for fertility. But, anti-mullerian hormone (AMH) may be a better surrogate for ovarian reserve. The goal of this study is to delineate the extent of ovarian damage from specific treatments by using AMH level and menstrual calendars and to determine if chemo-induced amenorrhea and AMH levels correlate. Here we report results from the largest longitudinal study with a pretreatment evaluation to measure the impact of chemo on ovarian reserve in women with BC. **Methods:** A multi-institutional IRB-approved study was performed in 207 premenopausal women with stage 0-III BC. AMH levels were evaluated at baseline and 1 yr post adjuvant chemo. Menstrual calendars were completed monthly. After the exclusions (failure to f/u, serum sample inadequacy, presumed PCOS, Tam only treatment and consent withdrawal), 104 women ages 26-46 (median 38) were available for analysis at 1 yr post treatment. AMH levels were measured in frozen sera with an ultrasensitive ELISA assay and were log transformed due to non-normal distribution. Results were analyzed with Wilcoxon rank sum test and repeated measures ANOVA to adjust for age, tam use and stage. **Results:** In the104 evaluable women, 95 pts had HR+ and 21 had triple negative BC. 78 pts received anthracycline-based (ddAC-T/EC-T) chemo and 26 non-anthracycline-based chemo (TC/CMF/TH). In the 104 pts who received chemo,compared to baseline (median0.20ng/ml, 0.001-3.9 ng/ml), AMH levels declined significantly (median 0.12 ng/ml, 0.001-4.47 ng/ml; $p < 0.0001$) at 1 yr post chemo. The type of chemo, stage and adjuvant tam use post-chemo did not significantly impact the results. Despite a significant decline in ovarian reserve by AMH, 73% (74/102) of women who received chemo and completed menstrual calendars had return of menses by 1 yr post treatment. There was no difference in AMH levels between the women whose menses returned and those who remained amenorrheic. **Conclusions:** This longitudinal study shows that BC chemo is detrimental to ovarian reserve. The fact that the majority of pts resumed their menses despite a significant decline in their ovarian reserve by AMH indicates that resumption of menses is not a reliable measure of ovarian normalcy/fertility.

9523 Poster Discussion Session; Displayed in Poster Session (Board #182), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Treatment-related amenorrhea among young women one year following diagnosis of early-stage breast cancer. *First Author: Philip Daniel Poorvu, Dana-Farber Cancer Institute, Boston, MA*

Background: Treatment-related amenorrhea (TRA) is common among premenopausal women treated for early-stage breast cancer and is associated with important reproductive, sexual, and metabolic side effects. Few prior studies have prospectively evaluated factors associated with TRA among young women receiving modern treatment regimens. **Methods:** As part of a prospective cohort study of women age $\leq$ 40 diagnosed with breast cancer, participants were surveyed at enrollment and one year following diagnosis (dx) regarding sociodemographics, medical history, menstrual status, and treatment. TRA at one year was defined as the absence of menses within the six months prior. Participants with stage IV disease or on ovarian suppression were excluded from this analysis. Univariable and multivariable modeling were used to determine demographic and treatment factors associated with TRA. **Results:** Among the 504 women included, 38% were age $\leq$ 35. Overall, 31% experienced TRA (Table 1). Univariable analysis revealed that TRA was associated with age, tamoxifen (TAM) use, and chemotherapy, but not race, BMI, smoking, co-morbidity (Charlson), or weight change since dx. Multivariable modeling revealed that relative to women age 36-40, women age 21-30 experienced significantly less TRA (OR 0.18, $p < 0.0001$). This difference was not statistically significant between women age 31-35 and women age 36-40 (OR 0.67, $p = 0.09$). TAM use (OR 1.97, $p = 0.0002$) and chemotherapy (OR 3.89, $p < 0.0001$) were also independent predictors of TRA. Effects of different modern regimens on TRA in this young cohort will be presented. **Conclusions:** This analysis represents the largest evaluation to date of very young women and confirms that older age and treatment with TAM and chemotherapy are predictors of TRA. Further research to identify differences in short and long-term risk of TRA with modern treatment, including specific chemotherapy regimens, is warranted.

	No TRA	TRA
Age (years)		
21-30 n (%)	59 (88)	8 (11)
31-35 n (%)	88 (70)	38 (30)
36-40 n (%)	200 (64)	111 (36)
Tamoxifen		
No n (%)	144 (77)	44 (23)
Yes n (%)	203 (64)	113 (36)
Chemotherapy		
No n (%)	136 (76)	26 (24)
Yes n (%)	211 (62)	131 (38)
Total n (%)	347 (69)	157 (31)

Key: TRA (Treatment-related amenorrhea).

9524 Poster Session (Board #183), Sat, 1:15 PM-4:45 PM

Differences in attitudes and beliefs toward end-of-life treatments between hematologic (Heme) and solid tumor (ST) oncology specialists. *First Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients with Heme malignancies often receive intensive care at the end-of-life. To better understand the end of life decision making process among oncology specialists, we compared the cancer treatment recommendations, and attitudes and beliefs toward palliative care between Heme and ST specialists. **Methods:** We randomly surveyed 120 Heme and 120 ST oncology specialists at our institution. Respondents completed a survey examining two aspects of end of life care: palliative systemic therapy using standardized case vignettes and palliative care proficiency. We compared the two groups using the Wilcoxon rank sum tests and Chi-square tests, and conducted multivariate logistic regression to identify predictors of treatment preferences. **Results:** 182/240 (76%) clinicians responded. Compared to ST specialists, Heme specialists were significantly more likely to favor prescribing systemic therapy with moderate toxicity and no survival benefit for patients with ECOG performance status (PS) 4 and an expected survival of 1 month (P<0.0001, Table). This decision was highly polarized. Heme specialists felt less comfortable discussing death and dying (72% vs. 88%, P=0.007) and hospice referrals (81% vs. 93%, P=0.02), and were more likely to feel a sense of failure with disease progression (46% vs. 31%, P=0.04). They were also less likely to refer patients with newly diagnosed cancer (21% vs. 43%, P=0.002) to palliative care. On multivariate analysis, Heme specialty (odds ratio 2.77, P=0.002) and comfort level with prescribing treatment to ECOG 4 patients (odds ratio 3.79, P=0.02) were associated with the decision to treat in the last month of life. **Conclusions:** We found significant differences in the attitudes and beliefs toward end-of-life care between Heme and ST specialists, and identified opportunities to standardize end-of-life care.

Treatment recommendations for case vignettes.

Patients	Heme*	ST*	P
Expected survival 1 month, PS 4	4 (2, 6)	1 (1, 3)	<0.0001
Expected survival 3 months, PS 3	4 (3, 6)	3 (2, 5)	0.0002
Expected survival 6 months, PS 2	5 (4, 6)	5 (4, 6)	0.18

*Median (IQR), where 1=strongly against treatment, 7=strongly favors treatment.

9525 Poster Session (Board #184), Sat, 1:15 PM-4:45 PM

Quality of life, depression, and end-of-life outcomes in hospitalized patients with advanced cancer. *First Author: Kathryn Elizabeth Hudson, Duke University Medical Center, Durham, NC*

Background: Hospitalized cancer patients are more likely to have advanced disease and are at risk for poor outcomes, yet little is known about their quality of life (QOL) and rates of depression. We aimed to assess QOL, mood, and end-of-life outcomes in this population. **Methods:** From 2008-10 we enrolled hospitalized patients at Duke University with acute leukemia or stage III/IV solid tumor or lymphoma and whose physician stated that they "would not be surprised if they died in less than one year." 150 patients completed surveys, including demographics and validated instruments measuring QOL (FACT-G) and mood (brief CES-D). We retrospectively reviewed charts to assess end-of-life outcomes including presence of advance directives, use of palliative care, and rate of death in the hospital. Descriptive statistics, linear regression and sensitivity analyses were performed. **Results:** Mean FACT-G score was 66.9 (SD 11), 14 points worse than published cancer patient norms. QOL was significantly worse in all FACT-G subscales except for social wellbeing (24.2 vs. 22.1, $p < 0.001$). 30% of patients ($n = 45$) had a brief CES-D score of > 4, suggestive of depression. Higher scores were associated with lower performance status ($p < .05$). Patients with lower education levels had lower QOL (FACT-G 59.9 vs 68.4, $p < .05$). There were no significant differences between tumor type and performance status, QOL, or depression scores; and there was no association between time until death and QOL or depression. Markers of end-of-life care quality were poor. By this analysis, 86% (127) of patients had died. While physicians correctly estimated death within one year in 69% of cases, only 25% of patients used hospice, and only 2.7% received an in-hospital palliative care consult. 60.5% had a do-not resuscitate order, and 43% of patients died in the hospital. **Conclusions:** Hospitalized patients with advanced cancer have poor quality of life compared to established cancer patient norms and a high rate of depression. While physicians expected these patients to die within a year, end-of-life quality outcomes were poor. Hospitalized patients with advanced cancer may benefit from interventions aimed at improving mood, quality of life, and end-of-life care.

9526 Poster Session (Board #185), Sat, 1:15 PM-4:45 PM

Trends and regional variation of end-of-life cancer care in the Medicare program. *First Author: Shi-Yi Wang, Yale School of Public Health, New Haven, CT*

Background: Although there has been substantial concern of aggressiveness of cancer care near the end-of-life (EOL) in the United States, little is known about recent trends in EOL cancer care and associated regional variation in the Medicare program. **Methods:** Using the Surveillance, Epidemiology, and End Results–Medicare data, we identified 82,245 beneficiaries who had breast, prostate, lung, colorectal, pancreas, liver, kidney, melanoma, or hematological cancer diagnosed in 2004-2009 and died within 2 years as a result of cancer by December 2009. Aggressiveness of EOL care was measured by 1) chemotherapy received within 14 days of death; 2) $>$ 1 emergency department (ED) visit within 30 days of death; 3) $>$ 1 hospitalization within 30 days of death; 4) $\geq$ 1 intensive care unit (ICU) admission within 30 days of death; 5) hospital death; and 6) hospice enrollment $\leq$ 3 days before death. Using hierarchical generalized linear models, we assessed regional variation of EOL care adjusting for patient demographics, tumor characteristics and hospital referral region (HRR)-level market factors. **Results:** Proportions of receipt of at least one potentially aggressive EOL care increased from 48.3% in 2005 to 48.7% in 2009 ($P<$ .001). From 2005 to 2009, increasing proportions of patients had repeated hospitalization (14.0% vs. 14.8%; $P=$ .0113) or ICU admission (15.2% vs. 19.5%; $P<$ .001), whereas in-hospital death declined (24.1% vs. 22.0%; $P<$ .001). Proportions of receiving chemotherapy (4.4% vs. 4.0%), repeated ED visits (34.0% vs. 32.9%) and very short hospice enrollment (7.2% vs. 8.3%) did not change significantly over time. The proportions of decedents who experienced aggressive EOL care varied substantially across HRRs. After adjusting for patient and HRR-level factors, the difference in the proportion of patients receiving potentially aggressive EOL care between HRRs in the lowest and the highest quintiles was 16.9 percentage point (57.2% vs. 40.3%). **Conclusions:** Despite growing focus on providing appropriate EOL care, nearly 50% of cancer decedents in the Medicare Program received aggressive EOL care with no evidence of demonstrable improvement in reducing aggressive EOL cancer care.

9527 Poster Session (Board #186), Sat, 1:15 PM-4:45 PM

Burden of inpatient care and treatments in terminally-ill cancer patients: results from a population-based, retrospective study from administrative data in France. *First Author: Lucas Morin, Aging Research Center, Karolinska Institutet, Stockholm, Sweden*

Background: Over the past decades, dramatic changes in the treatment of advanced cancer have raised concerns regarding the quality of end-of-life care in terminally-ill patients. However, Earle et al.'s indicators of aggressive care near the end of life have never been used in population-based studies in Europe. We aimed to examine the use of inpatient care and treatments in the last months of life of cancer patients who died in hospitals in France. **Methods:** A nationwide, retrospective cohort study was conducted using administrative data. We included all cancer patients (irrespective of the tumour type) aged 20 years or older, who died in acute and rehabilitation hospital facilities between January 2010 and December 2013 in France. **Results:** Among 516,244 cancer decedents, 39% were female and 48% were 75 years or older. Main primary malignancies were gastrointestinal (30%), respiratory (20%) and haematological (10%). 17% of the patients spent their last 30 days of life in a hospital facility, 10% died in ICU, 10% in a palliative care unit, 2% within the emergency department and 64% in acute care wards. 33.8% received chemotherapy during their last 3 months of life, 28.0% over the last 2 months, 17.9% over the last month and 10.9% over the last 2 weeks before death. Between 2010 and 2013, while adjusting for sex, age and cancer type, we measured a significant increase in the likelihood of receiving chemotherapy over the last month of life (OR = 1.05, 95%CI = 1.03-1.07). Younger decedent, patients with hematological malignancies and patients with metastatic cancer were the most likely to be prescribed such treatments over the last 90 and 30 days before death ($p < 0.001$). Over the course of the last month before death, 3.3% of the decedents had more than one emergency department visit, 22.4% were admitted to an Intensive Care Unit and 21% received blood transfusion. **Conclusions:** This population-based study provides unprecedented insight into the burden of care and treatment in the last months of life of cancer patients in France. We believe these results can provide useful support for discussions regarding cancer care management near the end of life.

9528 Poster Session (Board #187), Sat, 1:15 PM-4:45 PM

Exploring the preferences for place of death among cancer patients and their caregivers. *First Author: Marieberta Vidal, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Understanding the preferred place of death (POD) for advanced cancer patients (pts) is very important when they are approaching the end of life. Meeting the preferences of pts is considered an important palliative care outcome. Prior studies reported that more than 80% of pts with terminally ill cancer prefer to die at home. In many countries such as the UK, Italy, Greece, South Korea and Japan home deaths have been falling, but in some states of the US/Canada there are indications of a reversal of trends. Dying at home may be more difficult for pts in severe physical and psychosocial distress, or when there are social or financial difficulties. The purpose of this study was to determine POD preference among palliative care pts in the outpatient center (OC) and the palliative care unit (PCU). **Methods:** A sectional anonymous questionnaire was administered to advanced cancer pts and caregivers (PCU pts and OC) between August 2012 and September 2014. PCU pts responded when there was no delirium and the primary caregiver responded when the patient (pt) was unable to respond. In the case of outpatients dyads were assessed. **Results:** Overall 141/216 (65%) preferred home death. PCU pts preferred home death less than outpatients (table). Patient and caregiver agreement regarding preferred place of death was 86% ($p < 0.001$). The preferred POD was the same as one month ago for 82/99 (83%) PCU pts and 111/116 (96%) outpatients, with significant difference between groups ($p = 0.002$). **Conclusions:** Although home is the preferred POD in advanced cancer pts, a substantial minority prefer hospital death or no difference. Pts admitted to the PCU have a higher preference for hospital death in comparison to the outpatients, likely reflecting more severe distress because they already tried home care. Pts and caregivers agree on POD in most cases. Personalized assessment of POD preference for both patient and caregiver is needed.

Preferred POD per location.

	Total		PCU*		OC**		
Preference	N=216	%	N=100	%	N= 116	%	P
Home	141	65	58	58	83	72	0.02775
Hospital	40	19	27	27	13	11	
No preference	28	13	12	12	16	14	
Others	7	3	3	3	4	3	

P-values are from Fisher's exact test comparing preference of POD between PCU & OC; *PCU = Pts (N = 24) Caregivers (N = 76); ** OC = Patients (N = 116)

9529 Poster Session (Board #188), Sat, 1:15 PM-4:45 PM

Practice pattern treating older women with early stage breast cancer at Johns Hopkins. *First Author: YaoYao Guan Pollock, Johns Hopkins School of Medicine, Baltimore, MD*

Background: The National Comprehensive Cancer Network (NCCN) Guidelines incorporated omission of radiation therapy (RT) after breast-conservation surgery in woman age ≥ 70 years with stage I, estrogen receptor positive breast cancer who plan to receive endocrine therapy (ET). This guideline change was based on The Cancer and Leukemia Group B C9343 trial. A follow up study demonstrated that there is a wide variation in implementing this change across 13 different NCCN institutions. We evaluated the practice pattern at Johns Hopkins, and sought to construct an internal guideline. **Methods:** We identified women treated at our institution from 2009-2013 age ≥ 70 years at the time of diagnosis and met the C9343 inclusion criteria. RT omission rate was calculated for each year. We explored associations between RT omission and year, age, tumor size, race, nodal status and tumor type with t tests and Fisher's exact tests. **Results:** A total of 544 women age ≥ 70 years sought treatment at our institution, and 98 (18%) were candidates for RT omission based on the NCCN guidelines. Mean age was 76.2 years (Range 70-95). Overall RT omission rate was 36/98 (37%), but varied greatly by year (Range 8-56%, $p = 0.03$). This variation in omission rate was still present after excluding women who did not tolerate ET (Range 9-67%, $p = 0.02$). Older age was associated with higher RT omission rate (mean age 78.7 vs. 74.8, $p = 0.002$). Women who did not undergo nodal evaluation had higher RT omission rate (68%) than women who had nodal evaluation (29%) even when the evaluated node(s) were negative ($p = 0.003$). The RT omission rate did not vary by race (Caucasians: 24/69, 35%; Non-Caucasians: 11/27, 40%; $p = 0.64$), tumor type (ductal: 27/72, 38%; non-ductal: 9/26, 35%; $p > 0.99$), or tumor size (< 1cm: 17/37, 46%; 1-1.4cm: 10/34,29%; 1.5-2cm: 8/25, 32%; $p = 0.35$). **Conclusions:** The implementation of the NCCN guideline, which was based on category I evidence, is not consistent at our institution. Our results suggest that other tools should be used to apply the guidelines more consistently. To achieve this, we have developed a Quality Improvement Protocol that incorporates life expectancy estimate and a brief geriatric assessment to the treatment of all woman age ≥ 70 years at our breast centers.

9530 Poster Session (Board #189), Sat, 1:15 PM-4:45 PM

Frailty and outcomes in older adults undergoing pancreaticoduodenectomy. *First Author: Tri Minh Le, University of Virginia, Charlottesville, VA*

Background: Pancreaticoduodenectomy (PD) is the only potentially curative treatment for pancreatic cancer. Studies show older adults are at higher risk for poor outcomes. The Balducci Frailty Criteria have been shown to risk-stratify older adults with cancer in non-surgical settings. The purpose of this retrospective, single-institution review is to examine the correlation between preop frailty criteria and postop outcomes in older cancer pts undergoing PD. **Methods:** Pts ≥ 65y who underwent PD for cancer of the pancreas, ampulla, duodenum, or bile ducts between January 2002 and October 2013 were eligible for the study. A pt was considered "frail" if at least 1 were true: 1. Age ≥ 85y; 2. ≥ 3 significant comorbidities; 3. Dependent for ≥ 1 ADL; 4. Geriatric syndrome present. Primary study endpoints were 30 and 90 day mortality, with secondary endpoints of postop surgical site infections, pneumonia, UTI, sepsis, ventilator dependence > 48 hours, unplanned re-intubation, 30-day readmission, discharge to home versus assisted living, and median hospital stay. P-values were calculated using a chi-square test. Length of hospital stay was analyzed using the Wilcoxon rank-sum test. **Results:** 201 consecutive pts were included, and 88 were considered "frail". A significant increase was noted in the "frail" group for rates of postop UTI (OR = 2.86, 95% CI = 1.10-7.44, $p = 0.025$), ventilator dependence > 48 hours (OR = 4.8, 95% CI = 0.97-23.69, $p = 0.035$), unplanned re-intubation (OR = 3.67, 95% CI = 0.94-14.25, $p = 0.047$), assisted living discharge (OR = 2.34, 95% CI = 1.18-4.67, $p = 0.014$) and median hospital stay (7.0 vs 9.0 days, $p = 0.008$). There were no differences between groups for 30 day mortality (OR = 1.31, 95% CI = 0.32-5.41, $p = 0.42$), 90 day mortality (OR = 2.29, 95% CI = 0.80-6.59, $p = 0.26$) or other study endpoints. Increasing age was independently associated with increases in UTI ($p = 0.017$) and assisted living discharge ($p = 0.037$), but not other endpoints. **Conclusions:** There was no difference in early mortality between groups, but "frail" pts had higher rates of several adverse outcomes. These findings suggest that preoperative evaluation of frailty may help identify older adults at risk of complications following PD for malignant disease.

9531 Poster Session (Board #190), Sat, 1:15 PM-4:45 PM

Evaluation of two different doses of weekly nab-paclitaxel (NP) in older breast cancer (BC) patients (pts). *First Author: Laura Biganzoli, Sandro Pitigliani Medical Onc Unit, Prato, Italy*

Background: NP compares favorably with conventional taxanes in terms of safety, efficacy and convenience of administration. These features make NP an interesting agent for evaluation in elderly pts. **Methods:** Pts aged ≥ 65 years (y) with HER2-negative (or HER2-positive but with contraindication to anti-HER2 therapy) advanced BC are randomized to receive as first-line chemotherapy NP at either 100 (Arm A) or 125 mg/m2 (Arm B), days 1, 8, 15 q 28 until an event (defined as progressive disease, functional decline or death) unacceptable toxicity (tox) or maximum benefit according to the Investigator. Due to the absence of prospective data on weekly NP in older BC pts, compliance and adverse events (AE) data in this population, even if preliminary, are clinically relevant and are reported in the present analysis. **Results:** 81 pts have been randomized so far. Evaluable for the present analysis are 44 pts who have received ≥ 1 cycle of NP and have a documented interruption of study treatment. Pts's median age is 75y (65-84) in Arm A and 74y (65 -82) in Arm B. ECOG Performance status is 0 in both arms. No impairments in Instrumental Activities of Daily Living is reported in 16 pts in both arms. Median number of affected domains at Cumulative Illness Rating Scale-Geriatric is 2 with range 0-3 in Arm B and 0-4 in Arm B. Treatment's compliance and safety data are reported in the Table. **Conclusions:** Both doses of weekly NB can be safely administered to older BC pts. Fatigue and neurotoxicity are the most frequently reported AE in both arms. Only 1 patient experienced G4 non hematological tox. Clinical trial information: 2012-002707-18.

	Arm A	Arm B
N. pts	23	21
Total/median n. cycles (range)	131/5 (2-19)	119/6 (1-10)
Pts/cycles with dose reduction (%)	17 (74)/39 (30)	15 (71)/54 (45)
Pts/cycles with delay (%)	7 (30)/13 (10)	8 (38)/13 (10)
AE (CTC v4.0 criteria) occurring, if grade (G)2 in > 1 pt N.pts (%)	G	G
	2 3 4	2 3 4
Anemia	6(26) - -	8(38) - -
Leucopenia	6(26) - -	8(38) 4(19) -
Neutropenia	5(22) 3(13) -	2(10) 8(38) 1(5)
Infection	2(9) - -	1(5) - -
Nausea	3(13) - -	5(24) - -
Vomiting	1(4) - -	2(10) - -
Stipsis	3(13) - -	3(14) - -
Diarrhoea	1(4) - -	2(10) 1(5) -
Anorexia	1(4) - -	2(9) - -
Fatigue	5(22) 1(4) 1(4)	11(52) 3(14) -
Neurotoxicity	1(4) 2(8) -	10(48) 2(10) -
Myalgia	2(8) 1(4) -	1(5) - -

9532 Poster Session (Board #191), Sat, 1:15 PM-4:45 PM

Novel method to stratify elderly patients with prostate cancer. *First Author: Ruben Carmona, UC San Diego, La Jolla, CA*

Background: Standard prognostic methods do not optimally stratify patients according to the risk of cancer death relative to competing events. In contrast, competing event (CE) models (ref: PMID 24969798) have the potential to better inform practitioners regarding when to treat elderly patients with localized prostate cancer (PC). **Methods:** Using SEER-Medicare data, we identified 68,259 patients with localized PC treated with either radical prostatectomy (RP) or radiotherapy (RT) alone, splitting each group into 60% training / 40% test sets. Using patients' demographic, tumor, and clinical characteristics, we trained risk scores based on CE models vs. standard Cox models for cancer-specific and all-cause mortality (ACM). In test sets, we compared how well models stratified subpopulations according to the ratio (ω) of the hazard for prostate cancer mortality (PCM) to the hazard for ACM. We tested the predictive ability for the cause-specific events, using the area under the curve (AUC). **Results:** For patients treated with RP, the CE risk score was associated with increased risk of PCM (HR 1.93, $P < .001$). Similar findings were observed for the cancer-specific and ACM risk scores. However, unlike standard models, increasing CE risk score was not associated with second cancer mortality (HR 0.90, $P = .19$) or non-cancer mortality (HR 0.96, $P = .56$). For patients treated with RT, the CE risk score was associated with increased risk of PCM (HR 2.13, $P < .001$), but was not associated with second cancer mortality (HR 0.90, $P = .19$), and was associated with decreased risk of non-cancer mortality (HR 0.84, $P < .001$). For patients treated with RP, the AIC was superior for CE models, relative to the cancer-specific and ACM models (AIC, 50.1 vs. 54.6 vs. 53.8, respectively). Similar findings were observed for RT patients (AIC, 43.4 vs. 45.2 vs. 54.4). The CE models also created greater separation in AUC for cancer mortality vs. non-cancer mortality, compared to the cancer-specific and ACM models ($P < .001$). **Conclusions:** Compared to standard methods, CE models more efficiently stratify elderly PC patients according to likelihood to benefit from therapy.

9533 Poster Session (Board #192), Sat, 1:15 PM-4:45 PM

Health related quality of life (HRQOL) in older adults with cancer: The potential of a single-item screen. *First Author: Mackenzi Pergolotti, UNC Chapel Hill, Chapel Hill, NC*

Background: Older adults with cancer often value maintaining or recovering their HRQOL over overall survival. This study aims to (1) describe patient reported global measures of physical and mental HRQOL in a large sample of older adults with cancer and (2) to evaluate associations with demographics and other measures of health status to better screen and identify populations at-risk of poor HRQOL. **Methods:** The Health Registry/Cancer Survivorship Cohort is an institutional database at University of North Carolina designed to aid in cancer survivorship research (http://unchealthregistry.org). Outcome measures of patient-reported HRQOL included FACT-G (range 0-108), PROMIS global Physical and Mental health (mean = 50, SD = 10 in general US population). Higher scores indicate better HRQOL. Other measures of health status: the single item Patient-Generated Subjective Global Assessment Performance Assessment (PG-SGA-PA), number of co-morbidities, FACT Cognitive Function, PROMIS Sexual Function, and global physical activity. **Results:** Of the 807 older adults (65y+) with cancer, mean age was 72y, 60% female, and 88% Caucasian. The cohort was comprised of 25% genitourinary, 24% breast, 22% gastrointestinal, and 15% gynecologic malignancies. Only 37% reported a high level of physical activity, 24% had ≥ 4 co-morbid conditions, and 25% reported that they lived alone. Mean scores for HRQOL were: FACT-G (85, range: 25-108); PROMIS-Physical (48, range: 16-67) and PROMIS-Mental (51, range: 21-67). In the multivariable models including demographics and health status measures, ≥ 4 comorbidities, poor PG-SGA-PA and lower levels of cognition were associated with poor HRQOL for each outcome measure (all $p < .0001$). **Conclusions:** Older adults with cancer with a high comorbidity burden, reduced cognition, and poorer scores on the PG-SGA-PA have poorer HRQOL. This study found that the single item PG-SGA-PA was independently associated with complex measures of global physical and mental health and with further validation could be a useful tool for oncologists to quickly identify older adults with poor HRQOL.

9534 Poster Session (Board #193), Sat, 1:15 PM-4:45 PM

Novel method to stratify elderly patients with head and neck cancer. *First Author: Ruben Carmona, UC San Diego, La Jolla, CA*

Background: Head and neck cancer (HNC) patients are at high risk of death due to competing events. We hypothesized that a competing event (CE) modeling approach (ref: PMID 24969798), which is used to optimize patients according to the risk of cancer death relative to competing events, would improve stratification of the elderly HNC population compared to standard methods. **Methods:** Using SEER-Medicare data, we identified 9,677 patients with advanced stage HNC, who were treated with radiotherapy (RT) ± surgery and chemotherapy, split into 60% training and 40% test sets. Using patients' demographic and clinical characteristics, we trained a risk score based on the CE approach versus standard Cox proportional hazards models for HNC-specific mortality and all-cause mortality (ACM). Using the test set, we compared how well the CE risk score stratified patients according to the ratio (ω) of the cause-specific hazard for HNC mortality to the hazard for ACM, using the Akaike Information Criterion (AIC). We tested the predictive ability for the cause-specific events, using the area under the curve (AUC). **Results:** Using the CE model, an increasing risk score was associated with increased HNC mortality (HR 2.16, $P < .001$) and second cancer mortality (HR 1.39, $P < .001$), but *decreased* non-cancer mortality (HR 0.62, $P < .001$). Both increasing HNC-specific and ACM risk scores were associated with increased risk of HNC mortality, second cancer mortality and non-cancer mortality. The AIC was superior for the CE model (50.1), relative to the HNC-specific (54.6) and ACM (53.8) models. The difference between the predictive ability for cause-specific events was also greater for the CE model (AUC: HNC mortality = 0.64 vs. non-cancer mortality = 0.47, $P < .001$) than the HNC-specific Cox model (AUC: HNC mortality = 0.72 vs. non-cancer mortality = 0.64, $P < .001$) and the ACM Cox model (AUC: HNC mortality = 0.72 vs. non-cancer mortality = 0.69, $P > .05$) **Conclusions:** Compared to standard methods, CE models more efficiently stratify elderly HNC patients according to likelihood to benefit from therapy. This method could improve the efficiency of clinical trials and help personalize therapeutic decisions.

9535 Poster Session (Board #194), Sat, 1:15 PM-4:45 PM

Construction of a frailty index for older adults with cancer using a geriatric assessment. *First Author: Emily Jean Guerard, UNC Chapel Hill, Chapel Hill, NC*

Background: Frailty is a state of increased vulnerability to adverse outcomes and can be defined by counting the number of health deficits an individual acquires. This study constructs a frailty index from a geriatric assessment (GA), defines the prevalence of frailty in older adults (65+) with cancer, and evaluates associations of frailty with sociodemographic and GA variables. **Methods:** The Carolina Senior Registry (CSR) is an institutional database (NCT01137825) that contains GA data on older adults with cancer. From the CSR, a 32-item frailty index (range 0-1) was developed by deficit counting as previously reported [Searle *et al.* BMC Geriatrics 2008] and categorized as robust (0-0.2), pre-frail (0.2-0.35), and frail (> 0.35) based on prior studies. Fisher's exact tests and linear regression were used to evaluate associations. **Results:** Of the 1179 total patients, the median age was 72, 87.7% Caucasian, 69.6% female, 90.7% had at least a high school education, 58.7% married, and 44.3% had a breast cancer diagnosis. Overall 59% were robust, 25.3% were pre-frail, and 15.7% were frail. Frailty and pre-frailty were more prevalent among lung cancer patients (54.6%) compared to patients with hematologic malignancies (46.5%) and breast cancer (34.1%). In a multivariable model, increasing age, African American race, lower education, increasing number of daily medications, and decreasing Karnofsky Performance Status were significantly associated with increased frailty (all $p < 0.001$). Gender, marital status, and cancer type were not associated with frailty in this model. Frailty status was also associated with measures of physical function such as falls and a Timed Up and Go of greater than 14 seconds ($p < 0.001$). **Conclusions:** We created a 32-item frailty index using GA data from a cohort of older adults with cancer. Frailty was prevalent and significantly associated with sociodemographic variables. Additional work will be focused on validating our frailty index by using outcomes data. Because frail older adults with cancer are at an increased risk for adverse outcomes, a frailty index constructed from a cancer-specific GA may provide a straightforward way to identify frail patients who should be targeted for further intervention.

9536 Poster Session (Board #195), Sat, 1:15 PM-4:45 PM

Feasibility of administering a geriatric assessment to older adults with cancer using web-based and touchscreen platforms. *First Author: Jerome G. Kim, City of Hope, Duarte, CA*

Background: A geriatric assessment (GA) can help identify factors that increase the risk for chemotherapy-related toxicity in older patients with cancer. A GA has been developed which is primarily self-completed by patients using a paper and pencil questionnaire. With the shift to electronic medical records and the prospects of Big Data, a transition to an electronic GA is imperative to allow convenient deployment of this tool. The goal of this study is to 1) evaluate the feasibility of capturing patient reported GA data using 2 separate computer-based applications: web-based (REDCap [RC]) and a touchscreen (Support Screen [SS]), and 2) compare the computer responses to those obtained via paper-pencil. **Methods:** Patients (pts) aged > 65 yrs with cancer were eligible. Pts were randomized to 1 of 4 arms (RC /Paper; RC / RC; SS/Paper; SS/SS). The feasibility of each computer methodology was determined by the % of pts who could complete the GA independently, time to complete the GA (first time), and pt satisfaction with the survey platform. Correlations between the paper version and electronic version responses were evaluated. **Results:** 100 pts were accrued: median age 72 yrs (65-92 yrs), 51% female, and 63% stage IV disease. Primary cancers included lung (22%), breast (21%), GU (20%), GI (17%), and leukemia (9%). Pts' self-reported computer skills were None + Beginner (N+B, 42%) or Intermediate + Advanced (57%). The mean (SD) time to completion using RC, SS, and Paper were 23 (8), 17 (7), and 16 (5) mins. Pts with limited computer skills (N+B) were able to complete the electronic assessment independently: RC (75%), SS (100%), and preferred the computer version over the paper survey (RC 67%, SS 76%). The correlations between the paper version and the electronic versions (SS, RC) were 0.91, 0.96 for Instrumental Activities of Daily Living and 0.82, 0.96 for Medical Outcomes Survey-Physical Health scales, respectively. **Conclusions:** The majority of patients in this cohort could complete an electronic GA using either a web-based or touchscreen platform independently. A higher proportion of patients preferred the touchscreen methodology. The electronic versions have high reproducibility compared to the paper GA.

9537 Poster Session (Board #196), Sat, 1:15 PM-4:45 PM

Is standard dose appropriate in elderly non-small cell lung carcinoma (NSCLC) patients treated with erlotinib? *First Author: Frederic Bigot, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France*

Background: Given the median age of 70 years in patients (pts) presenting NSCLC, the impact of age on outcomes including efficacy and toxicity of erlotinib remains unclear. In the BR21 study, analysis of subgroup based on age have reported similar survival benefits of erlotinib compared with placebo; however, elderly pts (³ 70 years) had significantly more toxicity, and were more likely to discontinue treatment (*Paul Wheatley-Price et al.*, J Clin Oncol 2008*).* Thus we hypothesized that elderly were more exposed than younger pts. **Methods:** All consecutive pts with advanced or metastatic NSCLC treated with erlotinib between 2010 and 2014 were eligible in this prospective cohort. Erlotinib concentrations in plasma were determined using high-performance liquid chromatography at Day 15 after treatment initiation. We compared dose-normalized concentrations between pts < or ³ 75 years old using the Mann-Whitney U test and the occurrence of acute grade ³ 2 adverse events (AE) or treatment modifications by Fisher's test. AE reports were graded using the National Cancer Institute Common Terminology Criteria V4. Lean body mass was estimated using Janmahasatian's equation. **Results:** Out of 55 pts, erlotinib plasma concentration was analyzed in 45 pts. Median age was 65.6 (range 25-83), and 14 pts were over 75 years old. Among these 45 pts, 58% were female, 93% had an adenocarcinoma subtype; 44% were never smoker. Eighty-six percent of the pts had a performans status at baseline ≤ 2. Elderly pts had significantly lower estimated lean body mass (36.6 kg vs 47.7 kg; p = 0.00038). Within 2 weeks, grade ³ 2 AE occurred in 20% of pts, and 28 % in elderly. In the subgroup of pts over 75 years old, there was a trend for higher dose-normalized concentration at day 15 (1923.3 mg/L vs 1380.9 mg/L; p = 0.07), and the difference was significant in pts older than 80 (7 pts; 2484.6 mg/L vs 1377.4 mg/L; p = 0.0074). Four pts > 75 years old had dose reduction or discontinuation versus 0 in younger pts (p = 0.014, CI95% [1.2532; infinite]). **Conclusions:** Elderly patients are susceptible to be overexposed to erlotinib at 150mg/day, resulting in increased acute toxicity and treatment discontinuation.

9538 Poster Session (Board #197), Sat, 1:15 PM-4:45 PM

Functional decline during first-line chemotherapy in elderly patients can be predicted by abnormal G8 score and performance status. *First Author: Camille Chakiba, Department of Medical Oncology, Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France*

Background: Predicting major adverse events such as functional decline during chemotherapy is an important issue in geriatric oncology. Recent studies have shown that different parts of comprehensive geriatric assessment (CGA) (Geriatric Depression Scale and Instrumental Activities of Daily Living) were predictive of functional decline. However CGA is time-consuming and has to be performed by trained geriatricians who are not in sufficient number to face the increasing demand of elderly cancer patients. Thus screening tools, such as G8-score validated on 1435 patients, have been developed to identify patients who may benefit from CGA. In addition to its value as a screening tool, the value of the G8 as a predictive tool of survival has been suggested and we here investigate whether it can be used to predict functional decline during chemotherapy. **Methods:** We tested on a cohort of 364 patients over 70 year-old treated with first-line chemotherapy the value of clinical (G8, age, sex, performance status –PS-, disease localization, extension) and biological factors (platelets, creatinine clearance, albumin, CRP, neutrophils) in predicting early functional decline, defined as a decrease of 0.5 points on the Activities of Daily Living (ADL) scale between the beginning of chemotherapy and the second cycle. We performed a multivariate analysis using logistic regression model. **Results:** Of the 364 patients, 312 were assessable for functional status and 68 experienced functional decline. On univariate analysis, PS 2 to 4, low platelets, metastatic disease and abnormal G8 (≤ 14) score were associated with functional decline. On multivariate analysis, abnormal G8 score (OR, 3.56; 95% CI 1.22; 10.34; p = 0.02) and PS 2 to 4 (OR, 2.0; 95% CI 1.1; 3.6; p = 0.04) were significantly associated with increased likelihood of early functional decline. **Conclusions:** G8 has been developed as a screening tool to predict abnormal geriatric assessment. We have shown here that it could also be used together with performance status to select elderly patients more likely to develop functional decline during chemotherapy. These data reinforce the routine use of G8 in all elderly patients treated for cancer.

9539 Poster Session (Board #198), Sat, 1:15 PM-4:45 PM

Association of baseline pro-inflammatory (IL-6, CRP) and coagulation (D-dimer) markers with relative dose intensity (RDI) in women with breast cancer (BC) undergoing (neo) adjuvant chemotherapy (chemo). *First Author: Yuan Yuan, City of Hope, Duarte, CA*

Background: Chemo decreases the risk of relapse and mortality from BC. Chemo efficacy depends on RDI, and patients (pts) who receive <85% RDI have poorer overall survival. Pro-inflammatory and coagulation factors such as IL-6, CRP and D-dimer serve as biomarkers for aging. The utility of these markers as biologic correlates of the ability to deliver chemo (i.e. RDI) in pts with BC is unknown. This study was performed to determine if prechemo IL-6, CRP and D-dimer correlate with RDI in women with stage I-III BC requiring chemo. **Methods:** This is a prospective longitudinal study that enrolled 153 women with BC who had pre-chemo peripheral blood assayed for IL-6, CRP, and D-dimer. (Neo)Adjuvant chemo regimens were prescribed at the physician's discretion. Univariate analyses evaluated the association of these 3 markers with <85% RDI and clinical factors (patient age, physician rated Karnofsky performance status (KPS) and number of co-morbidities). Multivariate analyses were performed to evaluate the association of each biomarker and clinical factor with RDI. **Results:** 153 pts (mean age of 56 y, range 30-81 y) with stage I-III BC (Stages I [23%], II [54%], III [24%]) were enrolled. Chemo regimens include: doxorubicin+cyclophosphamide /paclitaxel (AC-T: 44%), docetaxel+cyclophosphamide (TC: 35%), docetaxel/carboplatin/trastuzumab (TCH: 7%) and other regimen (14%). RDI was less than 85% for 26% of pts. There were associations between RDI <85% and higher D-dimer (p<0.01) and IL-6 (p=0.02) levels pre-chemo (Table 1). There was no association between RDI <85% and CRP or above clinical factors. **Conclusions:** Higher pre-chemo levels of IL-6 and D-dimer correlate with reduced RDI (<85%). Future studies are underway to validate these findings. Table 1. Association of pre-chemo biomarkers, clinical factors and RDI <85%. Clinical trial information: NCT01030250.

Biomarkers/ Clinical factors	OR (95%CI)	p value
D-dimer	2.47 (1.35-4.73)	0.01
CRP	1.00 (1.00-1.00)	0.82
IL6	1.10 (1.02-1.21)	0.02
Age	1.01 (0.95-1.06)	0.49
KPS	1.01 (0.98-1.04)	0.32
No. Comorbidities	0.97 (0.66-1.40)	0.33

9540 Poster Session (Board #199), Sat, 1:15 PM-4:45 PM

Combination of eribulin (E) and capecitabine (C) in elderly metastatic breast cancer (MBC): Update of a new option suitable in older elderly. *First Author: Ignazio Ugo Carreca, University of Palermo, Palermo, Italy*

Background: E mesylate, a nontaxane microtubule dynamics inhibitor is widely prescribed for MBC pts pretreated with at least 1-2 lines of chemotherapy, including anthracyclines and taxanes (A&T). Elderly Patients (EP) develop rapid and sometimes fatal toxicity during standard treatments because of their pharmacokinetic features. We designed a new combination schedule (E+C) to evaluate its suitability for elderly MBC patients. **Methods:** Treatment plan: E 0.96 mg/sqm IV on d1 every 21d - C 900 mg/sqm bid d1-14 every 28d (Dose-adjustement if necessary was according to Kintzel-Dorr's formula for EP), schedule would be continued until progression or intolerable toxicity. Eligibility criteria: histologically confirmed diagnosis of MBC, written informed consent, at least 1 measurable lesion, at least 1 site of visceral mts (not brain mts), age $>$ 70 years, previous treatment with A&T, Comprehensive Geriatric Assessment evaluation (CGA) permissive for chemotherapy, adequate renal, bone marrow and liver function. Charlson's Score Comorbidity Scale was also considered. Evaluations tools: Clinical Benefit (CB) as Stable Disease + Objective Response Rates according to WHO criteria, toxicity profile using NCI-CTC v2.0 and Quality of Life (QoL) score through EORTC QLQ-C30 questionnaires. **Results:** From 2013 jan to 2014 dec 39 metastatic EP, mean age 80.5 (range 71 - 90) were treated and 37 are still under maintenance therapy (2 pts discontinued treatment for personal reasons). A total of 599 cycles were delivered to the 37 pts without G4 toxicity. No delay in therapy delivery was needed. QoL score shows no worsening with improvement in about 55% (72-78 y/o group) after treatment in comparison with baseline. Total CB was 80%. **Conclusions:** A further period of monitoring allowed to confirm our previous report in this setting with this combination schedule. It appears more fit with comorbidity or frailty than other standard chemotherapy regimens for MBC. In this updated analysis this schedule has showed non-inferiority vs standard treatments and more suitability for older EP. This study will be extended to confirm these outcomes in order to validate a schedule devoted to EP.

9541 Poster Session (Board #200), Sat, 1:15 PM-4:45 PM

Safety of biosimilar filgrastim in elderly patients undergoing neutropenia-inducing chemotherapy: a subanalysis of the NEXT study. *First Author: Didier Kamioner, Hopital Prive de l'Ouest Parisien, Trappes, France*

Background: Febrile neutropenia (FN) is a serious and frequent complication of cytotoxic chemotherapy (CT), especially in elderly patients (pts). Biosimilar filgrastim (Nivestim, Hospira Inc.) is a granulocyte-colony stimulating factor (G-CSF) licensed for the treatment of neutropenia and FN induced by myelosuppressive CT. This subanalysis of the NEXT (Nivestim safety profile in patiEnts treated with cytotoXic in real-life clinical pracTice) study explored tolerability and efficacy of biosimilar G-CSF in elderly pts. **Methods:** NEXT was a prospective, non-interventional, longitudinal, multicentre study conducted in France to evaluate the safety of biosimilar filgrastim. Recorded data included pt demographic and clinical characteristics, biosimilar filgrastim treatment-related data on efficacy and safety, such as adverse events (AEs) and FN. Pts were monitored for 1–6 CT cycles with three visits at inclusion, during treatment, and following CT. Here we present a subanalysis of pts aged $\geq$ 70 years. **Results:** Overall, 2114 pts were enrolled in the study; this subanalysis includes 708 pts aged $\geq$ 70 years (55.9% male; mean age $\pm$ standard deviation (SD) 76.3$\pm$4.7 years; performance status rated 3 or 4:10.5%; 68.2% solid tumours; 31.8% haematological malignancies). The majority (98.3%) of pts received prophylactic biosimilar filgrastim (primary prophylaxis: 91.7%; secondary prophylaxis: 8.3%).For pts receiving prophylactic biosimilar filgrastim, the median time to treatment initiation was 2 days after the last CT dose; mean treatment duration $\pm$ SD was 6.1$\pm$4.3 days. In this subanalysis, 18.9% of pts had $\geq$ 1 AE with 11.4% of pts reporting muscle and/or bone disorders. During the study, 4.5% and 3.0% of pts had FN and infection respectively (vs 4.9% and 3.1% in the overall population). FN and/or infection led to hospitalisation of 3.5% of pts (mean duration $\pm$ SD: 11.6$\pm$15.6 days), a CT dose reduction in 3.6% of pts and a delay in administration of CT in 7.0% of pts. **Conclusions:** Biosimilar filgrastim was effective and well tolerated in in the treatment and prevention of FN in the elderly and is an alternative therapeutic option for pts with CT-induced neutropenia. Clinical trial information: NCT01574235.

9542 Poster Session (Board #201), Sat, 1:15 PM-4:45 PM

Association of geriatric assessment factors with falls in older adults initiating chemotherapy. *First Author: Tanya Marya Wildes, Washington Univ School of Medicine, St. Louis, MO*

Background: In older adults with cancer, falls are common and associated with injury, functional decline, and poorer quality of life and survival. Prior oncology studies have been inconsistent in identifying factors associated with or predictive of fall risk. Identifying individuals with cancer at greater risk for falls is essential to allow targeted intervention to prevent falls. **Methods:** In a previously reported prospective study (Hurria et al, JCO 2011), 500 older adults with cancer underwent geriatric assessment (GA) prior to initiation of a new course of chemotherapy. In this analysis, we examined cross-sectional demographic, cancer and GA factors associated with falls in the 6 months before GA using logistic regression with bidirectional stepwise selection ($p<0.15$ for factor retention). **Results:** We analyzed 401 evaluable patients. The median age was 73 (range 65-91); 58% were female; 87% were white race, and just over half (59%) had stage IV disease. The most common cancers included lung (28%), gastrointestinal (27%) and gynecologic (19%). The median MD-rated Karnofsky performance status was 90 (range 50-100). About 18% (73 patients) reported one or more falls in the previous 6 months; of these, 62%, 15%, and 23% reported 1, 2, and 3+ falls respectively. On multivariate analysis, antidepressant use, benzodiazepine use and dependence in instrumental activities of daily living (IADLs) were associated with increased odds of falls (Table). The area under the curve of our model is 0.71, with positive and negative predictive values of 0.5 and 0.84, respectively. **Conclusions:** In older adults with cancer, falls are associated with antidepressant use, benzodiazepine use and dependence in IADLs. Prospective study of incident falls will be required to confirm that the presence of these factors at baseline increases the risk of subsequent falls.

Predictor	Adjusted Odds Ratio	95% Confidence Intervals	p
Antidepressant use	2.96	(1.40, 6.16)	0.004
Hospital Anxiety and Depression Scale Anxiety score ≥8	1.72	(0.81, 3.52)	0.15
Benzodiazepine use	2.17	(1.00, 4.65)	0.05
Proton Pump Inhibitor use	1.73	(0.98, 3.04)	0.06
Age ≥75	1.70	(0.98, 2.97)	0.06
IADL dependence	1.77	(1.01, 3.11)	0.05
Timed Up & Go ≥13.5sec	1.66	(0.90, 3.01)	0.10

9543 Poster Session (Board #202), Sat, 1:15 PM-4:45 PM

Feasibility of a home-based walking program in female breast cancer patients age 60+ during chemotherapy. *First Author: Kirsten A Nyrop, UNC Chapel Hill, Chapel Hill, NC*

Background: National guidelines recommend 150 minutes a week of moderate-intensity physical activity for adults with a cancer diagnosis. Our study investigated the feasibility of a self-directed walking in women age 60 or older undergoing cytotoxic chemotherapy treatment for breast cancer. *Feasibility* was defined as at least 50% of study participants reporting an average of 150 minutes or more of walking/week for exercise or pleasure during the first 6 weeks of chemotherapy. **Methods**: *Eligibility*: Female, age 60+; Stage I-III breast cancer; scheduled for chemotherapy; physician permission to engage in physical activity; English speaking. *Intervention*: Evidence-based physical activity program for adults with arthritis – "Walk With Ease". *Measures*: Patients self-reported the average number of days and number of minutes per day of walking for exercise or pleasure during chemotherapy. Study participants also maintained a daily walking diary throughout the first 6 weeks of chemotherapy. *Data analysis*: Descriptive statistics. **Results**: Study sample (N = 22): mean age 68 (60-79), 95% Caucasian, 41% high school degree or less, mean Body Mass Index/BMI 31 (20-50), 50% two or more comorbidities. At baseline (pre-chemotherapy), 29% of participants reported walking at least 150 minutes/week. During chemotherapy, the proportion walking $>$ 150 minutes/week: 41% Week 1, 54% Week 2, 32% Week 3, 45% Week 4, 50% Week 5, 45% Week 6. During chemotherapy, the proportion walking $>$ 100 minutes/week: 68% Week 1, 73% Week 2, 77% Week 3, 64% Week 4, 68% Week 5, 65% Week 6. **Conclusions:** A home-based, self-directed walking program can encourage older female breast cancer to engage in regular exercise during chemotherapy at a level that is higher than pre-chemotherapy. Achievement of the goal of 150 minutes per week is challenging, and more feasible at a level of 100 minutes per week. This pragmatic physical activity intervention is now being tested in a 4-year efficacy trial with a large sample of female breast cancer patients age 65 or older during chemotherapy treatment, to evaluate the impact of exercise on $p16^{INK4a}$ (biomarker of aging), fatigue and other patient-reported outcomes. Clinical trial information: NCT01789983.

9544 Poster Session (Board #203), Sat, 1:15 PM-4:45 PM

Do quality of life, physical function, or the Wheatley Index at diagnosis predict 1-year survival with intensive chemotherapy in older and younger acute myeloid leukemia patients? *First Author: Narhari Timilshina, University of Toronto, Brampton, ON, Canada*

Background: Treatment decision-making is complicated in older adults with acute myeloid leukemia (AML) because of poor prognosis and significant treatment toxicities. Improved prognostication at the time of diagnosis, such as with the Wheatley Index, may aid clinical decision-making. However, the Wheatley Index has not been validated outside clinical trials. Additionally, quality of life (QOL) or objective physical performance measures (PPM) may predict outcomes such as survival in oncology. We investigated the predictive value of baseline QOL, physical function, and the Wheatley Index at diagnosis on 1-year survival during IC in younger ($<$ 60 years) and older (60+ years) AML patients. **Methods:** AML patients undergoing intensive chemotherapy (IC) at the Princess Margaret Cancer Centre were enrolled in a prospective study. At the baseline assessment (pre-IC), patients completed the EORTC QLQ-30 questionnaire in addition to 3 PPMs (grip strength, 2-minute walk test, and timed chair stands). The prognostic risk category (good, standard and poor) was categorized according to the index defined by Wheatley et al. for older adults and modified for younger adults. Predictive value for 1-year survival was analyzed with multivariable Cox proportional hazards regression. **Results:** 140 younger and 97 older patients were recruited. Overall 1-year mortality was 22.1% in younger and 37.1 % in older patients. One-year mortality was significantly higher among the poor Wheatley risk category than the other 2 risk categories in both younger and older groups (40.0% and 63.3%, $P < 0.05$, respectively). Global health and PPMs were not predictive of 1-year survival. Poor Wheatley risk category was the most significant predictor in both univariate and multivariate survival models ($p < 0.001$) in both older and younger groups. **Conclusions:** Although QOL and PPMs at diagnosis were not good predictors of 1-year survival among younger and older AML patients, the Wheatley index may help inform clinicians and patients about up-front therapy in AML.

9545 Poster Session (Board #204), Sat, 1:15 PM-4:45 PM

Differences between patient and caregiver assessments and their association with caregiver burden in caregivers of older adults with cancer. *First Author: Tina Hsu, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

Background: Caregivers are a valuable support for patients and an important source of information about patient health, particularly in older adults who are more likely to be frail or have cognitive impairment. We sought to determine whether a) differences exist between patient and caregiver assessments and b) these differences were associated with increased caregiver burden. **Methods:** 100 cancer patients, age $\geq$ 65, and their caregivers independently assessed patient function, comorbidities, nutrition, psychological status, social activity and social support. Caregiver Strain Index (CSI) was used to assess caregiver burden. Patient-caregiver assessments were compared using the Wilcoxon signed rank test. The relationship between caregiver burden and variables in which patient-caregiver assessment differed was determined using a linear regression model and adjustment for confounders was done. **Results:** Median patient age was 70, 70% had advanced disease, 62% were on chemotherapy. Patients reported a median of 2 comorbid conditions, no falls within 6 months, and 39% reported $>$ 5% weight loss. Patients reported good function (median KPS 90 and Medical Outcomes Study (MOS)-physical function 67), independence with most instrumental activities of daily living (IADL) (median OARS-IADL 13), having good social support (median MOS-social support survey 92), and good mental health (median Mental Health Index 85). 75% of caregivers experienced some caregiver burden (mean CSI 3.1 ± 3.2; 15% had high burden). Caregivers were more likely than patients themselves to rate patients as having poorer function [needing more help with IADLs ($p = 0.008$), lower KPS ($p = 0.02$), and lower MOS-physical function ($p < 0.0001$)], poorer mental health ($p = 0.0002$), but more social supports ($p = 0.03$). Only a difference in patient-caregiver assessment of a patient's need for help with IADLs was associated with increased caregiver burden ($p = 0.002$). **Conclusions:** Patients and caregivers differ in their assessment of patient function, mental health, and social support. However, only differences in patient-caregiver reported need for help with IADLs were associated with increased caregiver burden.

9546 Poster Session (Board #205), Sat, 1:15 PM-4:45 PM

Advanced cancer patients' reported priorities regarding wishes at the end of life: A randomized controlled study. *First Author: Marvin Omar Delgado-Guay, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Conversations about wishes around the end-of-life(EOL) are challenging and difficult for all clinicians. There is limited literature about the type and stability of patient's reported EOL priorities. We compared a set of 36 cards ("Go-wish-Game":GWG) v. a paper list to assist patients in establishing priorities. **Methods:** Randomized controlled study. Patients were randomized to GWG or to a list of 36 Wishes/Statements(LOS) and were asked to categorize them as very, somewhat, or not important; Group A received LOS followed by LOS 4-24 hours later; group B: GWG-GWG; group C: GWG-LOS, and group D: LOS-GWG. The State-Trait Anxiety inventory for Adults (STAI) was done after the first set of questionnaires. **Results:** 100 patients. Median age (IQR range): 56(27-83)years. 60% female. 68% White, 17% Hispanic, and 9% African-American. Age, education and cancer diagnosis weren't significant different among groups. All patients were able to complete GWG. 43/50(88%) agreed GWG had clear instructions and easy to understand (92%). 31/50(63%) patients exposed to both tools, preferred GWG. 31/50(63%) expressed having conversations about priorities near EOL was beneficial to them. STAI median (IQR) score after GWG was 48(39-59) v. 47(27-63) for LOS, $p = 0.2952$. 39/50(80%) expressed that GWG did not increased their anxiety. The 10 most common "Very important" wishes expressed by patients the first and second time they received the test(%; Spearman, p-value) were: to be at peace with God(74% v. 71%; $r = 0.73$, $p < 0.0001$), to pray(62% v. 61%, $r = 0.53$, $p < 0.0001$), to have my family with me(57% v. 61%; $r = 0.23$, $p = 0.02$), to be free from pain(54% v. 60%, $r = 0.31$, $p = 0.001$), not being a burden to my family(48% v. 49%, $r = 0.23$, $p = 0.02$), to trust my doctor(44% v. 45%; $r = 0.49$, $p < 0.0001$), to keep my sense of humor(41% v. 45%; $r = 0.53$, $p < 0.0001$), to say goodbye to important people in my life(41% v. 37%; $r = 0.46$, $p < 0.0001$); to have my family prepared for my death(40% v. 49%; $r = 0.48$, $p < 0.0001$), and to be able to help others(36% v. 31%; $r = 0.73$, $p < 0.0001$). **Conclusions:** End-of-life wishes were similar and persistent using both GWG and LOS. All patients were able to complete and most preferred GWG. Completing both GWG and LOS did not increase anxiety.

9547 Poster Session (Board #206), Sat, 1:15 PM-4:45 PM

Evaluation of the MPM2 score versus clinical predictions of mortality in a tertiary cancer center. *First Author: Alison Wiesenthal, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Prognostication is an essential yet challenging clinical skill for oncologists, even as patients approach death. Goals-of-care discussions may be improved by giving patients and families objective reference for likelihood of mortality, but tools are needed to assist clinicians in identifying which patients are at the highest risk of dying in hospital. The aim of this study was to evaluate the transferability of the ICU-derived Mortality Probability Models Version 2 (MPM2) score to the general wards at a comprehensive cancer center, and to compare it to clinical predictions of dying in hospital (CPDH). **Methods:** Prospective case series of inpatients receiving palliative medicine consultations over a 3 month period. Prior to calculating MPM2 score, the CPDH was estimated in categories: unlikely ($<$10%), less likely (25%), possible (50%), probable (75%), consistent with ($>$90%). Overall survival was determined 6 months after end of enrollment. Calibration of MPM2 in these patients was evaluated by logistic regression. For survival analysis, MPM2 scores were grouped as $<$10%, 10-50%, $>$50%. **Results:** Of 79 patients consecutively evaluated, 18 (22%) died in hospital. Another 41 (52%) died after discharge. MPM2 score and CPDH were each significantly predictive of dying in hospital ($p<0.001$). Agreement between CPDH categories and corresponding MPM2 categories was fair (weighted kappa 0.37), CPDH being more pessimistic overall and avoiding use of the middle category (see Table). Overall survival was significantly different between the three MPM2 groups (median 131.5, 36 and 6 days respectively; log rank test df 2, $\chi 2=42.6$, $p<0.001$). **Conclusions:** The MPM2 score shows promise as a clinical tool for determining in-hospital mortality outside of the ICU. It was most helpful for identifying and correctly classifying patients with intermediate likelihoods of surviving. Larger studies in this and other settings are needed.

CPDH category	n	Died in hospital n (%)	Categorized MPM2 score	n	Died in hospital n (%)
Unlikely	36	3 (8)	0-10%	49	6 (12)
Less likely	20	1 (5)	10.1-25%	13	2 (15)
Possible	0	--	25.1-74.9%	11	5 (45)
Probable	15	7 (47)	75-90%	3	3 (100)
Consistent with	8	7 (88)	>90%	3	2 (67)

9548 Poster Session (Board #207), Sat, 1:15 PM-4:45 PM

Distress in older adult cancer patients approaching end of life. *First Author: Elizabeth Ann Kvale, Birmingham VA Medical Center, Birmingham, AL*

Background: Lay health navigators are able to address various issues that cause distress in older cancer survivors by administering and responding to distress thermometers (DT). **Methods:** Lay navigators in the UAB Patient Care Connect Program assist cancer patients ≥ 65 years old with traditional Medicare insurance at 12 cancer centers in Alabama, Mississippi, Georgia, Florida, and Tennessee. Navigators documented distress levels, causes of distress, and requests for intervention.. Distress screening data from the final DT administered prior to death were used to describe care gaps for older adults with advanced cancer. **Results:** DTs were collected on a representative sample of 1060 patients who were evenly divided with respect to gender and 18% minority. Median number of days from date of last DT to date of death was 42(1-544). Distress score ≥ 4 were observed in 43% of patients;10% reported scores ≥ 8. Forty four percent of patients attributed distress to physical symptoms such as pain and fatigue. Twenty two percent indicated mobility issues contributed while 15% indicated informational needs related to their illness or treatment. Patients were more likely to ask for help from navigators with informational issues related to their illness (63%) or hospice (75%) than mobility (35%) or physical symptoms (33%). **Conclusions:** Through distress screening lay navigators are able to help older adults with advanced cancer with informational or logistical needs and advocate for proactive assistance with issues related to symptom burden. The project described was supported by Grant Number 1C1CMS331023 from the Department of Health and Human Services, Centers for Medicare & Medicaid Services. The contents of this abstract are solely the responsibility of the authors and do not necessarily represent the official views of the U.S. Department of Health and Human Services or any of its agencies.

9549 Poster Session (Board #208), Sat, 1:15 PM-4:45 PM

"Months, Not Years": Impact of Clinical Discussions of Advanced Cancer Life-Expectancy on Patient Illness Understanding. *First Author: Andrew S. Epstein, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients' understanding of their illness often guides best practice, and this is no less true at the end of life. Data showing the influence of patients' acknowledgment of prognostic discussions on the accuracy of patients' illness understanding could inform the debate regarding how to engage in these difficult discussions. **Methods:** To evaluate the effects of recent and past oncologist-patient discussions about prognosis/life-expectancy (P/LE) on changes in advanced cancer patents' illness understanding (acknowledgement of their illness as 1. terminal; 2. incurable; 3. advance staged; and 4. associated with an estimated life-expectancy in months, not years), 208 patients (with advanced lung or upper gastrointestinal cancers that progressed on 1 chemotherapy regimen, or advanced colorectal cancers that progressed on 2) from Coping with Cancer II, a prospective observational cohort study, were interviewed before and after a visit with their oncologists who discussed scan results regarding potential additional progression. **Results:** Median time between pre- and post-scan interviews was 38 days. Controlling for potential confounds (i.e., patients' race) and adjusting for patients' pre-scan illness understanding, patients who acknowledged ever having discussions of P/LE with their oncologists were more likely to recognize that their disease was incurable (Adjusted Odds Ratio [AOR] = 2.97, p = 0.009) than those who did not. Compared to patients who denied ever having a discussion of P/LE, those who reported having both recent and past discussions of P/LE were more likely to recognize that their disease was at an advanced stage (AOR = 4.88, p = 0.012), and those who reported having only recent discussions, or both recent and past discussions, of P/LE were more likely to estimate their life-expectancy in terms of months as opposed to years (AOR = 10.1, p = 0.050, and AOR = 17.5, p = 0.006, respectively). **Conclusions:** Advanced cancer patients who acknowledge having discussions of P/LE with their oncologists have a better understanding of the terminal nature of their illnesses as compared to those who do not, and thus may be better prepared to make informed end-of-life care decisions.

9550 Poster Session (Board #209), Sat, 1:15 PM-4:45 PM

Standardizing measurement of tobacco use in cancer clinical trials. *First Author: Stephanie R Land, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD*

Background: ASCO and AACR recommend assessment of tobacco use (TU) for all cancer patients, but there is little consensus regarding approaches for reliable, valid, and clinically meaningful TU measurement. Our aim was to develop clinically efficient evidence-based assessments that can be applied across research settings, and to provide expert recommendations for the timing of assessment. **Methods:** In 2013-2014, an expert Task Force developed candidate TU measurement items via consensus dialog and systematic evaluation of existing tools. From 9/2014-1/2015, in-depth, semi-structured cognitive interviews were conducted with three rounds of cancer patients to evaluate patient comprehension, memory retrieval, and judgment of draft versions of the instrument. Interviews were abstracted into structured reports tabulating cognitive difficulties. A subcommittee convened to recommend modifications. **Results:** Two tiers of TU measurement items were developed: a core set for all cancer studies, and a longer menu of curated items for use when comprehensive assessment is feasible. Domains include TU history, status and intensity relative to cancer diagnosis and treatment; other tobacco products; cessation approaches; and second hand smoke. We interviewed 22 participants (mean age 64; 68% male; 50% college educated; with cancers of the prostate (n = 8), bladder (3), colon & rectum (1), lung (7), pancreas (1), testis (1), thymus (1)). Numerous instrument improvements addressed patients' understanding of wording, response options, and recall periods. The final version performed well. Task Force recommendations also include a protocol for assessments at baseline and follow-up. **Conclusions:** These results provide preliminary support for content validity of the TU assessment instrument. Standardized TU assessment implemented in research across a range of disease sites and treatment modalities will permit data pooling and comparisons between populations. Recommendations facilitate TU assessment in clinical trials and will enable researchers to identify novel clinical interactions, better understand the effects of TU on cancer treatment efficacy and toxicity, address cessation, and ultimately improve clinical outcomes.

9551 Poster Session (Board #210), Sat, 1:15 PM-4:45 PM

Dissonance reduction as prominent coping strategy in phase I study participants. *First Author: Diane A.J. van der Biessen, Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Phase I trials are essential for progress in cancer treatment but the reasons for patients to participate in these trials remain relatively ill-explored (Van der Biessen et al, 2013). This study aims to understand how psychological factors like coping strategies, locus of control, and hope affect the motivation to participate in these trials. **Methods:** In this prospective study we asked patients to complete a survey before initial informed consent for the phase I study was obtained for the first time. We used questionnaires regarding treatment motivation (TM, Van der Helm et al, 2012), hope (Herth Hope Index), coping (assimilation and accommodation coping-scale of Brandtstädter and Renner), locus of control (Rotter locus of control scale) and Quality of Life (QoL, EORTC QLQ-C30). To investigate relations between the scales a structural equation model (SEM) was fitted to the data. **Results:** During 18 months 135 patients enrolled in the questionnaire survey. 65 (48%) of the patients were male, with a mean age of 62 (range 30-83). The SEM-analysis showed 'hope' was significantly predicting treatment motivation $X^2(5) = 5.119$. Fit indices showed a close fit: NFI = 0.996; CFI = 0.999; TLI = 0.996; RMSEA = 0.013. An unique combination of flexible ($p < 0.01$) and tenacious ($p < 0.01$) coping, together with internal locus of control ($p < 0.01$) was predicting for 'hope'. **Conclusions:** Patients entering phase I studies seem to combine seemingly contradictory coping strategies: tenacity and flexibility. Also locus of control contributes towards hope. These data suggest a specific psychological adaptation, called dissonance reduction. This process that unconsciously discounts threatening information (i.e. about fatal prognosis of the disease) predicts for the motivation to participate in oncology phase I trials. Clinical trial information: NTR3354.

9552 Poster Session (Board #211), Sat, 1:15 PM-4:45 PM

Twelve-month prevalence of mental disorders in cancer patients across major tumor entities. *First Author: Anja Mehnert, University Medical Center Leipzig, Leipzig, Germany*

Background: Many studies have shown high levels of emotional and psychosocial distress in cancer patients. However, it is not well known yet to what extent psychological problems meet the criteria of a mental disorder according to clinical diagnosis classification systems (ICD-10, DSM-IV/V). We investigated the 12-month prevalence of mental disorders in a representative sample of cancer patients treated in different care settings in order to provide epidemiological data for evidence-based psycho-oncological service care planning. **Methods:** We interviewed a representative sample of patients with different tumour entities (N = 2,141) in outpatient, inpatient and rehabilitation settings using the standardized computer-assisted Composite International Diagnostic Interview for mental disorders adapted for cancer patients (CIDI-O). **Results:** The overall 12-month prevalence for any mental disorder was 39.4% (95%CI: 37.3-41.5%). The following prevalence rates were diagnosed: 15.8% (95%CI: 14.3-17.4%) for anxiety disorders, 12.6% (95%CI: 11.2-13.9%) for mood disorders, 9.5% (95%CI: 8.3-10.8%) for somatoform disorders, 7.3% (95%CI: 6.2-8.4%) for nicotine abuse, 3.7% (95%CI: 3.0-4.5%) for disorders resulting from a general medical condition, 1.1% (95%CI: 0.6-1.5%) alcohol abuse or dependence and 0% eating disorders. Highest prevalence of mental disorders was found in patients with head and neck cancer, breast cancer, malignant melanoma and kidney/urinary tract cancers. **Conclusions:** Mental disorders are highly prevalent in cancer patients. Having shown differences regarding type and amount of mental disorders across different tumour entities, our results emphasize a different need for psycho-oncological and psychotherapeutic support leading to an appropriate allocation of direct personnel and others resources.

9553 Poster Session (Board #212), Sat, 1:15 PM-4:45 PM

Psychosocial distress and its effects on the health-related quality of life of primary brain tumor patients. *First Author: Dina M Randazzo, Duke University Medical Center, Durham, NC*

Background: Primary brain tumor patients experience a high level of psychosocial distress, not only due to their diminished functional and neurocognitive capacities, but also due to the psychosocial stigma of being a primary brain cancer patient. The purpose of this study is to evaluate the level of psychosocial distress, the different sources of this stress, and its effect on health-related quality of life (HRQoL) in primary brain tumor patients. **Methods:** Demographic and clinical information in the PRoGREss registry at Duke's Preston Robert Tisch Brain Tumor Center was queried retrospectively for December 2013 through February 2014. Data was also obtained from patient-reported outcome questionnaires including the National Comprehensive Cancer Network's Distress Thermometer (NCCN-DT), the Functional Assessment of Cancer Therapy-Brain Cancer (FACT-Br), and the Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F). **Results:** Among the 845 subjects completing the NCCN-DT, 385 (46%) were female and 460 (54%) were male. 98% reported physical problems with the most frequent being memory/concentration (40%) and fatigue (42%), and 41% complained of an emotional problem with nervousness (22%) and worry (29%) being the most reported concerns. 12% reported insurance/financial concerns. 94% of the subjects completed the distress thermometer with a mean score of 2.68 (SD = 2.70). There was no difference in distress between tumor grades (low grade: mean = 2.73, SD = 2.89; high grade: mean = 2.67, SD = 2.62; p = 0.8297). Females (mean = 3.05, SD = 2.81) experienced significantly more distress than males (mean = 2.39, SD = 2.57; p = 0.0007), as well as a higher rate of practical (p = 0.0026), family (p = 0.0209) and emotional (p < 0.0001) problems. Patients who reported at least one practical, family, or emotional problem had significantly lower HRQoL scores (p < 0.0001). **Conclusions:** Primary brain tumor patients experience memory dysfunction, fatigue, nervousness, worry, and financial concerns which have a negative effect on the patient's HRQoL. By identifying and addressing these stressors during a clinic visit, it may be possible to improve patient HRQoL.

9554 Poster Session (Board #213), Sat, 1:15 PM-4:45 PM

Patient-reported outcomes following choice for contralateral prophylactic mastectomy. *First Author: Eun-Sil Shelley Hwang, Duke University Medical Center, Durham, NC*

Background: Retrospective data show that the rate of contralateral prophylactic mastectomies (CPMs) is increasing; meanwhile, parallel information informing impact of CPM on quality of life (QOL) is lacking. We undertook this study to ascertain whether patient-reported outcomes (PRO), and more specifically QOL, differed between women who did or did not elect CPM. **Methods:** Women recruited from the Army of Women (AOW) with a history of breast cancer surgery took electronically-administered surveys including a background survey to collect patient, disease, and procedure specific factors, as well as the BREAST-Q, a well-validated breast surgery outcomes patient reporting tool. Descriptive statistics, univariate hypothesis testing, and regression analysis were used to evaluate the association of CPM with PRO scores in 4 QOL domains incorporated in the BREAST-Q (satisfaction with breasts, and psychosocial, physical and sexual well-being). **Results:** 7628 women completed questionnaires; of these, 4152 had mastectomy and 1519 (37%) reported receipt of CPM. Women undergoing CPM were younger (median age 53.7 y vs. 59.3 y, p < 0.0001) and reported earlier breast cancer stage at presentation than those who did not choose CPM. In univariate analysis, mean breast satisfaction was significantly higher among the CPM group (60.4 vs. 58.1, p = 0.0005) and mean physical well-being was significantly higher among those who did not have a CPM (76.6.vs. 74.6, p = 0.0002). The groups did not differ with respect to psychosocial or sexual well-being. On multivariable linear regression the CPM group continued to report higher breast satisfaction (p = 0.0019) but reported no difference from the non-CPM group in the other QOL domains. Psychosocial well-being improved over time for both CPM and non-CPM groups (p < 0.0001), but did not differ significantly within time interval since surgery. **Conclusions:** Choice for CPM was only associated with improved QOL in the breast satisfaction domain and did not impact psychosocial, physical and sexual well-being after adjustment for other factors known to influence QOL. Such PRO data are important to consider when counseling women contemplating CPM as part of their breast cancer treatment.

9555 Poster Session (Board #214), Sat, 1:15 PM-4:45 PM

Relationship between physician-adjudicated adverse events (AE) and patient-reported health-related quality of life (HRQoL) in a phase II clinical trial of patients (pts) with metastatic uveal melanoma (UM). *First Author: Thomas Michael Atkinson, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Clinical trials typically use physician-adjudicated AE assessment with the Common Terminology Criteria for Adverse Events (CTCAE) for decision-making. Since the capture of patient-reported HRQoL data is becoming more frequent, we compared CTCAE and HRQoL ratings for pts treated on one clinical trial to explore how this information may inform clinical trial conduct. **Methods:** Data from a phase II trial of pts with metastatic UM (Carvajal et al. JAMA. 2014) were analyzed. Pts were randomized to receive Selumetinib (sel), an oral MEK inhibitor (n = 50), or chemotherapy (n = 51); 19 pts received sel without randomization. Those randomized to chemotherapy could receive sel at disease progression. Pts reported HRQoL via the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) at baseline, after 1 month and end of treatment (EOT; n = 118). Independent samples *t*-tests were used to compare mean FACT-M scores between sel, chemotherapy and crossover pts. Pearson correlations were calculated to determine the association between mean FACT-M scores and whether a patient had their dose reduced due to AEs. **Results:** 94% (median age = 62; 44% female) had a physician-adjudicated CTCAE grade > 0 for at least one treatment-associated AE of diarrhea, edema, nausea, rash, or vomiting. 20% of these pts had dosage reductions. 38 pts from the chemotherapy group progressed and received sel. Mean FACT-M scores did not significantly differ ($p > 0.05$) across sel, chemotherapy or crossover groups at each of the three time points. There were no significant correlations between dose reduction status and FACT-M scores (r = 0.07, -0.01 and 0.03 for baseline, 1 month and EOT). **Conclusions:** Despite the high rate of physician-adjudicated AEs, patient-reported HRQoL was not impacted by treatment. HRQoL did not differ in the subgroup of pts who received dosage reductions due to AEs, indicating that the patient may be willing to tolerate that level of AEs and continue the current dosage (if medically appropriate). More research is needed to determine how to best integrate HRQoL data into clinical trial conduct. Clinical trial information: NCT01143402.

9556 Poster Session (Board #215), Sat, 1:15 PM-4:45 PM

Change in second-hand smoke exposure after a lung and head and neck cancer diagnosis and subsequent patient smoking cessation. *First Author: Lawson Eng, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Exposure to second-hand smoke (SHS) after a cancer diagnosis is associated with continued smoking in lung and head and neck (HN) cancer patients (PMID: 24419133, 23765604). We evaluated whether complete reduction/cessation of SHS exposure around and after a diagnosis of lung or HN cancer is associated with smoking cessation in the cancer patient. **Methods:** Lung and HN cancer patients from Princess Margaret Cancer Centre (2006-12) completed questionnaires at diagnosis and follow-up (median 2 years apart) that assessed smoking history and SHS exposures (cohort design). These cancers were chosen because these patients had the highest rates of smoking at the time of diagnosis. Multivariate logistic regression analysis evaluated the association of cessation of SHS exposure after a diagnosis of cancer with subsequent smoking cessation, adjusted for significant covariates. A cross-sectional study (2014) of 90 lung and HNC smoking patients assessed consistency in associations. **Results:** For the cohort, 261/731 lung and 145/450 HN cancer patients smoked at diagnosis; subsequent overall quit rates were 69% and 50% respectively. 91% of lung and 94% of HN cancer patients were exposed to SHS at diagnosis while only 40% (lung) and 62% (HN) were exposed at follow-up. Cessation of SHS exposure was associated with smoking cessation in lung (aOR = 4.76, 95% CI [2.56-9.09], $P< 0.001$), HN (aOR = 5.00 [1.61-14.29], $P< 0.001$), and in both cancers combined (aOR = 5.00 [3.03-8.33], $P< 0.001$). The cross-sectional study had a similar trend for cessation of SHS with smoking cessation, but a lower magnitude of association (OR = 2.73, $P= 0.09$). However, when asked directly, only 13% of patients quit smoking with another individual. **Conclusions:** Cessation of SHS exposure was a frequent occurrence around cancer patients. This cessation of SHS exposure is significantly associated with smoking cessation in lung and HN cancer patients. However, few patients quit smoking at the same time as their friends, family or household. Changing the environment around cancer survivors to reduce SHS exposure and encouraging households/friends to quit smoking may both improve cessation rates in cancer patients.

9557 Poster Session (Board #216), Sat, 1:15 PM-4:45 PM

Psychological distress during hospitalization for hematopoietic stem cell transplantation to predict lower quality of life and high post-traumatic stress disorder symptoms at 6 months post-transplant. *First Author: Harry VanDusen, Massachusetts General Hospital, Boston, MA*

Background: Patients undergoinghematopoietic stem cell transplantation (HCT) experience a steep deterioration in quality of life (QOL) and mood during hospitalization for HCT. The impact of this deterioration on patients' long-term QOL and post-traumatic stress disorder (PTSD) symptoms is unknown. **Methods:** We conducted a prospective longitudinal study of patients hospitalized for HCT. At baseline (day-6), day+1, day+8, and 6 months post-HCT, we assessed QOL (Functional Assessment of Cancer Therapy-Bone Marrow Transplantation [FACT-BMT]) and mood (Hospital Anxiety and Depression Scale [HADS]). We used the PTSD Checklist to assess for PTSD symptoms at 6 months. We used multivariable linear regression models to identify predictors of QOL and PTSD symptoms at 6 months post-HCT. **Results:** We enrolled 97% (90/93) of consecutively eligible patients undergoing autologous (n = 30), myeloablative allogeneic (n = 30), or reduced intensity allogeneic (n = 30) HCT. Overall, patients' QOL at 6 months (mean FACT-BMT: 110, 95%CI [104-116]) recovered to baseline pre-transplant values (mean FACT-BMT: 110, 95% CI [107-115]). At 6 months, 28.4% of participants met provisional diagnostic criteria for PTSD. In multivariable regression analyses, depression and anxiety symptoms during hospitalization for HCT predicted impaired QOL (HADS-depression β = -1.8, P = 0.04; HADS-anxiety β = -1.7, P = 0.05) and PTSD symptoms (HADS-depression β = 1.0, p = 0.05; HADS-anxiety 1.2, P = 0.01) at 6 months post-HCT. **Conclusions:** While patients' overall QOL at 6 months post-HCT returned to baseline values, a significant proportion met provisional diagnostic criteria for PTSD. Psychological distress during hospitalization for HCT was the most important predictor of long-term QOL impairment and PTSD symptoms. Future studies should evaluate whether interventions to reduce psychological distress during HCT may improve long-term QOL and reduce the risk of PTSD symptoms.

9558 Poster Session (Board #217), Sat, 1:15 PM-4:45 PM

Treatment-adherence beliefs and behaviors in patients with chronic myeloid leukemia (CML). *First Author: Joanne S. Buzaglo, Cancer Support Community, Research and Training Institute, Philadelphia, PA*

Background: Tyrosine kinase inhibitors (TKIs) are effective yet chronic indefinite therapy for CML. Strong links exist between TKI adherence and optimal outcomes. Suboptimal adherence is common, affecting clinical outcomes and healthcare costs. Nonadherent patients underrecognize missed-dose impact on response. This study explored the link between belief and behavior vis-à-vis adherence. **Methods:** With outreach to online, national and community networks from 10/13 to 7/14, 484 CML patients enrolled in the Cancer Experience Registry: CML, an online project to advance CML knowledge and patient engagement. 393 (81%) completed a web-based survey including questions assessing accord with 2 statements (1) It is okay to miss a dose of my CML medicine every now and then, and (2) I need to take every dose of my CML medicine or it might not work; as well, participants reported missed TKI-dose frequency. Logistic regression was used to study the beliefs-behavior link among US patients taking TKIs (n = 318). Regression models were adjusted for age, gender, time since diagnosis, and TKI cost/month. **Results:** Responders averaged 56 y of age and 5.2 y from diagnosis; the majority was female (68%) and white (90%). 23% reported TKI spending of ≥ $100/month; 19% spent $50-100; 58% spent < $50. Regarding statement 1 and missed TKI dose, 5% strongly agreed, 28% agreed, 24% disagreed, 43% strongly disagreed. For statement 2, 6% strongly disagreed they needed to take every dose, 17% disagreed, 32% agreed, 45% strongly agreed. 19% reported missing a dose at least monthly. Compared to those who disagreed/strongly disagreed, those who agreed/strongly with statement 1 were significantly more likely to have reported missing doses monthly (OR = 7.04; 95% CI = 3.65, 13.57). Also, those who disagreed/strongly disagreed with statement 2 vs. those who agreed/strongly agreed were significantly more likely to have reported missing doses at least once monthly (OR = 5.36; 95% CI = 2.81, 10.2). **Conclusions:** CML patients' medication beliefs were strongly associated with suboptimal adherence. The results suggest multifaceted patient education would impact adherence, outcome and survival. The relationship between beliefs and drug adherence merits further study.

9559 Poster Session (Board #218), Sat, 1:15 PM-4:45 PM

Association between oncologists' dispositional affect and depressive symptoms in their patients with metastatic cancer. *First Author: William F. Pirl, Massachusetts General Hospital, Brookline, MA*

Background: While caring for patients with metastatic cancer can be emotional, relationships between the emotions of oncologists and their patients have not been examined. As patients and oncologists read emotional cues in encounters, emotions of one or both may impact the other. We explored associations between dispositional affect, tendencies to emotionally respond to situations in certain ways, in oncologists and depressive symptoms in their patients with newly diagnosed metastatic lung and gastrointestinal (GI) cancers. **Methods:** As part of an ongoing trial of early palliative care, participants were assessed at baseline for depressive symptoms (Patient Health Questionnaire-9, PHQ9) within 8 weeks of diagnosis with metastatic lung and GI cancers. Oncologists providing care for these patients completed the Positive and Negative Affect Scale (PANAS), a validated measure of dispositional affect with positive and negative dimensions. Associations between patient depressive symptoms and positive and negative dispositional affect were tested with rank sum tests and multivariate linear regressions. **Results:** Sixteen of the 18 oncologists with patients in the trial completed the PANAS. Among 323 participants with baseline assessments, 277 (86%) had oncologists who completed the PANAS. Mean age = 64.6, 129 (46%) were female, 159 (57%) had GI and 118 (43%) lung cancer, and mean PHQ9 score = 6.5. Positive and negative dispositional affect were not associated with oncologists' sex, years from training, hours in clinic, and cancer specialization. Patient depressive symptoms were significantly higher if their oncologists reported greater negative dispositional affect (p = .04). The relationship remained significant adjusting for patient age, sex, cancer type, ECOG PS, smoking, and number of oncology visits (β = .13, t= 2.1, p = .04). PHQ9 scores were not associated with oncologists' positive dispositional affect. **Conclusions:** Depressive symptoms in patients with metastatic lung and GI cancers appear to be associated with their oncologists' negative dispositional affect. Determining the direction of the association may lead to new ways of improving patients and/or oncologists moods.

9560 Poster Session (Board #219), Sat, 1:15 PM-4:45 PM

Mild cognitive impairment (MCI) in chemotherapy-treated breast cancer survivors. *First Author: Abigail Gifford, Wake Forest University, School of Medicine, Winston-Salem, NC*

Background: This abstract uses the National Institute on Aging/Alzheimer's (NIA/AA) criteria to report the prevalence of MCI in a cohort of breast cancer survivors who received adjuvant chemotherapy. **Methods:** Wake Forest NCORP Research Base prospective clinical trial 97211 enrolled 62 breast cancer survivors 1-5 year post adjuvant chemotherapy between 7/12-1/13 to test the efficacy of donepezil on cognitive function. Subjective cognitive complaints were evaluated with the Functional Assessment of Cancer Therapy-Cognition. Objective cognitive performance was assessed using standardized/validated neurocognitive measures. Functional status was evaluated with the FACIT-Fatigue. The NIA/AA MCI criteria as applied to this study were: 1) self-reported cognitive complaints (FACT-Cog score $<$ 63), 2) significant cognitive impairment ($\geq$ 1.5 SD below the normative mean) in $\geq$ 1 cognitive domains, 3) preservation of functional independence, and 4) not demented. MCI was further classified as amnestic/non-amnestic and single-/multi-domain. **Results:** Sixty women between the ages of 39 and 79 completed the objective cognitive battery. At baseline, 80% demonstrated significant cognitive impairment. 58% met the NIA/AA criteria for MCI (of those, 26% were amnestic/multi-domain, 9% amnestic/single-domain, 17% non-amnestic/multi domain, 49% non-amnestic single domain MCI). 22% had significant cognitive impairment with loss of functional independence. **Conclusions:** In this cohort, 58% met the accepted NIA/AA criteria for MCI. The American Heart and Stroke Associations have adopted these criteria to define Vascular Cognitive Impairment (VCI), vascular MCI (vMCI), and Vascular Dementia (VaD). Similarly, standard criteria to characterize cognitive dysfunction should be applied in the cancer setting. We propose implementing the terms Cancer Cognitive Impairment (CCI), cancer MCI (cMCI), and Cancer Dementia (CaD) to describe the spectrum of cancer- and cancer-treatment associated cognitive impairment.

9561 Poster Session (Board #220), Sat, 1:15 PM-4:45 PM

The price of survival: Breast cancer patient preferences about fertility. *First Author: Amirrtha Srikanthan, Princess Margaret Hospital, Toronto, Ontario, Canada*

Background: Fertility is a concern for young women diagnosed with breast cancer. Concerns have been raised that women may avoid effective anti-cancer treatments to have an opportunity to preserve fertility. Here, we explore patient preferences for chemotherapy and whether women are willing to trade-off survival benefit to maintain fertility. **Methods:** During a standardized interview, outcomes associated with adjuvant chemotherapy and 5 years of tamoxifen (CT) or 5 years of tamoxifen alone (ET) were described to breast cancer survivors diagnosed within the past 2 years. A threshold task was performed in which each participant participated in two scenarios: (1) 10% absolute survival benefit from treatment and (2) 25% absolute survival benefit from treatment. Each participant was asked which treatment option they preferred when baseline fertility post treatment was reduced initially to 50% for both scenarios (i.e. 50% chance of conceiving naturally). If the participant indicated CT, post-treatment fertility was systematically reduced further until the participant's preference changed from CT to ET. This threshold point represented the reduction in fertility the participant would accept before they would trade-off CT benefit. Descriptive statistics were used to characterize participants. Demographic factors (age, marital status, number of children at diagnosis and education) associated with willingness to trade-off survival benefit were evaluated with logistic regression. **Results:** Analysis comprised 50 women with a median age of 34.5 years (range 25-39 years). 39 (78%) women had completed university education. 34 (68%) and 45 (90%) women in scenario 1 and 2, respectively, were willing to trade-off all fertility (i.e. reduce fertility to 0% chance of conceiving naturally) in order to undertake CT and maintain survival benefits. 8 (16%) and 3 (6%) women in scenario 1 and 2, respectively, chose to not pursue CT at all in order to maintain fertility. Regression analysis did not identify any variables that were predictive of the participants' preferences. **Conclusions:** Most young women with breast cancer are not willing to trade-off survival benefits of adjuvant therapy to maintain fertility.

9562 Poster Session (Board #221), Sat, 1:15 PM-4:45 PM

Young adult cancer survivors' expectations of physicians for reproductive and sexual health care. *First Author: Ying Wang, University of British Columbia, Vancouver, BC, Canada*

Background: Infertility and sexual dysfunction resulting from cancer therapies are often inadequately addressed by physicians, even though these issues cause significant distress for young adult cancer patients. In this study, we examined survivors' expectations of their physicians regarding reproductive and sexual healthcare, and identified factors associated with these expectations. **Methods**: We surveyed patients aged 20 to 39 years who were diagnosed with solid tumors, evaluated at any 1 of 5 regional cancer centers in British Columbia, and alive at 2 or more years after their original diagnosis. Using multivariate regression models, we explored the relationships between patient expectations of their care and the factors associated with these expectations, while controlling for potential confounders. **Results:** With a survey response rate of 56%, a total of 447 patients were analyzed: median age was 35 years (IQR 31-38), 30% were men, 89% had ECOG 0, and 75% reported being in a relationship. Tumor sites included breast (222; 50%), testicular (126; 28%), gynecological (76; 17%), and colorectal (23; 5%). A significant proportion of patients received chemotherapy (65%) and radiation (47%) that posed the potential for infertility or sexual dysfunction. While the majority of patients expected their primary care providers (PCPs) and cancer specialists (CS) to share responsibility in addressing fertility and sexual health concerns (85% and 74%, respectively), a fair number of patients preferred that reproductive health be fully managed by CS (16% vs. 10%, $p = 0.005$) and that sexual health be mainly addressed by PCPs (31% vs. 21%, $p < 0.0001$). In regression analyses, prior discussions about infertility or sexual dysfunction conducted by oncologists increased the patient's expectations of their ongoing involvement in these areas ($p = 0.047$ and $p = 0.006$, respectively). **Conclusions:** Young adult cancer survivors have specific expectations about physician roles in addressing reproductive and sexual health. As discussions can modify patient expectations, early and appropriate engagement of both CS and PCPs in such conversations can facilitate the development of effective shared-care models of follow-up.

9563 Poster Session (Board #222), Sat, 1:15 PM-4:45 PM

Second primary malignancies in hepatocellular carcinoma: A population-based study. *First Author: Binay Kumar Shah, St. Joseph Regional Medical Center, Lewiston, ID*

Background: A second primary malignancy is a serious long term complication in cancer survivors. The aim of this study was to evaluate the risk of second primary malignancies in patients with hepatocellular carcinoma. **Methods:** We selected all adult patients ($\geq$ 18 years) diagnosed with hepatocellular carcinoma (HCC) from National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 13 database. We calculated risk of second primary malignancies in the hepatocellular cancer patients using multiple primary standardized incidence ratio (MP-SIR) session of SEER* stat software. Second primary malignancy (SPM) was defined as a metachronous malignancy diagnosed six months or more after an index HCC. **Results:** A total of 15,296 patients with a diagnosis of primary hepatocellular carcinoma were reported in the SEER* 13 registry during January 1992 to December 2011. A total of 446(2.83%) developed 466 SPMs with an observed/expected (O/E) ratio of 1.07 (95% confidence interval = 0.97-1.17, $p < 0.164$) and absolute risk of 7.17 per 10,000 populations persons. The median age at diagnosis of HCC was 66.16 years (range: 42.33 - 95.5 years), and median follow up duration of patients was 28 months (range: 6 months – 18.5 years). Significant excess risk was observed for oral and pharyngeal cancers (N = 29, O/E = 1.73, confidence interval = 1.73-3.7, $P < 0.01$), stomach cancer (N = 20, O/E = 1.78, confidence interval = 1.09-2.75, $P < 0.02$), hepatobiliary cancer (N = 43, O/E = 2.71, confidence interval = 1.96-3.66, $P < 0.002$), lung and bronchial cancer (N = 82,O/E = 1.33,confidence interval = 1.05-1.65,$P < 0.01$),and hematological malignancies (N = 54,O/E = 1.52,confidence interval = 1.14-1.98, $P < 0.005$). Risk of head and neck cancer, thyroid, Kaposi sarcoma and hematologic malignancies was increased within the first two years of after diagnosis of HCC. Risk of lung and hepatobiliary cancers was increased after two years of latency. **Conclusions:** There is significant increased risk of second primary malignancies in adult patients with HCC compared to general population. Risk of specific SPM depends on latency.

9564 Poster Session (Board #223), Sat, 1:15 PM-4:45 PM

A comparison of the natural history of oxaliplatin- and paclitaxel-induced neuropathy (NCCTG N08C1, N08CB/Alliance). *First Author: Kathryn Jean Ruddy, Mayo Clinic, Rochester, MN*

Background: We examined the similarities and differences of paclitaxel and oxaliplatin neuropathy symptoms. **Methods:** Acute and chronic neuropathy data were pooled from pts receiving 1) adjuvant oxaliplatin (FOLFOX) in protocol N08CB (346 pts) and 2) weekly paclitaxel or every 3 week paclitaxel/carboplatin in protocol N08C1 (179 pts). In both trials, pts completed daily questionnaires for several days after each chemotherapy dose (to evaluate acute neuropathy) and the EORTC CIPN20 tool before each chemotherapy dose and at 1, 3, 6, and 12 months post treatment (to assess chronic neuropathy). **Results:** The acute neuropathy symptoms from both drugs peaked on day 3, with acute symptoms experienced in cycle 1 predicting occurrence in the subsequent cycles. Paclitaxel-induced acute symptoms were similar in intensity in each cycle and largely resolved between cycles. Oxaliplatin-induced acute symptoms were about half as severe in the first cycle, as in later cycles, and did not resolve completely between cycles. For chronic neuropathy, both drugs caused a predominantly sensory neuropathy (numbness and tingling much more common than pain). Oxaliplatin-induced chronic neuropathy worsened after the completion of treatment (coasting phenomenon) and began to improve 3 months post-treatment. In contrast, paclitaxel-induced chronic neuropathy typically began improving immediately after chemotherapy cessation. During treatment, paclitaxel numbness/tingling symptoms were similar in hands and feet; with oxaliplatin, hands were affected more than feet. After treatment completion, hand symptoms improved faster than foot symptoms, for both drugs, so that foot symptoms were more problematic one year later. Both paclitaxel- and oxaliplatin-induced acute neurotoxicity appeared to predict the severity of chronic neuropathy (more prominently with oxaliplatin). **Conclusions:** Patients receiving paclitaxel or oxaliplatin should be counseled regarding these patterns of neuropathy symptoms and recovery. Understanding the similarities and differences between these neuropathy syndromes should provide insight into the underlying pathophysiology and help find preventative treatment approaches. Clinical trial information: N08C1/N08CB.

9565 Poster Session (Board #224), Sat, 1:15 PM-4:45 PM

Effects of strength training intervention in breast cancer survivors. *First Author: Joanne Monterroso, University of Vermont Medical Center, Burlington, VT*

Background: Oncology rehabilitation programs provide a potential avenue for improving fitness, function and quality of life. Few studies evaluate how cancer survivors respond to such interventions. Objectives: 1. Compare upper and lower body strength of breast cancer survivors (BCS) to normative data. 2. Evaluate changes in strength after 12 weeks of resistance training. **Methods:** Participants received a 12 week, 2x per week aerobic and resistance training intervention as part of the University of Vermont Medical Center oncology rehabilitation program. One repetition maximum strength testing of upper and lower body strength was completed before and after the intervention. Strength was compared to American College of Sports Medicine normative values. Pre/post comparisons were completed for participants attending $\geq$ 25% of sessions. Breast cancer survivors were included in the analysis. **Results:** Baseline assessments were obtained on 130 participants, 91 completed at least 25% of exercise sessions. 90% completed $\geq$ 66% of training sessions. Over 90% of BCS had upper extremity strength at $< 25^{th}$ percentile and over 74% had lower extremity strength at $< 20^{th}$ percentile. Upper and lower extremity strength remained $< 25^{th}$percentile for the majority of participants after the intervention but percentiles improved 8 and 16 points respectively. For participants completing the intervention, upper extremity strength increased from 57 $\pm$ 31lbs to 70 $\pm$ 31lbs ($p < 0.001$). Lower extremity strength increased from 125 $\pm$ 45 to 154 42lbs ($p < 0.001$). There were no significant differences in strength improvement between BCS who did and did not receive chemotherapy. The upper extremity strength of women age $\leq$ 55 improved to a greater degree than women over age 55 ($p = 0.01$). **Conclusions:** Breast cancer survivors entering an oncology rehabilitation program have markedly lower upper and lower body strength compared to normative data. Strength training intervention results in improved strength in this population but strength remains below expected. The benefit of resistance training was seen regardless of age or previous exposure to chemotherapy. Opportunities for breast cancer survivors to participate in resistance training interventions should be encouraged.

9566 Poster Session (Board #225), Sat, 1:15 PM-4:45 PM

A randomized controlled trial (RCT) of a supportive care package (SurvivorCare, SC) for survivors of colorectal cancer (CRC). *First Author: Michael Jefford, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia*

Background: Colorectal cancer (CRC) and its treatments can cause distressing short and long-term side effects as well as significant functional consequences. Current models of follow-up do not adequately address these issues. We conducted a multi-center RCT of an innovative program (SurvivorCare (SC)); designed to have a beneficial effect on psychological distress, supportive care needs (SCN) and quality of life (QOL). **Methods:** At the end of active treatment for stage I-III CRC, eligible patients ($\geq$ 18 years, adequate English) were randomized 1:1 to usual care (UC) or to UC+SC. SC comprised educational materials, needs assessment, an individualized survivorship care plan, nurse-led end-of-treatment session and three follow up (FU) phone calls. Distress (BSI-18), SCN (CaSUN) and QOL (EORTC QLQ-C30, CR29) were assessed at baseline, 2 (FU1) and 6 (FU2) months. Primary hypothesis: SC would have a beneficial effect on distress at FU1. Secondary hypotheses: SC would have a beneficial effect on (1) SCN and QOL at FU1; and (2) distress, SCN and QOL at FU2. 15 items assessed satisfaction with survivorship care. Sample size of 180 (90/arm) was based on 80% power, 2-sided alpha of 0.05, to detect a between groups difference of 3.6 on BSI-18 at FU1. Outcome analysis was ITT. **Results:** Of 221 patients randomized (111 UC, 110 SC), 4 were ineligible and 1 lost to FU, leaving 110 UC, 106 SC. Groups appeared well balanced. Median age was 64, 52% male, 56% colon, 35% rectal cancer, 10% overlap. Stage I 7%, II 22%, III 71%. Intervention fidelity was acceptable. Baseline distress and QOL were similar to population norms. Between groups differences in distress at FU1 (primary outcome), distress at FU2 and SCN and QOL at FU1 and FU2 were small and non-significant. SC patients were more satisfied with survivorship care than UC patients (significant differences on 10 of 15 items). **Conclusions:** The addition of SC to UC did not have a beneficial effect on distress, SCN or QOL outcomes but SC patients were more satisfied with survivorship care. Clinical trial information: ACTRN12610000207011.

9567 Poster Session (Board #226), Sat, 1:15 PM-4:45 PM

Results of the ASCO survey of cancer survivorship research: Summary and implications. *First Author: Paul B. Jacobsen, Moffitt Cancer Center, Tampa, FL*

Background: The ASCO Survivorship Committee identified the need to better understand the current scope of cancer survivorship research in order to identify future research priorities. A committee workgroup recently completed a survey addressing this issue. **Methods:** A survey was conducted previously to assess engagement of ASCO members in survivorship care and research. Of 14,098 members contacted, 2,899 (20.6%) responded. Of this group, 679 self-identified as (co-)principal investigator of a survivorship-related study. A follow-up survey was subsequently sent to these members and to 838 individuals at NCI-designated Cancer Centers identified through other means as being engaged in cancer survivorship research. The survey asked respondents to describe study characteristics (e.g., design, participants, outcomes) for each IRB-approved cancer survivorship-related study for which they served as (co-)principal investigator. **Results:** 609 of 1517 recipients (46%) responded and reported on 714 studies. 65% of studies were observational (OBS) and 35% were interventional (INT). OBS studies mostly focused on lymphoid/hematopoietic (26%), breast (19%), and more than one (13%) cancer, while INT studies mostly focused on breast (34%), more than one (15%) and lymphoid/hematopoietic cancers (10%). Age at time of diagnosis/treatment was most commonly 40-64 years for OBS (26%) and INT (32%) studies and least commonly $>$ 65 years for OBS studies (24%) and $<$ 21 years for INT studies (11%). Time since diagnosis was most commonly $<$ 2 and least commonly $>$ 5 years for OBS (39%, 29%) and INT (48%, 15%) studies. The most common primary/secondary objectives were physical (32%), quality of life (27%) and health behavior (22%) outcomes for OBS studies and quality of life (34%), physical (31%) and health behavior (25%) outcomes for INT studies; the least common objective was patterns and quality of care for OBS (2%) and INT ($<$ 1%) studies. **Conclusions:** Findings identify key gaps in current research that should be prioritized for future study. These include the relative lack of research on several common cancers (e.g., colorectal, prostate, and lung), on long-term and older ($>$ 65) and younger ($<$ 21) survivors, and on survivorship care delivery and quality.

9568 Poster Session (Board #227), Sat, 1:15 PM-4:45 PM

Household secondhand smoke exposure among community-dwelling cancer survivors in the United States. *First Author: Oladimeji Akinboro, Montefiore New Rochelle Hospital, New Rochelle, NY*

Background: There is little extant data regarding the prevalence of secondhand smoke exposure among cancer survivors. We sought to estimate the prevalence of household secondhand smoke exposure, as well as its association with active smoking, among community-dwelling cancer survivors in the United States (US). **Methods:** We abstracted data from the US National Health and Nutrition Examination Survey for 1,742 community dwelling adults, aged 20 years and older sampled nationwide from 2005-2012, who had survived at least 2 years since their first cancer diagnosis. We calculated the age-adjusted population-based prevalence of household secondhand smoke exposure. Multivariable logistic regression was utilized in examining the association between household secondhand smoke exposure and survivors' smoking status while controlling for age, gender, race, marital status, education, income, having a regular source of routine care, and cancer site. Survey weights were applied in estimating the population-based prevalence rates, odds ratios (OR), and 95% confidence intervals (CI). **Results:** The age-adjusted prevalence of household smoke exposure among adult cancer survivors was 22.4% (CI 17.5-27.3%). Among those exposed, 76% were females (CI 69.8-81.8%), 82% were active smokers (CI 75.5-87.1%), and 55% had survived a smoking-related cancer (CI 45.3-64.5%). Higher odds of household secondhand smoke exposure were seen with: i) active smoking (OR = 92.56, CI 46.31-185.01); ii) former smoking (OR = 2.07, CI 1.27-3.39); iii) living below federal poverty level (OR = 2.66, CI 1.29-5.48); and iv) cancers caused by active smoking (OR = 2.62, CI 1.70-4.04). **Conclusions:** The risk of household secondhand smoke exposure was highest among actively smoking adult cancer survivors but the direction of causality between active smoking and household secondhand smoking among cancer survivors cannot be inferred from this cross-sectional analysis. Nonetheless, these findings suggest that smoking cessation programs for smoking cancer patients may also need to target the households of such patients. Prospective studies are needed to parse out the effects of secondhand smoking on long-term outcomes among adult cancer survivors.

9569 Poster Session (Board #228), Sat, 1:15 PM-4:45 PM

Racial differences in upper extremity function for breast cancer survivors. *First Author: Lorraine Tiera Dean, University of Pennsylvania, Philadelphia, PA*

Background: Over 35% of breast cancer survivors face upper extremity disability due to breast cancer surgery, radiation, or chemotherapy to the upper body region. Race may be a key patient characteristic in disability, given that race is associated with factors related to poor functioning, including weight gain after breast cancer, disease stage, and treatment type. Studies of breast cancer survivors have not explicitly evaluated the associations between race and upper extremity disability using validated tools. **Methods:** The Quick-DASH (Disabilities of the Arm, Shoulder and Hand) is an 11-item self-administered questionnaire that has been validated for breast cancer survivors to assess global arm function over the past 7 days. The cross-sectional analysis assessed whether or not Black or White women had greater upper extremity disability, evidenced by higher Quick-DASH scores, in a population of 697 breast cancer survivors in the Wellness After Breast Cancer-II study. Linear regression estimated the relationship between race and Quick-DASH score, adjusting for demographics, body mass index (BMI), treatment type (lumpectomy, mastectomy, radiation, chemotherapy, and reconstruction), and other physical factors. **Results:** Black women had significantly higher BMI and age, were less likely to have had mastectomy, and had 7.7 points higher average Quick-DASH score than White ($p < 0.001$) women. After adjustment for demographics, BMI, treatment type, and other physical factors, Black women had an average 4.1-point (95% CI: 0.96-7.92) higher Quick-DASH score ($p = 0.01$) compared with White women. Mediation analysis suggested that BMI reduced the association between race and disability by 29.7%. **Conclusions:** Black women's Quick-DASH scores indicated clinically significant worse functioning, which were partially mediated by higher BMIs. Black patients may present in clinic with both worse functioning and higher BMI. Findings suggest that more research is needed to elucidate the relationship between race, BMI, and upper extremity disability, including determining additional factors beyond BMI that account for the relationship between race and disability.

9570 Poster Session (Board #229), Sat, 1:15 PM-4:45 PM

Comprehensive characterization of cisplatin-related hearing loss in U.S. and Canadian Testicular Cancer Survivors (TCS). *First Author: Heather E. Wheeler, Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL*

Background: Cisplatin is one of the most ototoxic drugs in use, causing permanent, bilateral sensorineural hearing loss in substantial numbers of patients, with many developing permanent tinnitus. Few studies, however, have systematically quantified the entire range of hearing loss (0.25-12 kHz) in patients given homogenous cisplatin-based chemotherapy using comprehensive audiometric methods and patient-reported outcomes. **Methods:** We performed detailed audiometry for 359 patients enrolled in an ongoing multi-center clinical study of TCS given cisplatin-based chemotherapy at centers in North America (NCI R01CA157823). Air conduction thresholds were measured at frequencies ranging from 0.25-12 kHz and bone conduction thresholds from 0.25-4 kHz in each ear. **Results:** Median age at evaluation was 39 years (range 20-63 years) with approximately 43% previously having seminomas and 57% nonseminomas. Over 90% of patients were white, while most (66%) had Stage II or III disease. Chemotherapy consisted largely of standardized regimens and doses, i.e., BEP X 3 (51%), EP X 4 (19%), slight modifications (27%) of either regimen, or VIP (3%). We identified 85.2% patients with hearing loss ($>$ 20 dB) at any frequency for either ear. Of these, 48.7% had conductive hearing loss and 39.2% showed evidence for noise-induced hearing loss for either ear. For each patient, we compared the area under the air conduction audiogram curve (AUC) (mean of both ears) to the expected AUC for this age group. Patients with AUCs greater than respective normal-aging AUCs were considered to have cisplatin-induced hearing loss (32.6%). Measured on a Likert scale from 0-3, 39.2% and 29.8% reported tinnitus and hearing loss (score 1+), respectively. The audiogram AUC correlated strongly with both self-reported tinnitus ($R = 0.31$, $P = 1.1e-08$) and self-reported hearing loss ($R = 0.36$, $P = 7.0e-11$). **Conclusions:** Cisplatin-induced ototoxic phenotypes affect 29-40% of TCS in this North American study. Future analytic investigations will focus on genetic and mechanistic investigations to facilitate the development of predictive, management and preventive efforts for ototoxicity in high-risk patients.

9571 Poster Session (Board #230), Sat, 1:15 PM-4:45 PM

TOPS: A randomised controlled trial of a multidisciplinary intervention for post-cancer fatigue. *First Author: Carolina Sandler, University of New South Wales, NSW Cancer Survivors Centre, Sydney, Australia*

Background: Cancer related fatigue is prevalent and disabling. When persistent and unexplained, it is termed post-cancer fatigue (PCF). Cognitive behavioural therapy (CBT) and graded exercise therapy (GET) may improve symptoms and functional outcomes. **Methods:** A randomised control trial - Treatment of Post-cancer fatigue Study (TOPS) assigned patients to an education intervention, or a 12 week integrated CBT and GET intervention supervised by an exercise physiologist and clinical psychologist. Three months post treatment for breast or colon cancer, eligible patients had: clinically-significant fatigue; no co-morbid medical or psychiatric conditions which explained the fatigue; and no clinical or laboratory evidence of cancer recurrence. The education arm included a single visit with clinicians describing the principles of CBT/GET and an education booklet. The CBT/GET arm included fortnightly individually tailored consultations. The primary outcome measures were self-reported fatigue (SOMA subscale - SPHERE questionnaire; (0 – 12)) and functional status (Role limitation due to physical health problems – SF36 questionnaire (0 – 100)) comparing baseline, end treatment (12 weeks), and follow-up (24 weeks). Outcomes were analysed by 'clinically-significant' improvement designated *a priori* as $\geq$ one standard deviation improvement in fatigue scores. **Results:** 160 patients were screened, and 34% ($n = 55$) were eligible. The primary reason for ineligibility was sub-threshold fatigue ($n = 61$, 58%). 46 patients were enrolled, including 43 women (94%), with a mean age of 51 years. Intention-to-treat analysis showed that fatigue severity improved in all enrolled subjects improved from a mean of 5.2 ± 3.1 to 3.9 ± 2.8 at week 12, suggesting a natural history of improvement. Clinically significant improvement was observed in 7 of 22 subjects in the intervention group compared to 2 of 24 in the education group ($p < 0.05$, $\chi 2$). These subjects had a mean improvement in functional status (SF-36) of 25.4 ± 33.3 compared to non-responders (6.0 ± 15.3, $p < 0.01$, t test). **Conclusions:** Combined CBT/GET improves fatigue and functional outcomes for a subset of patients with PCF. Further studies to improve the response rate are warranted. Clinical trial information: ACTRN12611000338965.

9572 Poster Session (Board #231), Sat, 1:15 PM-4:45 PM

Phase II feasibility study of a physical activity and dietary change weight loss intervention in a subset analysis of breast cancer survivors (SWOG S1008). *First Author: Heather Greenlee, Columbia University Medical Center, New York, NY*

Background: Weight loss among overweight and obese breast and colorectal cancer survivors is hypothesized to be associated with improved disease-free survival. Phase III trials are needed to test effective and implementable weight loss interventions in breast and colorectal cancer survivors. **Methods:** We conducted a feasibility study of a 12-month community-situated physical activity and telephone-based dietary change weight loss intervention in female breast and colorectal cancer survivors. We report the primary outcomes for the breast cancer (BC) cohort. Sedentary postmenopausal women with prior Stage I-III BC and BMI $\geq$ 25 kg/m^2 were eligible. Primary objectives were to assess feasibility and weight loss at 12 months. Target accrual was 25 BC participants (ppts). Ppts were assigned a telephone counselor and given a 12-month membership to a local Curves fitness center, which offers a 30-minute circuit-based exercise program. Ppts were counseled 14 times over 12 months and were instructed to exercise 150 minutes/week, walk 10,000 steps/day, and decrease caloric intake by 500 kcal/day. The intervention would be considered feasible if full accrual was met within 10 months, $\geq$ 68% of ppts met minimum goals for exercise (attend $\geq$ 2 exercise sessions/week for $\geq$ 36 weeks) and diet (reduce caloric intake by $\geq$ 100 kcal/day and/or increase fruit/vegetable intake by $\geq$ 1 serving/day) (adherence), and $\geq$ 68% of ppts provided anthropometric measures at 12 months (retention). **Results:** Among 25 evaluable ppts, median age was 57.3 years with median BMI 37.5 kg/m^2 (range 27.7-54.6), 64% Stage I, and median 2.1 years from diagnosis. Accrual occurred in 10 months, 80% of ppts provided anthropometric measures at 12 months, 96% of ppts met the diet goal, and 28% of ppts met the exercise goal. Thus feasibility goals were met, with the exception of exercise adherence as defined a priori. At 12 months, average weight loss was 7.6% (95% CI -3.9%, 19.2%) with median weight loss of 7.1%. **Conclusions:** It is feasible to recruit and retain BC survivors in a multicenter weight loss trial using dietary change plus physical activity to achieve clinically meaningful weight loss over 12 months. Clinical trial information: NCT01453452.

9573 Poster Session (Board #232), Sat, 1:15 PM-4:45 PM

Survival outcome of cancer patients with pericardial effusions. *First Author: Danielle El Haddad, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pericardial effusion is a common finding in cancer patients and can be related to the tumor infiltration of the pericardial space or can be secondary to cancer therapy (chemotherapy or chest radiation). Impact of mechanism of effusions (malignant versus non-malignant effusions) on cancer patient's outcome is not well defined. Our aim was to evaluate survival outcome of these patients based on the presence or absence of malignant cells in their effusions. **Methods:** A total of 212 cancer patients who underwent pericardiocentesis for pericardial effusion between November 2009 and October 2014 at UT/MDACC were included in the study. **Results:** Overall median survival of the cohort was 143 days (95% CI, 95 to 221) and 130 (61%) patients died within 2 years from the procedure. The two most common solid tumors associated with pericardial effusions were lung [61(29%)] and breast [22 (10%)] cancer. In a multivariable analysis model, age $>$ 65y, lung cancer, platelet counts $<$ 20.000, and the presence of malignant cells in the pericardial fluid were independently associated with poor prognosis. Malignant pericardial effusion was pathologically confirmed in 37 (61%) patients with lung cancer and 16 (73%) patients with breast cancer. Lung cancer patients with proven malignant effusions had a significantly shorter overall median survival compared to those with non-malignant effusions (24 patients or 39% of lung cancer patients) (1-year survival estimate of 16.2% (95% CI, 5.6%-31.6%) versus 49.0% (95% CI, 26.7%-68.0%) respectively. Log-rank test p-value = 0.0101). Such finding was not observed in the subgroups of breast cancer patients (1-year survival estimate of 40.2% (95% CI, 16.0%-63.6%) versus 40.0% (95% CI, 5.2%-75.3%) respectively. Log-rank test p-value = 0.4170). **Conclusions:** The presence of proven malignant cells in pericardial effusion appears to significantly impact survival outcome of patients with lung cancer, but not those with breast cancer.

9574 Poster Session (Board #233), Sat, 1:15 PM-4:45 PM

Cancer survivors' experiences with insurance, employment and personal finances: Results from a multi-site study. *First Author: Larissa Nekhlyudov, Harvard Medical School and Harvard Vanguard Medical Associates, Boston, MA*

Background: Prior studies have shown that cancer has significant implications for survivors' insurance coverage, employment and financial status. We aimed to examine whether these implications may differ for survivors depending on the type of cancer experienced. **Methods:** Using the Cancer Survivorship Supplement of the Medical Expenditures Panel Survey, we surveyed a cohort of cancer survivors enrolled in one of three health plans in Massachusetts, Colorado and Washington State in 2013. We stratified our sample to include those diagnosed with breast, colorectal, lung, and prostate cancers and melanoma between 2003 and 2008. **Results:** Of the 615 eligible respondents, 590 reported having had insurance at some point during/since their diagnosis, and few of those reported coverage barriers in seeing doctors or facilities of their choice. About half (n = 334) of the respondents reported having been employed at some time during/since their cancer; of those, approximately 25% reported they or their spouses remained at their jobs due to concerns about losing insurance, with no significant differences observed by cancer type. Further, of those employed, the majority (63%) reported making changes in their jobs (e.g., taking extended time off, working part time) or career choices due to cancer. These changes were more common among those with lung (80%), colorectal (74%) and breast cancer (68%) compared to prostate cancer (53%) and melanoma (38%) ($p < 0.001$). Additionally, 42% reported that cancer interfered with their physical and/or mental tasks at work or reduced their productivity. These limitations were again more common among lung, colorectal, and breast cancer survivors ($p = 0.001$). Of all survivors, approximately 15% reported financial hardships due to their cancer; most often among those with lung (23%) and breast cancer (22%) ($p < 0.001$). **Conclusions:** In this insured population, few experienced restrictions with their cancer care coverage, though maintaining coverage often drove employment decision making. Having cancer was associated with significant impact on survivors' work schedules, job productivity and personal finances, particularly among those with lung, breast and colorectal cancer.

9575 Poster Session (Board #234), Sat, 1:15 PM-4:45 PM

Distress in cancer survivors attending a multidisciplinary survivorship clinic. *First Author: Tara Beth Sanft, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Distress is defined as an unpleasant emotional experience that may interfere with the ability to cope with cancer or its treatment. Distress screening is recommended during transitions including survivorship. We describe distress in cancer survivors before and after participation in a multidisciplinary survivorship clinic. **Methods:** All patients participating in the Yale Adult Survivorship Clinic were asked to complete the National Comprehensive Cancer Network Distress Thermometer (DT) immediately before and after a visit. Survivors ranked distress from 0 (none) to 10 (extreme) and indicated associated problems from a 39-item list. A score $\geq$ 4 was considered clinically significant. Survivors were seen by an MD/APRN, social worker, registered dietitian and physical therapist. Survivors received individual counseling on topics including survivorship care, diet and exercise, and coping. All were offered a follow-up visit approximately 8 weeks later. Distress screening was repeated at the follow-up visit. Distress scores before and after each visit were compared using paired t-tests. **Results:** 377 survivors completed DTs before and after a survivorship clinic visit in 18 months. Survivors were mostly female (91%), white (77.2%), with a history of breast cancer (73%). The mean distress score prior to the initial visit was 4.82 (+/-2.82), and 2.45 (+/-2.15) after the visit (mean change -2.34, +/- 2.06, $p < 0.0001$). The top problems identified were worry (53%), fatigue (43%), and fears (30%). 191 survivors (51%) had clinically significant distress ($\geq$ 4) before the initial visit; however, only 74 (20%) reported significant distress after the visit ($p < 0.001$) Of survivors who returned for a follow-up visit (N = 107), avg distress score was 4.20+/-2.97 before and 1.86+/-2.01 after (mean change -2.42, +/- 2.50 $p < 0.0001$). At the follow-up, 49 (46%) had clinically significant distress before and 17 (16%) after ($p < 0.0001$). **Conclusions:** More than half of all survivors participating in a multidisciplinary survivorship clinic reported clinically significant distress. Distress scores were significantly lower after the visit. These results suggest participation in a survivorship clinic is an intervention for distress.

9576 Poster Session (Board #235), Sat, 1:15 PM-4:45 PM

Prevalence of hypogonadism in patients with previously treated germ cell tumors. *First Author: Trent James Miller, Indiana Univ, Indianapolis, IN*

Background: The vast majority of men with germ cell tumors (GCT) will be cured of their disease and may face long-term risks associated with survivorship. This may include hypogonadism (HG), which can be associated with depression, fatigue, and a lower quality of life (QOL). It is thus important to identify the prevalence of HG and correlation with symptoms in survivors of GCT, both in patients treated with platinum combination chemotherapy (PCC) as well as chemo-naïve patients. **Methods:** Patients treated with chemotherapy (Group 1) or with orchiectomy and/or other surgery or radiotherapy for GCT (Group 2), were 18-50 yrs of age, and not receiving supplemental testosterone at baseline were eligible. Total testosterone was measured at baseline and at 3, 6, and 12 mos. Either A.M. and P.M. lab draws were done depending upon time of patient follow-up. HG was defined as a serum total testosterone $<$ 300 ng/dl. Cancer diagnosis and treatment variables were obtained from medical records. Patients completed a validated QOL questionnaire at baseline, 3, and 6 mos. **Results:** We evaluated 172 patients treated for GCT. The overall prevalence of HG at baseline was 49.4% (95% CI 41.9-57.0). In Group 1 (N = 103), prevalence was 51.5% (95% CI 41.7-61.2). In Group 2 (N = 69), prevalence was 46.4 (95% CI 34.5-58.3). Overall prevalence of HG was not statistically different between the two groups (p = 0.5371). Within Group 1, there was no difference in prevalence of HG when patients were divided into those who received $<$ 3 cycles of PCC, 3 cycles of PCC, $>$ 3 cycles of PCC, or salvage chemo (p = 0.8131). Overall, compared to patients with testosterone $\geq$ 300, patients with baseline testosterone $<$ 300 reported worse perceived general health (p = 0.0003) and worse sleep quality (p = 0.0344), but no statistically significant difference in depression (p = 0.3131) or fatigue (p = 0.0622). **Conclusions:** The overall prevalence of HG is higher than would be expected in the general population. Testosterone levels are lower in the P.M., so the prevalence may have been artificially high due to P.M. as well as A.M. lab draws. There was no difference between the prevalence of HG between the two groups. HG can be a potential cause of medical and psychological distress if not recognized and treated.

9577 Poster Session (Board #236), Sat, 1:15 PM-4:45 PM

Self-efficacy through survivorship: Results from the LIVESTRONG Cancer Navigation Study. *First Author: Bree Hemingway, LIVESTRONG Foundation, Austin, TX*

Background: With more than 13.7 million cancer survivors in the U.S., two-thirds of whom will live beyond five years post-treatment, creating programs to support survivors can be challenging as their needs evolve through each stage of survivorship. LIVE**STRONG** Cancer Navigation (LCN) offers services designed to address survivors' needs at all stages of the cancer experience. Survivors experience new challenges and concerns when they transition from treatment to post-treatment care. We present the results of a LCN research study to describe how clients' self-efficacy (SE) and needs vary depending on their stage of survivorship. **Methods:** In 2012, researchers studied LCN to determine how well the program enables cancer survivors to manage their health and practical concerns. Participants (n = 1388) completed surveys at intake, two, and six weeks post-intake to measure quality of life outcomes including cancer-related concerns, SE and distress. The SE score is based on three items that assess the individual's confidence related to: emotional support; communication with their doctor; and making themselves feel better. Participants' needs were documented at intake and those who completed two or more surveys (63%) were included in the analytical sample (n = 874) and were categorized into three groups: in treatment (60.9%), $<$ 5 years post-treatment (24%) and 5+ years post-treatment (4.5%). **Results:** At all three time points, SE was lowest among individuals who finished treatment 5+ years ago. Significant differences in the mean number of needs were also found between participants at different stages of survivorship ($p<$ .003). Participants in treatment reported the most needs (6.6), followed by participants 5+ years post-treatment (6.3). Participants 5+ years post-treatment reported significantly higher cancer concern score than participants who had completed treatment $<$ 5 years ago. Additional outcomes will be shared. **Conclusions:** Findings suggest that SE decreases post-treatment. Understanding the various challenges and type of support survivors need at all stages of survivorship can inform service design in clinical and community-based settings that can continue to support clients into survivorship.

9578 Poster Session (Board #237), Sat, 1:15 PM-4:45 PM

Cardiac care after myocardial infarction in cancer survivors: A population-based study. *First Author: Kelvin K. Chan, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Cancer survivors (CS) may receive suboptimal non-cancer related care, such as lower rates of bypass surgery after myocardial infarction (MI) in the US. Secondary prevention (SP) after MI is an important aspect of survivorship care. We aim to examine the use of medications and interventions for SP after MI in CS vs. non-cancer patients (NCP). **Methods:** All acute MI patients (pts) hospitalized in Ontario between 1995 and 2012 were identified from the Canadian Institute of Health Information databases, and linked to the Ontario Cancer Registry to determine whether they were CS or NCP. Those who were diagnosed with cancer $<$ 1 year before their MI were excluded. The cohort was linked to other administrative databases to determine demographics, comorbidities, cardiac risk factors, hospital-based interventions and, for those over age 65, outpatient-based medication use. Propensity scores derived from baseline characteristics were used to create a 1:4 (CS:NCP) matched cohort. The use of medications and interventions within the first 90 days of MI, and medication adherence (measured by proportion of days covered (PDC) within the first year of MI) were compared between CS and NCP using matched analyses. **Results:** We identified 102,415 MI pts (CS = 20,483; NCP = 81,932) with 57% male and 86% $>$ age 65. Slightly fewer CS vs. NCP received angiograms (37.4% vs. 38.6%; p = 0.003) and percutaneous coronary interventions (17.0% vs. 17.8%; p = 0.01), but similar CS and NCP received bypass surgery (2.5% vs. 2.5%). For pts who were $>$ age 65 and active users of the public drug programs with MI $<$ 5 years after cancer diagnosis, fewer CS vs. NCP received ACEi/ARB (67.0% vs. 70.6%; p $<$ 0.001), statins (54.9% vs. 60.0%; p $<$ 0.001), and clopidogrel (27.8% vs. 33.8%; p $<$ 0.001), but the differences for those with MI $>$ 5 years after cancer diagnosis were much less (all interaction p $<$ 0.01). Similar CS and NCP received beta-blockers and nitrates. Both groups had similar degree of medication adherence, except for ACEi/ARB (PDC: 76.0% (CS) vs. 76.9% (NCP), p = 0.03). **Conclusions:** Slightly fewer CS than NCP received SP after MI, especially for those occurred within 5 years after cancer diagnosis. Further studies are needed to examine the outcome implications of this finding.

9579 Poster Session (Board #238), Sat, 1:15 PM-4:45 PM

Healthcare plan and provider ratings among cancer survivors. *First Author: Michael T. Halpern, University of Arizona Coll of Public Health, Tucson, AZ*

Background: Providing optimal healthcare for cancer survivors is important to address symptoms from cancer and cancer treatment, reduce risks of subsequent cancers, and improve quality of life. However, little is known about patient-level factors influencing ratings of healthcare plans or providers by survivors. **Methods:** This study used ratings provided by cancer survivors in the Consumer Assessment of Healthcare Providers and Systems (CAHPS) Medicare Survey linked to data from NCI's Surveillance, Epidemiology, and End Results (SEER) Program (SEER-CAHPS). CAHPS data on self-reported general and mental health status and three rating categories (overall care [OC], physician [MD], and healthcare plan [HP]) were linked to SEER data on patient sociodemographics and cancer characteristics. Medicare beneficiaries diagnosed with cancer in SEER regions 1997-2011 who participated in the CAHPS Medicare Survey at least one year after cancer diagnosis were included. The study included only individuals alive at least one year following CAHPS survey completion, age $>$66, and diagnosed with non-metastatic breast, colorectal, lung, or prostate cancer. **Results:** We identified 23,969 cancer survivors with linked SEER-CAHPS data. Higher self-rated general health was largely associated with higher ratings for OC, MD, and HP for all four included cancer types. However, other factors significantly associated with ratings tended to differ by both rating category and cancer type (see table). Time since diagnosis and type of Medicare plan (FFS vs. HMO) were not significantly associated with any ratings. **Conclusions:** Beyond self-rated general health, survivor characteristics predicting higher ratings varied substantially by cancer and rating type. These results suggest that the experience of care among cancer survivors is diverse and is significantly influenced by their cancer type. Efforts to improve care for cancer survivors will need to be tailored for each survivor group.

Significant (p<0.01) predictors of higher (+) or lower (-) CAHPS ratings.

	Breast			Colorectal			Lung			Prostate		
	OC	MD	HP	OC	MD	HP	OC	MD	HP	OC	MD	HP
Higher Mental Health		+	+			+	+			+		
Older Age	+		+			+						+
Asian	-											
Black					+							+
Hispanic			+			+						
College Graduate	-	-	-			-			-			-
Stage 2/3 at Dx	+	+		+								
Yrs Since Dx												
FFS healthplan												

9580 Poster Session (Board #239), Sat, 1:15 PM-4:45 PM

Using survivorship care plans (SCP) to improve cancer communication and care coordination. *First Author: Deborah Mayer, UNC Chapel Hill Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: There is a need for closer collaboration between oncologists and primary care providers (PCP) to improve survivorship care. However, PCPs often feel unprepared to manage survivor needs. We conducted a pilot study to evaluate SCP +/- a coordinated PCP visit effect on confidence in survivorship care for patients (pt) and PCP. **Methods:** Pts completed baseline measures and then received a SCP after completing curative treatment during a scheduled post-treatment visit; half were randomized to attend a PCP visit within 30 days to review the SCP. Pre-Post measures for pts and PCPs included Confidence in Survivorship Information (CSI), Assessment of Survivor Concerns (general and cancer worries), Expectations for Care, and Patient Activation Measure. Wilcoxon signed-rank and rank sum tests were used for comparisons. **Results:** Pts (n = 34) were male (65%), age 57 (29-73), Caucasian (82%), and married (79%). PCPs (N = 30) were male (50%), age 48 (26-67), Caucasian (83%) with 19.5 years in practice (range 2-39); 52% were in family medicine. Patient: After receipt of the SCP, all pts had improved knowledge about next steps ($p = 0.06$) and less contradictory information about care ($p < .0001$). CSI and concerns improved after SCP receipt ($p < 0.0001$). While no significant differences at baseline, SCP benefits were greater in highly activated patients (n = 26) who had more CSI ($p = 0.008$) and less concerns ($p = 0.007$) than lower activated patients (n = 8). The general worry score rose for the controls and decreased for the intervention group ($p = 0.05$). At follow-up, most patients (82%) discussed with their oncologist being followed by them for cancer but only 32% discussed this with their PCP. Provider: PCPs reported improved CSI ($p = 0.001$) after receiving the SCP. They agreed it was their role to provide non-cancer related health care but were less clear about cancer surveillance and screening. Only 30% had discussions with pts' other providers over who would follow cancer issues. **Conclusions:** SCP led to greater benefits for highly activated patients in CSI and concerns about cancer care; survivors who had a PCP visit after receiving the SCP had fewer worries than controls. PCP also had improved confidence in survivorship care after SCP receipt. Clinical trial information: UNC HENC LCCC 1325.

9581 Poster Session (Board #240), Sat, 1:15 PM-4:45 PM

Cancer patients' attitudes, knowledge, and preferences for smoking cessation (SC). *First Author: Lawson Eng, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Smoking tobacco by cancer patients can lead to poorer treatment outcomes, prognosis and quality of life. We evaluated ambulatory cancer patients' understanding of SC. **Methods:** 295 lung and head and neck cancer (HNC) patients (85% curative) at any point in their disease course were surveyed cross-sectionally about their knowledge on the effect of smoking on cancer treatment/prognosis and their interest/preferences towards SC. Multivariate logistic regression analyses identified predictors of knowledge gaps and interest in SC. **Results:** 52% of patients had HNC; 31% smoked at diagnosis, 35% were ex-smokers. Half of patients reported being unaware that continued smoking negatively impacts cancer surgery (48%), radiation (57%), chemotherapy (49%) and treatment efficacy (55%); some patients were unaware it impacted prognosis (38%) and second-primary risk (36%). This lack of knowledge was not associated with stage, specific treatments, or SC. Compared to HNC, lung cancer patients more likely believed that continued smoking negatively impacted surgery (aOR = 1.82, 95% CI[1.06-3.10]), efficacy (aOR = 2.10[1.26-3.50]), prognosis (aOR = 2.29[1.20-4.40]) and second-primaries (aOR = 2.02[1.05-3.89]). Receiving any recent (< 3 months) treatment was associated with believing that smoking negatively impacts treatment ($aOR_{radiation}$= 2.34[1.36-4.04], aOR_{chemo}= 1.73[1.05-3.44]). Although 75% felt a SC program would be beneficial and 67% felt it should be part of routine cancer care, only 43% of smokers at diagnosis wished to take part; mainly lung cancer patients (aOR = 5.14[1.79-14.80]) and early-stage cancer patients (aOR = 3.42[1.11-10.50]). 51% preferred discussing SC at their first visit, 52% through a smoking counsellor, and 93% preferred same-day programs with their clinic visits. 50% of patients uninterested in a SC program described wishing to quit on their own. **Conclusions:** Cancer patients undergoing treatment were more likely to feel that smoking can impact treatment; interventions during this time may improve SC rates. Compared to lung cancer, HNC patients were less aware of the impact of smoking on outcomes, and less interested in SC programs.

9582 Poster Session (Board #241), Sat, 1:15 PM-4:45 PM

Degradation of extracellular matrix measured in serum for predicting mortality risk in women diagnosed with cancer: The Prospective Epidemiologic Risk Factor (PERF I) study. *First Author: Nicholas Willumsen, University of Southern Denmark, Odense, Denmark*

Background: Extracellular matrix (ECM) turnover mediated by matrix metalloproteinase (MMP) has been speculated to be associated with cancer diagnosis and mortality. No tools have so far been able to quantify this. Degradation of ECM is part of the malignant changes that drives cancer. The most abundant ECM protein is type I collagen. MMP mediated degradation of type I collagen in serum can be quantified by the novel C1M ELISA assay. The aim of the current study was to investigate whether MMP mediated ECM degradation (C1M) was predictive of cancer mortality in a large prospective study. **Methods:** In the period 1999-2001, 5,856 women aged 60-85 participated in the Prospective Epidemiologic Risk Factor (PERF I) study. Demographics and serum samples were collected at time of enrollment. Cancer diagnoses, cause and time of death were obtained from Danish registries ultimo 2014. Serum C1M levels were assessed by ELISA and divided into quartiles (Q1-Q4). Hazard ratios (HR) for all-cause and cancer-specific mortality were determined by Cox-regression analysis and adjusted for common risk factors: age, smoking, alcohol intake, exercise and BMI. Women deceased >3 years after enrollment was excluded from analysis. **Results:** Within 3 years from PERF I enrollment subjects with high serum C1M levels at baseline showed significant increased mortality (see Table). The 3-year HR for all-cause mortality and cancer-specific mortality was >2 when comparing Q1 to Q4 for all women. Women diagnosed with cancer (n=1280) had an HR for all-cause mortality of >2.5 compared to cancer survivors. Adjusting for common confounders did not change significance. **Conclusions:** MMP-mediated degradation of the ECM was predictive of cancer mortality by 2.3 fold, and predicted for mortality for cancer patients with >2.5-fold within 3 years of follow-up.

Cohort	All		With cancer diagnosis
Mortality	All cause	Cancer specific	All cause
n, total	4408	4333	1280
n, death within 3 years from enrollment	187	112	112
HR (95% CI), C1M Q4 relative to Q1, p-value	2.08 (1.30-3.33), p=0.0024	2.31 (1.27-4.19), p=0.0064	2.59 (1.45-4.63), p=0.0014

9583 Poster Session (Board #242), Sat, 1:15 PM-4:45 PM

Outcomes and predictors of hospital mortality in metastatic cancer patients receiving life sustaining treatments (LSTs). *First Author: Kah Poh Loh, Baystate Medcl Ctr, Springfield, MA*

Background: Hospital mortality for patients with metastatic cancer is high, especially for those who receive LSTs. Information on predicting the probability of surviving the hospitalization will help patients and clinicians make an informed decision. **Methods:** We used the 2010 California Healthcare Cost and Utilization Project - State Inpatient Database to identify metastatic cancer patients (≥18 years). Using ICD-9-CM diagnosis codes, we limited the dataset to patients receiving LSTs (mechanical ventilation, tracheostomy, PEG tube, TPN and acute use of dialysis). We described characteristics and outcomes in patients who survived hospitalization and who did not. We used multivariate logistic regression models to identify predictors for hospital mortality. **Results:** We identified 9,438 admissions among metastatic cancer patients who received LSTs. Mean age (65 years) and gender distribution were similar in both groups. Hospital mortality was 33%. Of those who survived, 31% were discharged to acute or post-acute facilities. Other outcomes are listed below. Predictors of hospital mortality included non-white race, unscheduled admissions, infectious, cardiovascular and circulatory or pulmonary diagnosis (vs. cancer-related) and greater burden of comorbidities. Comorbidities including ESRD (OR 2.03, 95% CI 1.12-2.94) and liver disease (OR 1.94 95% CI 1.55-2.33) were significantly associated with hospital mortality. Compared to lung cancer, colorectal (OR 0.32, 95% CI 0.26-0.38) and GU (OR 0.58, 95% CI 0.46-0.70) cancers were less likely to die in the hospital. Admissions with DNR status were strongly associated with hospital mortality (OR 2.32, 95% CI 2.01-2.63). **Conclusions:** Patients with metastatic cancer who survived in the hospital had longer LOS and one-third of them were discharged to facilities. Predictors of hospital mortality include lung cancer, ESRD, liver disease, DNR status, higher co-morbidity score and an unscheduled admission.

Outcomes	Died (n=3055)	Alive (n=6273)	P-value
Comorbidity score[a]	3.1 (2.3)	2.5 (2.2)	<0.0001
Total charge per patient[b] ($100,000)	1.5 (2.1)	1.5 (1.9)	<0.01
Length of stay[a] (days)	13.4 (17.0)	15.5 (14.8)	<0.0001

a Mean (SD). b Median (IQR).

9584 Poster Session (Board #243), Sat, 1:15 PM-4:45 PM

Treatment-specific risks of second malignancy and cardiovascular disease in Hodgkin lymphoma survivors. *First Author: Simone de Vries, Department of Psychosocial Oncology and Epidemiology, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Hodgkin lymphoma (HL) survivors are at increased risk to develop late treatment-related complications, including second malignant neoplasms (SMNs) and cardiovascular disease (CVD). Research to date has focused on separate risk estimates and therefore, we aimed to assess the combined risk of developing SMN and/or CVD. **Methods:** Our multicenter cohort comprised 2,480 5-year HL survivors, treated before age 51 between 1965 and 1995. CVD endpoints (coronary heart disease [CHD], cardiomyopathy and congestive heart failure [HF], and valvular heart disease) were assessed through general practitioners. Data on SMN were derived from linkage with the Netherlands Cancer Registry. Standardized incidence ratios (SIRs) were estimated to compare SMN and CVD risk with the general population. Cumulative incidences of SMN and/or CVD were calculated with death from other causes as competing risk. Treatment-specific risks of developing SMN and/or CVD were quantified using Cox regression analysis. **Results:** After a median follow-up of 22 years, we identified 874 SMNs and 1368 CVDs. 1246 patients developed ≥ 1 major event, of whom 276 developed both SMN and CVD. HL survivors had a 5.2-fold increased SIR of any SMN (95%CI: 4.8-5.6), compared to the general population, corresponding to 141 excess cases/10,000 person-years. The SIRs of CHD and HF were 3.5 and 7.8, respectively (95%CI: 3.2-3.9 and 6.8-8.8), resulting in 83 and 60 excess cases/10,000 person-years. After 40 years, at a median attained age of 60 years, the cumulative incidence of SMN or CVD was 73.3% (95%CI: 70.6-75.7), whereas 22.5% (95%CI: 19.8-25.3) of patients had developed both events. Both supradiaphragmatic RT (Hazard Ratio [HR]: 2.6, 95%CI: 2.1-3.1) and anthracycline-containing CT (HR: 1.5, 95%CI: 1.3-1.7) independently increased the risk of SMN and/or CVD. Supradiaphragmatic RT was associated with a strongly increased (HR: 4.4, 95%CI: 2.6-7.7) risk of developing both SMN and CVD. **Conclusions:** HL survivors experience a high disease burden during follow-up, with the cumulative incidence of SMN and/or CVD rising to 73% after 40 years from initial treatment. Supradiaphragmatic RT most strongly increased this risk.

9585 Poster Session (Board #244), Sat, 1:15 PM-4:45 PM

Sexual morbidity and unmet needs among members of a metastatic breast cancer registry. *First Author: Joanne S. Buzaglo, Cancer Support Community, Research and Training Institute, Philadelphia, PA*

Background: An estimated 155,000 people are living with metastatic breast cancer (MBC) in the US. As the duration of survival increases, quality of life needs become more salient. Women treated for MBC often report adverse sexual effects, yet many surveys suggest that oncology providers rarely discuss sexual issues. Our objective was to study the impact of MBC on sexual morbidity. **Methods:** Since March 2013, we registered 909 people living with MBC to the Cancer Experience Registry: MBC, an online initiative designed to study the psychosocial impact of MBC. 599 registrants completed questions about sexual morbidity and a cancer-related distress screening tool, including a depression subscale. The sample was predominantly Caucasian (91%), well educated (69% had college degree), with a median age of 56 years. Median time since MBC diagnosis was 3 years. **Results:** Overall, 71% reported MBC negatively impacted their sexual life, and 50% reported sexual activity was a source of distress. Specifically, 80% reported they had no interest in sex, 76% reported vaginal dryness, 68% had pain during or after sex, 64% had difficulty having an orgasm, 71% felt anxious about having sex, and 64% did not enjoy sex. Having no interest in sex ($p = 0.014$), difficulty having an orgasm ($p = 0.020$), and feeling anxious about sex ($p = 0.002$) were significantly more common among those at risk for depression. Difficulty having an orgasm was more common among women concerned about body image ($p = 0.001$). More than half (59%) felt they could talk to a member of their health care team about sexual concerns, yet only 20% reported that a member of their health care team ever asked about sexuality. Only 17% sought treatment for sexual dysfunction, and 39% said they would never go to a mental health expert for sexual counseling even if it was free. **Conclusions:** MBC has a significant impact on sexual health. Patients report substantial sexual morbidity which is associated with symptoms of mood disorder. The direction of the association is unclear, and should be studied in prospective surveys. More efforts are needed in oncology settings to screen for sexual problems in people with MBC and make appropriate referrals for care. Research on effective treatment programs is also lacking.

9586 Poster Session (Board #245), Sat, 1:15 PM-4:45 PM

QOL at 3 years after diagnosis in aggressive lymphoma survivors. *First Author: Carrie A. Thompson, Mayo Clinic Rochester, Rochester, MN*

Background: Patients with aggressive lymphoma are potentially curable, but longer-term effects of treatment may adversely impact quality of life (QOL). We examined QOL scores at baseline enrollment and 3 year follow-up in survivors of aggressive lymphoma. **Methods:** Newly diagnosed lymphoma patients were prospectively enrolled within 9 months of diagnosis in the University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource (MER) and systematically followed. We measured baseline QOL at time of enrollment and at 3 years after diagnosis with the Functional Assessment of Cancer Therapy-General (FACT-G) scale. This scale measures well-being (WB) in 4 QOL domains—physical (PWB), social/family (SWB), emotional (EWB), functional (FWB)—along with a total FACT-G score (TOT). For this study, we defined "survivor" as alive at 3 year follow-up with no active disease or treatment within the previous year. **Results:** From 2002-2009, 1902 patients with aggressive lymphoma were prospectively enrolled. Of these, 477 completed QOL questionnaires at both baseline and 3 years and met the study definition of survivor. Median age at diagnosis was 62 years (range 18-87) and 58% were male. Distribution of NHL subtypes were 61% DLBCL, 12% mantle cell, 10% FL grade III, 9% T cell, and 8% other. Each FACT-G subscale was significantly higher than assessment at diagnosis with the exception of SWB, which was significantly lower (all $p < 0.0001$), with mean changes ranging from -1.8 (SWB) to 7.0 (TOT) points. After adjusting for baseline QOL, there was a modest association between older age and smaller change from baseline QOL for TOT ($p = 0.021$), PWB ($p = 0.012$), and FWB ($p = 0.001$); otherwise there were no other clinical associations between change in TOT from diagnosis to 3 years (all $p > 0.11$). Compared to the US general population, 3-year survivors have significantly higher QOL (EWB $p = 0.039$, all other $p < 0.0001$), while their QOL at baseline was similar to the general population for FWB ($p = 0.59$), higher for SWB ($p < 0.0001$) and TOT ($p = 0.0033$), and lower for PWB ($p = 0.0003$) and EWB ($p < 0.0001$). **Conclusions:** In survivors of aggressive lymphoma, QOL improves over time and is higher than the QOL for the US general population at 3 years post-diagnosis.

9587 Poster Session (Board #246), Sat, 1:15 PM-4:45 PM

Employment and quality of life (QOL) in human papillomavirus-related (HPV+) oropharynx cancer treated with definitive chemoradiation (CTRT). *First Author: Shrujal S. Baxi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: HPV+ oropharynx cancer affects younger patients and is often treated with CTRT. We aimed to assess the impact of CTRT on employment and QOL in these patients. **Methods:** We completed a cross-sectional survey of clinically cancer-free patients with advanced, M0, HPV+ oropharynx cancer ≥ 1 year from primary CTRT. We assessed employment status using study-specific items. QOL was measured using the EQ5D and EORTC QLQ-H&N35. We examined the association between sociodemographic and clinical factors on employment outcomes and QOL at time of survey. **Results:** 129 patients (mean 23 months. post-CTRT) completed the survey. Median age was 57 years (range 25-76); 91% were male; 56% had an ECOG functional status score of 0 (vs1/2); 83% had stage IVA disease. High-dose cisplatin was the most common chemotherapy (63%). 53% reported at least one problem on the EQ5D, most commonly pain (29%) and anxiety (24%). Despite high rates of dry mouth (88%), thick saliva (69%), coughing (54%) patients reported high overall QOL, as measured by EQ5D. At diagnosis, 107 (83%) patients were employed including 23/23, 58/65 and 26/41 of patients ages < 50, 50-59, and > 60 years, respectively ($p < 0.001$); 80% were professionals or managers. Employment at diagnosis did not vary by pretreatment functional status. During CTRT, 10 (9%) stopped working and did not return, 74 (69%) took time off but returned to work, 20 (19%) reduced responsibilities but kept working, and 3 (3%) continued working. Of the 74 patients who took time off, median time to return to work was 14 weeks (interquartile range 8-24 weeks). There was no significant difference in time off by chemotherapy type, ECOG status, or age. At time of survey, 75% were employed. Current employment status did not vary by overall QOL at the time of survey. **Conclusions:** Despite persistent effects of CTRT, survivors of HPV+ oropharynx cancer reported good QOL. CTRT interrupted employment in the majority of these patients, but most returned to work. More efforts are needed to evaluate the determinants of employment, return to work and the socioeconomic burden of CTRT in this working-age population.

9588 Poster Session (Board #247), Sat, 1:15 PM-4:45 PM

Young and strong: A randomized study to improve care for young women with breast cancer. *First Author: Ann H. Partridge, Dana-Farber Cancer Institute, Boston, MA*

Background: Research has revealed that needs of young women with breast cancer are not being met, particularly fertility concerns. A QOPI audit found rates of attention to fertility of < 30% in practices. We conducted a cluster-randomized study to determine the effect of an exportable education and support intervention for young women with breast cancer (YWI) and their oncologists. **Methods:** Sites were randomized 1:1 to YWI or a physical activity intervention (PAI) stratified by academic or community; up to 15 women age < 45 with newly diagnosed breast cancer were enrolled at each academic site, 10 at community sites. The primary endpoint was attention to fertility prior to systemic treatment by medical record review. Pts were surveyed at 3, 6, and 12 mos; physicians surveyed after enrolling their first patient. The study was designed to have 80% power to detect an improvement in attention from 10% with PAI to 38% with YWI using General Estimating Equations, two-sided alpha = 0.05. **Results:** 467 patients across 54 sites (14 academic, 40 community) enrolled between 7/2012 -12/2013. Median age at dx was 40yrs (range 22-45); patient characteristics did not vary by arm. Attention to fertility by 3 mos after enrollment was observed in 55% YWI pts and 58% on PAI (p = 0.88). Rates were strongly correlated with age (p < 0.0001), highest in pts < 30 (100% YWI, 94% PAI) vs. 30-40 (68% YWI, 59% PAI) vs. 40-45 (42% YWI, 52% PAI) although interaction testing age x intervention was not significant (p = 0.12). At 3 mos, pts rated YWI/PAI as valuable in educating them (64% YWI, 63% PAI). Of responding providers (145/171, 85%), most reported YWI/PAI educated providers (55% YWI/51% PAI) and pts (79% YWI, 77% PAI), and improved care (79% YWI, 60% PAI). **Conclusions:** This study failed to show improvement in attention to fertility with YWI vs. PAI. Rates were high in both arms, especially in women < 40 and the study had limited power to detect an age-dependent effect. Pts and providers valued both interventions. This work serves as a novel model to educate and support patients and providers to improve care. Clinical trial information: NCT01647607.

9589 Poster Session (Board #248), Sat, 1:15 PM-4:45 PM

A feasibility study of an electronic interface between Internet-based survivorship care plans and electronic medical records (EMR)/tumor registries. *First Author: Christine Hill-Kayser, University of Pennsylvania, Philadelphia, PA*

Background: SCP are recommended for all cancer survivors by the Institute of Medicine and Commission on Cancer (CoC). Barriers to implementation include time/ resource limitations, survivor access, and concerns about accurate treatment summary information. This study was performed to evaluate the feasibility of interface development between an SCP and an EMR and cancer registry. **Methods:** An information technology (IT) application was developed to extract data from the EMR in use at Penn Medicine (EPIC), as well as from the registry at Baptist Memorial Hospital in Memphis, a community hospital utilizing the CoC Rapid Quality Reporting System (RQRS). Data were transferred via XML tunnel to auto-populate an Internet-based tool for creation of SCP (LIVESTRONG Care Plan) that had been previously used for creation of more than 35,000 plans and available at www.oncolink.org / www.livestrongcareplan.org. **Results:** Design phase involved IT staff at Penn Medicine, RQRS, and OncoLink. Data (demographics, surgeries, chemotherapy drugs, radiation site) were extracted from EMR/RQRS, de-identified, and tunneled to the OncoLink platform, without transfer of PHI. Care plans were created and linked to EMR/registry via global unique identifiers; after auto-population and creation, SCP were tunneled back to the EMR to become part of the medical record, with the entire process occupying less than one minute. During clinical testing at the EMR site, SCP were created by nurse practitioners during scheduled clinic visits. Overall, 147 survivors were screened, 146 eligible, and 89 received SCP. Of these, 60 received breast cancer SCP, 27 colorectal SCP, and 2 both. Survivors were 85% women, 58% Caucasian, median age 56y (24-81y). **Conclusions:** This is a feasible and rapid solution for the auto-population of SCP with EMR and/or registries, taking less than 1 minute to complete. It represents a future methodology through which widespread implementation of SCP may be undertaken. Future directions include further clinical testing, as well as assessment of provider perceived usefulness, ease of use, and integration into routine clinical care.

9590 Poster Session (Board #249), Sat, 1:15 PM-4:45 PM

Failure to follow directions for prescription medications to save money among cancer survivors. *First Author: Ahmedin Jemal, American Cancer Society, Atlanta, GA*

Background: To examine the patterns of not following prescription medication due to financial reasons among nonelderly and elderly cancer survivors in the US. **Methods:** The 2011 to 2013 National Health Interview Survey data was used to identity recently diagnosed (≤ 1 year; n = 639) and previously diagnosed (1 year; n = 8,292) cancer survivors, and individuals without a cancer history (n = 93,058). Survey questions about not following prescription medication asked whether a participant took the following measures to save money: 1) skipped medication doses; 2) took less medicine; 3) delayed filing a prescription; 4) asked doctor for lower cost medication; 5) bought prescription drugs from another country; and 6) used alternative therapies. All analyses were stratified by age (nonelderly: 18-64; elderly: 65+). Multivariable logistic regressions were fitted to estimate the adjusted percentage of individuals reporting not following prescription medication controlling for age, sex, race/ethnicity, marital status, education, number of comorbidities, health insurance, and geographic region. **Results:** Previously diagnosed cancer survivors were more likely to report not following prescription medication in order to save money compared to individuals without a cancer history, primarily among nonelderly cancer survivors (28.4% vs 22.8%), i.e. skipping medication doses (8.6% vs 6.7%), took less medicine (9.3% vs 7.0%), delayed filing a prescription (11.7% vs. 8.8%), asked for lower cost medicine (22.5% vs 17.2%), bought prescription drugs from another country (2.5% vs 1.9%), and used alternative therapies (6.3% vs 5.0%) to save money (all p < .05). In contrast, all recently diagnosed cancer survivors were not statistically different from individuals without a cancer history in terms of not following prescription medication due to financial reasons. **Conclusions:** Compared to nonelderly individuals with no history of cancer, nonelderly long time cancer survivors were less likely to follow their prescription medication as needed in order to save money.

9591 Poster Session (Board #250), Sat, 1:15 PM-4:45 PM

Prediction models of smoking cessation in lung and head and neck cancer patients: Role of second-hand smoke (SHS) exposure. *First Author: Geoffrey Liu, Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Some cancer survivorship programs incorporate components of healthy lifestyle behavior modification. We evaluated the role that various clinical variables and smoking habits play in predicting which cancer survivors are more likely to quit smoking. Such knowledge may help with resource allocation within these programs. **Methods:** We focused on lung cancer (LC) and head and neck cancer (HNC) patients as these have the highest active smoking rates among all cancer sites at Princess Margaret Cancer Centre. Patients from 2006-12 completed questionnaires at diagnosis (baseline) and follow-up (median 2 years apart) that assessed smoking status. Baseline clinical and demographic information was obtained. Multivariate logistic regression analysis evaluated the association of smoking and clinical variables at diagnosis to subsequent smoking cessation. Predictive models were assessed for their discriminatory capabilities (concordance-index or area under the curve, AUC). **Results:** In this cohort, 261/731 LC and 145/450 HNC patients smoked at diagnosis; subsequent overall quit rates were 69% and 50% respectively. Univariate factors associated with smoking cessation included having LC (p = 0.001), being married (p = 0.02), having at least completed secondary school (p = 0.049), having less cumulative smoking (pack-years; p = 0.004), and having adequate social support (p = 0.009). In multivariate modeling, fewer pack-years, having LC and being married remained significant and this predictive model was associated with moderate predictive ability (AUC 0.68 [95% CI: 0.62-0.73]. However, the addition of either SHS household exposure (AUC 0.76 [0.71-0.81]) or spousal smoking (AUC 0.77 [0.71-0.82]) further improved the predictive model. The addition of SHS variables in other exploratory predictive models of smoking cessation improved those models in a similar manner. Similar improvements in prediction were seen in subgroup analysis of LC and HNC. **Conclusions:** SHS exposure significantly improves the predictive abilities to determine which patients who smoked at their cancer diagnosis would subsequently quit. Cessation programs may benefit from allocating resources accordingly.

9592 Poster Session (Board #251), Sat, 1:15 PM-4:45 PM

Sexual and marital dysfunction in women with gynecologic cancer: A multi-institutional, cross-sectional trial. *First Author: Saketh Guntupalli, University of Colorado Anschutz, Aurora, CO*

Background: Sexual dysfunction is a serious issue for women with gynecologic cancer. This study examines sexual function following cancer treatment and its impact on marital relationships. **Methods:** A multi-institutional study of women with gynecologic cancer was conducted with a 181item survey of instruments to assess sexual/marital dysfunction. Sexual dysfunction was measured by change in the Female Sexual Function Index (FSFI). A significant decline in sexual function was determined to be 7.6 point decrease using a Reliable Change Index Statistic (RCIS). Marital relationships were assessed using Intimate Bond Measure (IBM). Standard statistical analyses were used. **Results:** A total of 290 women were enrolled. Cancer diagnoses included uterine/endometrial (41%), ovarian (37%) cervical/other (22%). Treatments included surgery (92%), chemotherapy (62%), and radiation (30%). Among all women, sexual function declined from a score of 23.2±11.2 prior to diagnosis to 15.2±10.2 after treatment ($P<$ 0.001) and sexual activity decreased from 6.1±6.8 to 2.6±4.9 times/month following treatment ($P<$ 0.001). Sexual dysfunction after treatment was associated with younger age (51.8±12.2 to 57.3±12.1, $P=$ 0.004), being premenopausal (27% vs 13.5%, OR 2.38, 95%CI 1.23-4.71), chemotherapy (69.8% v 51.9%, OR 2.05, 95%CI 1.10-3.84), and being in a committed relationship (97.3% vs 82.7%, OR 7.43, 95%CI 1.67-33.11). IBM scores, relationship length, surgery and radiation therapies, cancer site diagnosis/stage and race were not associated with sexual dysfunction. Women with sexual dysfunction reported decreased sexual activity (Δ5.3±4.8 vs Δ2.1±3.8, $P<$ 0.001) and increased relationship counseling, 13.7% vs 4.9%, (OR 3.11, 95%CI 1.02-9.53) compared to those with no impairment. **Conclusions:** Women with gynecologic cancer are at significant risk for sexual dysfunction. Young, premenopausal women, chemotherapy, and women in committed relationships are at particularly risk for these issues. Patients with sexual dysfunction reported greater decline in sexual activity and sought counseling following treatment. Practitioners should address these issues and engage patients during treatment.

9593 Poster Session (Board #252), Sat, 1:15 PM-4:45 PM

National data on sorafenib therapy adherence for veterans with hepatocellular carcinoma. *First Author: Sheetal Malhotra, North Central Bronx Hospital, Bronx, NY*

Background: Medication adherence can help improve disease progression and survival. One way to improve adherence is to facilitate ease of administration, i.e., oral vs. intravenous. Our study of veterans with hepatocellular cancer (HCC) on Sorafenib therapy aimed to assess the factors that affect adherence and overall survival. **Methods:** A retrospective analysis of national level data from 2007 to 2013 collected by 120 VA medical centers across the country on diagnosing and treating patients with cancer was used for the study. Data on age at diagnosis, gender, race, marital status, comorbidities concurrent medication use, days from diagnosis to treatment, days medication was supplied for, and medication refills were obtained. Chemotherapy adherence was calculated from the medication supply and refill information. Survival till time of death or endpoint was also calculated. Data were analyzed through descriptive analysis, Chi Square tests, t-tests, Pearson correlations and Regression analysis to assess factors related to adherence and survival as well as differences in adherence and survival. **Results:** In our study, about 2,778 were prescribed Sorafenib. Most veterans were males (99%) with a mean age of 62 years. Of these, 2006 (72%) were adherent to the treatment in some way. Adherence was associated significantly with ethnicity ($P < 0.001$). Those adherent to their therapy were older at time of diagnosis compared to those who were not adherent (62.4 years vs. 61.4 years, $t = 3.041$, $P < 0.01$). There were no significant associations with marital status, gender, or presence of comorbidities. Increased adherence percentage was negatively related to cost of treatment ($r = -0.14$, $P < 0.001$) and positively related to overall survival ($r = 0.353$, $P < 0.001$). The number of concurrent medications (OR 0.969, 95% CI = 0.95- 0.99, $P < 0.01$) and total number of treatment days were (OR 0.997, 95% CI = 0.997- 0.998, $P < 0.001$) significantly related to chemotherapy adherence. In regression analysis, overall survival was also related to total treatment days ($r^2 = 0.503$, $P < 0.001$). **Conclusions:** Understanding and targeting factors that affect chemotherapy adherence can affect disease outcomes, including survival.

9594 Poster Session (Board #253), Sat, 1:15 PM-4:45 PM

A phase II randomized, double-blind, placebo-controlled study to evaluate naldemedine for the treatment of opioid-induced constipation (OIC) in patients with cancer pain. *First Author: Narikazu Boku, St Marianna University School of Medicine, Kawasaki, Japan*

Background: While opioid analgesics play a central role in managing cancer pain, opioid-induced constipation (OIC) is one of the most common side effects. Naldemedine is a novel peripherally-acting μ-opioid receptor antagonist (PAMORA) being developed to treat OIC. **Methods:** This study assessed naldemedine doses of 0.1, 0.2, or 0.4 mg once-daily (QD) for 2 weeks in cancer patients with OIC. Eligibility criteria included: regular opioid use for $\geq$ 2 weeks, $\leq$ 5 spontaneous bowel movements (SBMs) during a 14-day screening period despite laxative use. The primary endpoint was the change from baseline in frequency of SBM/week during the 2-week treatment period. The SBM responder rate, defined as $\geq$ 3 SBMs/week and an increase from baseline of $\geq$ 1 SBM/week, was a secondary endpoint. Safety assessments included adverse events (AEs), Clinical Opiate Withdrawal Scale (COWS) questionnaire and 11-point Numerical Rating Scale (NRS) pain questionnaire. Patients scored bowel movement (BM) consistency using the Bristol Stool Scale; BMs with a score of 7 were to be reported as AEs of diarrhea. The primary analysis was conducted using ANCOVA with frequency of SBM/week at baseline as a covariate. The planned total sample size was 212 (53 per group) to ensure at least 80% power in the two-sample t-test with a level of significance of 0.05 (two-sided). **Results:** A total of 227 patients were randomized to one of three naldemedine doses or placebo (PBO). The least-squares mean of change from baseline in frequency of SBM/week was 1.50 for PBO, 3.43 for 0.1 mg ($P = 0.0465$), 4.75 for 0.2 mg ($P = 0.0007$), and 7.29 for 0.4 mg ($P < 0.0001$). All three groups demonstrated a significantly higher SBM responder rate vs. PBO. The most common AE was diarrhea (25.0%, 26.8%, 39.7% and 51.8% in PBO, 0.1, 0.2, 0.4 mg groups, respectively). Most AEs of diarrhea were mild. No clinically meaningful changes in NRS scores or COWS scores were observed. **Conclusions:** In this study naldemedine was effective and generally well tolerated in patients with cancer pain with OIC. Based on its efficacy and safety profile, 0.2 mg QD was selected as the dose for phase 3 studies. (Clinical trial information: JapicCTI-111510) Clinical trial information: JapicCTI-111510.

9595 Poster Session (Board #254), Sat, 1:15 PM-4:45 PM

Can pregabalin prevent paclitaxel-associated neuropathy?: A pilot trial. *First Author: Shivani S. Shinde, Mayo Clinic, Rochester, MN*

Background: Paclitaxel, a commonly used chemotherapeutic drug, can cause an acute pain syndrome (P-APS), considered to be an acute form of neuropathy, and chronic chemotherapy-induced peripheral neuropathy (CIPN). There are no good means to prevent and/or treat these prominent clinical problems. The purpose of this randomized, placebo-controlled, double-blinded pilot study was to obtain pilot data to support or refute the utility of pregabalin for the prevention of P-APS and CIPN, based on anecdotal reports suggesting that gabapentinoids were helpful in this setting. **Methods:** Patients scheduled to receive adjuvant weekly paclitaxel (80 mg/m2/dose) were randomized to receive pregabalin 75mg or a placebo, twice daily, starting on the first night of chemotherapy and continuing during the 12 weeks of chemotherapy. Patients completed the EORTC QLQ-CIPN20 questionnaire at baseline, prior to each dose of paclitaxel, and monthly for 6 months post treatment. Patients completed an acute pain syndrome questionnaire daily, for 6 days after each dose of paclitaxel. The primary endpoint was to determine the effect of pregabalin on the maximum of the worst acute pain scores for the week following paclitaxel administration for cycle 1. Secondary endpoints included the effect of pregabalin on paclitaxel-induced peripheral neuropathy and pregabalin-associated toxicities. **Results:** 46 patients were randomized; data regarding the acute pain syndrome and CIPN are presented in the Table. There were no differences in pain score or evidence of toxicity differences between the two study arms. **Conclusions:** The results of this pilot trial do not support that pregabalin is helpful for preventing P-APS or paclitaxel CIPN. Clinical trial information: NCT01637077.

P-APS (Pain score over 6 days following initiation of paclitaxel; higher scores are worse)

	Placebo (N = 22)	Pregabalin (N = 19)	p-value
Worse pain: Mean (SD)	3.2 (3)	2.6 (2.5)	0.56
Average pain: Mean (SD)	2.2 (2.6)	2.6 (2.2)	0.48
EORTC CIPN20 Sensory Neuropathy (higher scores represent fewer symptoms)			
	Placebo (N = 22)	**Pregabalin (N = 19)**	**p-value**
Mean (SD)	84.5 (16.7)	88.4 (12.5)	0.46
Median (Range)	90.7 (36.5-100)	91.9 (56.5-100)	

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9596 Poster Session (Board #255), Sat, 1:15 PM-4:45 PM

Predictors of hand-foot syndrome (HFS) in randomised double-blind, placebo-controlled trial of pyridoxine for prevention of capecitabine induced HFS. *First Author: Yoon Sim Yap, National Cancer Centre Singapore, Division of Medical Oncology, Singapore, Singapore*

Background: Hand-foot syndrome (HFS)is a common side effect of capecitabine, although East Asian patients appear to have better tolerability. **Methods:** This study aimed to evaluate the incidence of grade ≥ 2 HFS in patients receiving pyridoxine versus placebo (primary objective), compare the time to onset of grade ≥ 2 HFS, and identify biomarkers predictive of HFS, including baseline folate and vitamin B12 levels, plus genetic polymorphisms (secondary objectives). Patients starting capecitabine single-agent chemotherapy for breast, colorectal and other cancers in National Cancer Centre Singapore were randomized to receive concurrent pyridoxine (200mg) or placebo daily for a maximum of 8 cycles of capecitabine, with stratification by gender and use in adjuvant/neoadjuvant versus palliative setting. Patients were withdrawn from the study upon development of grade ≥ 2 HFS or cessation of capecitabine. **Results:** The trial was terminated before reaching the original target of 296 patients due to slow accrual. Grade ≥ 2 HFS occurred in 33 of 105 patients (31.4%, 95% CI: 22.6% - 40.3%) receiving pyridoxine compared to 39 of 103 patients (37.9%, 95% CI: 28.5% - 47.2%) receiving placebo (p = 0.329). The median starting dose of capecitabine was 1000mg/m^2 (range 793-1250 mg/m^2) bid in the pyridoxine arm, and 1011mg/m^2 (range 845-1250 mg/m^2) bid in the placebo arm (p = 0.667). The median time to onset of grade ≥ 2 HFS was not reached in patients on pyridoxine, compared to 174 days in patients on placebo (p = 0.677). On multivariate analysis, baseline serum folate (odds ratio 1.27 for every increase of 5nmol/l; 95% CI: 1.10-1.47; p = .001) was associated with increased risk of grade ≥ 2 HFS. Pyridoxine did not significantly decrease the risk compared to placebo (odds ratio 0.50; 95% CI: 0.24-1.03; p = 0.061). Initial dose intensity and baseline red cell folate were associated with increased risk of grade ≥ 2 HFS on univariate, not multivariate analysis. Genotyping with Zhonghua SNP arrays is in progress. **Conclusions:** Pyridoxine did not significantly prevent or delay the onset of grade ≥ 2 HFS. Serum folate was a significant predictor of HFS. Clinical trial information: NCT00486213.

9597 Poster Session (Board #256), Sat, 1:15 PM-4:45 PM

Should all antiemetic guidelines recommend adding a NK_1 receptor antagonist (NK_1RA) in patients (pts) receiving carboplatin (carbo)? Efficacy evaluation of NEPA, a fixed combination of the NK_1RA, netupitant, and palonosetron. *First Author: Karin Jordan, University of Halle, Halle, Germany*

Background: Controversy continues whether a NK1RA should be added to a 5HT3RA + dexamethasone (DEX) in pts receiving carbo, with inconsistent guideline recommendations by NCCN, ASCO, and MASCC/ESMO. It is routine to use a NK1RA for pts receiving cisplatin where a 12%-20% benefit is seen. A subset analysis in 192 pts receiving carbo in a 2009 randomized trial (Rapoport, Supp Care Cancer) indicated a 14% benefit in pts receiving a NK1RA as part of triple antiemetic therapy (no emesis rate: 84%, 95% CI 77-91% versus 70%, 95% CI 59-79% with 2 drugs, p < 0.02). Similar results were seen in other trials. We undertook this post-hoc subset analysis of pts receiving carbo as part of a NEPA Phase 3 trial to determine if NEPA would show a consistent complete response (CR: no emesis/rescue) rate and to examine nausea control. **Methods:** 196 chemotherapy-naïve pts randomized to NEPA + DEX (n = 145) or aprepitant (APR) + PALO + DEX (n = 51) received carbo in cycle 1. CR and no significant nausea (NSN: score ≤25 on 100mm visual analog scale) rates were calculated for all pts and by gender / age for NEPA pts over multiple cycles. **Results:** The overall (0-120h) CR rates for cycles 1-4 were similar for NEPA (80%, 91%, 92%, and 93%) and APR (82%, 88%, 88%, and 90%). Cycle 1-4 NSN rates were also similar (NEPA 84-96%; APR 82-90%). In the NEPA pts, 54% had lung cancer and 21% ovarian; cycle 1 overall CR rates were 77% / 77%, respectively. NEPA results by risk groups are in the Table. **Conclusions:** This subset analysis of pts receiving carbo shows consistent 5-day CR rates with an added NK1RA in this and historical studies; additionally, it documents high control rates of nausea with NEPA even in women and younger pts. Given the consistency of the control rates for added NK1RAs, as seen for NEPA and APR, guideline groups and practitioners should consider giving a NK1RA antiemetic triplet in pts receiving carbo. Clinical trial information: NCT01376297.

Cycle 1	NEPA + DEX	
Overall 0-120h	CR [95% CI]	NSN
All Pts (N = 145)	80% [73, 86]	84% [77, 89]
Females (N = 66)	73% [61, 82]	88% [78, 94]
Males (N = 79)	86% [76, 92]	81% [71, 88]
< 55 years (N = 53)	85% [73, 92]	87% [75, 94]
≥ 55 years (N = 92)	77% [68, 85]	83% [74, 89]

9598 Poster Session (Board #257), Sat, 1:15 PM-4:45 PM

Palonosetron or granisetron for prevention of CINV in patients with breast cancer receiving dexamethasone and fosaprepitant following anthracycline plus cyclophosphamide (AC) regimen. *First Author: Koji Matsumoto, Hyogo Cancer Center, Akashi-shi, Japan*

Background: Superiority of palonosetron to granisetron is uncertain, for patients with breast cancer receiving both steroid and NK1 inhibitor against CINV caused by AC regimen. **Methods:** We conducted a randomized double-blind active-controlled study. 341 chemo-naïve patients treated with AC regimen were randomized 1:1 to either (1) palonosetron 0.75 mg + dexamethasone + fosaprepitant or (2) granisetron 1mg + dexamethasone + fosaprepitant. Stratification factor was age (< / > 55 yrs) and type of anthracycline (epirubicin / doxorubicin). Patients recorded episodes of emesis, nausea and rescue medication using a formed diary during 0 -120 hrs post-chemotherapy. Primary endpoint was complete response (CR = no emesis and no rescue medication) in delayed phase (> 24 -120 hrs). Secondary endpoints include CR in acute (0-24 hrs) and overall (0 - 120hrs) phase. Nausea and emesis in acute, delayed, or overall phase was also evaluated. Treatment comparisons were performed using chi-square test with Yates' continuity correction. **Results:** From Dec. 2012 to Oct. 2014, 326 evaluable patients were enrolled with comparable characteristics across groups; median age 54, 87 % of patients received epirubicin, 71 % of patients were light or no drinkers, 71 % of patients had no motion sickness, and 52 % of patients had morning sickness. CR rates were similar for patients treated with palonosetron and granisetron in delayed (62.3 vs 60.4 %; p = 0.8), acute (75.9 vs 73.2 %), and overall (54.9 vs 54.9 %) phase, respectively. Palonosetron reduced nausea (59.9 vs 72 %; p = 0.029) and emesis (10.5 vs 17.7 %; p = 0.088) in delayed phase. Adverse events occurred at similar rates across both groups. **Conclusions:** Although nausea and emesis in delayed phase was reduced, palonosetron at highest effective dose did not prove superiority to granisetron for prevention of CINV in patients with breast cancer receiving dexamethasone and fosaprepitant following AC regimen. Three drugs combination with steroid, 5-HT3 receptor antagonist, and NK1 receptor antagonist did not achieve CR in almost half of patients in this population. A new class of agents is needed. Clinical trial information: UMIN000008897.

9599 Poster Session (Board #258), Sat, 1:15 PM-4:45 PM

Use of mobile device technology to collect patient-reported symptoms during radiotherapy for head and neck cancer: A prospective feasibility study. *First Author: Aaron David Falchook, NC Cancer Hospital, Chapel Hill, NC*

Background: Accurate assessment of toxicity allows for timely delivery of necessary supportive measures during radiotherapy (RT) treatment for head and neck cancer. The purpose of this prospective trial is to evaluate the feasibility of using mobile device technology to collect daily patient reported symptoms. **Methods:** A HIPAA-secure mobile application was developed to allow patients receiving RT for head and neck cancer to report symptom severity in five domains (fatigue, pain, nausea/vomiting, decreased appetite, anxiety) using the Patient Reported Symptom Monitoring System questionnaire. Patients were asked to report symptoms using a smartphone and/or tablet at least once daily during treatment or more often as needed. Patient surveys regarding use of mobile devices were obtained after completion of RT. Descriptive statistics, linear regression, and Fisher's exact test were used to examine factors associated with symptom reporting. **Results:** 22 patients enrolled and 1 withdrew consent. A total of 921 symptom reports were collected during treatment. Median treatment duration was 45.5 days (interquartile range [IQR] 42-49). The median number of reports submitted per patient was 33.5 (IQR 21-54). Median reporting compliance (defined as number of days with report / duration between enrollment and end of RT) was 71% (IQR 44-81). There were no significant associations between reporting compliance and patient characteristics or symptom severity. Timing of symptom reporting is summarized (Table). Patients reported high levels of satisfaction with use of mobile devices to report symptoms. **Conclusions:** It is feasible and convenient for patients to use mobile devices to continuously report symptoms throughout an entire course of RT for head and neck cancer, including nights and weekends. Future studies will evaluate the impact of mobile device symptom reporting on improving patient outcomes.

Day of Week	Reports per Patient (Median)	IQR
Sun	5	3-7
Mon	5	3-8
Tue	5	4-8
Wed	5	3-8
Thurs	5.5	4-7
Fri	6	3-10
Sat	4	2-6
Week of Treatment		
1	7	3-10
2	6	5-7
3	6	5-9
4	6.5	4-9
5	6	4-8
6	5	3-7
7	6.5	5-12
Report During Clinic Hours (7AM-5PM, Weekdays)		
Non-clinic hours	17	10-30
Clinic Hours	14.5	9.5-27.5

9600 Poster Session (Board #259), Sat, 1:15 PM-4:45 PM

Association of severe pain with poor response to opioids, psychological distress, and aberrant drug taking behaviors in a large cohort of cancer patients. *First Author: Vinnidhy Dave, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pain is one of the most feared consequences of cancer. Systematic reviews indicate opioids are effective for cancer pain, but are often under-utilized. At the same time, there is increased societal concern about opioid abuse. Identifying patients with a history of cancer who are at risk for poor pain outcomes is important when considering opioid therapy. The aim of this study was to evaluate associations between pain intensity, analgesic effectiveness, disability, distress and aberrant drug taking in the subpopulation from Memorial Sloan Kettering Cancer Center of a pain clinic registry. **Methods:** At each outpatient encounter, patients completed the Brief Pain Inventory, Condensed Memorial Symptom Assessment Scale (CMSAS) and Current Opioid Misuse Measure (COMM). Though not yet validated in patients with cancer, in other chronic pain populations a COMM score greater than 9 has a positive likelihood ratio for diagnosing opioid misuse/abuse of 3.5. Data analysis performed by International Severity Information Systems, Salt Lake City, UT. **Results:** From 6/18/2011 to 12/10/2014, 1593 of 2085 (76.4%) patients completing 5599 surveys reported continuing pain despite taking opioids. Average pain score was mild (1-4) in 25%, moderate (5-6) in 41%, severe (7-10) in 34%. Those with severe pain reported less relief from their pain medicine, were more disabled (higher pain interference), and had more physical and psychological distress and higher COMM scores (see Table, all p values < 0.001). **Conclusions:** Ambulatory patients with a cancer history who report severe pain despite taking opioids are a challenging management problem. These data suggest they have concomitant disability, physical and psychological distress, and behaviors suggestive of opioid misuse/abuse. To improve their outcomes, more research is needed to understand the causal links between these associations.

Score	Mild	Moderate	Severe
Average pain intensity	3.2	5.5	7.8
Pain relief	62%	54%	45%
Pain interference	4.0	5.6	7.0
Physical symptom distress score, CMSAS	1.5	1.7	1.9
Psychological distress score, CMSAS	1.3	1.6	2.0
COMM score	8.1	8.5	10.7

9601 Poster Session (Board #260), Sat, 1:15 PM-4:45 PM

Minimal clinically important differences in the Edmonton Symptom Assessment Scale in cancer patients: A prospective study. *First Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ESAS is widely used for symptom assessment in the clinical and research settings. We determined the MCID for improvement and deterioration for each of the 10 ESAS symptoms using the anchor based sensitivity-specificity approach. **Methods:** This multicenter, prospective, longitudinal study enrolled patients with advanced cancer. ESAS was measured at a first palliative care clinic visit and a second visit 3 weeks later. For each symptom, we assessed the Patient's Global Impression (PGI) ("better", "about the same", or "worse") at the second visit as the external criterion. We determined the MCID based on the optimal cutoff for sensitivity/specificity in receiver-operating characteristic (ROC) curve using the Youden's J method. We conducted sensitivity analyses by estimating MCIDs using other anchor-based and distribution-based approaches. The planned sample size was powered to estimate sensitivity/specificity with 80% power at 0.5% significance (accounting for 10 symptoms). **Results:** Among the 796 cancer patients from 6 centers, the average age was 57 (range 19-85), 380 (48%) were female, and the median duration between the 2 study visits was 21 days (interquartile range 18-28 days). The area under the ROC curve varied between 0.70-0.87, suggesting good responsiveness. For all 10 ESAS symptoms, the optimal cutoff based on the ROC curve was ≥ 1 point for improvement and ≤ -1 point for deterioration, with sensitivities of 59%-85% and specificities of 69%-85%. Sensitivity analyses showed similar findings: in within-patient analysis, the MCIDs varied between 0.8 and 2.2 for improvement and between -0.8 and -2.3 for deterioration; in ½ standard deviation distribution approach, MCID varied between 1.2 and 1.6; in standard error of measurement approach, MCID varied between 1.3 and 1.7. Using ≥ 1 as the MCID cutoff, between 27% and 48% of patients experienced a clinical response. **Conclusions:** ESAS was responsive to change. The optimal cutoffs were ≥ 1 point for improvement and ≤ -1 point for deterioration for all 10 ESAS symptoms. Our findings have implications for sample size calculations and response determination.

9602 Poster Session (Board #261), Sat, 1:15 PM-4:45 PM

Safety and efficacy of eltrombopag (EPAG) vs placebo (PBO) for treatment of chemotherapy (CTx)-induced thrombocytopenia (TCP) in patients (Pts) with solid tumors receiving gemcitabine (GEM)-based CTx: A phase 2 study. *First Author: Eric S. Winer, Rhode Island Hospital, Providence, RI*

Background: A phase 1 EPAG study showed favorable results for the treatment of CTx-induced TCP in pts receiving GEM-based CTx. **Methods:** This was a phase 2, blinded, PBO-controlled, multicenter study in adults with solid tumors and TCP receiving ≤6 cycles of CTx. Pts received GEM on days 1 and 8 (every 21 days) and cisplatin on day 1 (or divided dose on days 1 and 8) or carboplatin on day 1, or received GEM alone on days 1, 8, and 15 (every 28 days). Pts were randomized (2:1) to EPAG 100 mg or PBO daily for 5 days before and after day 1 of CTx. **Results:** We report early results of 44 pts randomized to EPAG (n = 31) or PBO (n = 13). Data review with an external, independent physician after ≥ 2 cycles showed no safety concerns. Myelosuppression was the most common adverse event (AE), with lower rates of anemia, neutropenia, and TCP seen with EPAG versus PBO (Table). In the EPAG arm, 23% of patients developed TCP (all grade 3/4) vs 46% (31% grade 3/4) of PBO patients. Proportionately fewer serious AEs (SAEs)/deaths occurred with EPAG than with PBO. CTx dose delays/reductions for any reason, specifically for TCP, were lower for EPAG pts than PBO pts, with a greater difference shown in later treatment cycles. **Conclusions:** These early safety and efficacy results are encouraging, with a potential trilineage benefit as seen in other EPAG studies. Enrollment was completed in 2014, with a total of 75 pts. Study NCT01147809 was funded by GlaxoSmithKline. Clinical trial information: NCT01147809.

	EPAG (n = 31)	PBO (n = 13)
Any AEs (all grades) on therapy +30 days[a]	26 (84)	13 (100)
Blood/lymphatic system disorders	20 (65)	10 (77)
Thrombocytopenia	7 (23)	6 (46)
Anemia	11 (35)	7 (54)
Neutropenia	10 (32)	6 (46)
Gastrointestinal disorders	14 (45)	7 (54)
Blood creatinine increased	2 (6)	2 (15)
Vascular disorders	3 (10)	2 (15)
Deep vein thrombosis	2 (6)	0
Thrombophlebitis	0	1 (8)
Cardiac disorders	1 (3)	0
Myocardial infarction	1 (3)	0
SAEs	9 (29)	7 (54)
Deaths	5 (16)	4 (31)
CTx dose delays/reductions due to TCP (intent-to-treat population)		
Cycles 1–6	11/28 (39)	7/13 (54)
Cycles 2–6	7/19 (37)	5/10 (50)
Cycles 3–6	5/17 (29)	5/8 (63)

Data are shown as n (%) or n/N (%). [a]Pts could have >1 AE.

9603 Poster Session (Board #262), Sat, 1:15 PM-4:45 PM

Febrile neutropenia risk factors: A subanalysis of the NEXT study. *First Author: Nicolas Jovenin, Institut Jean Godinot, Reims, France*

Background: Biosimilar filgrastim is a Granulocyte-Colony Stimulating Factor (G-CSF) licensed for the treatment of neutropenia and febrile neutropenia (FN) induced by myelosuppressive chemotherapy (CT). This subanalysis of the NEXT study attempts to assess the impact of each of the FN risk factors defined in the EORTC guidelines for the use of G-CSF. **Methods:** NEXT was a prospective, post-marketing, non-interventional, longitudinal, national multicenter study aimed to assess the safety of biosimilar filgrastim in patients (pts) undergoing CT for malignancies (excluding chronic myeloproliferative and myelodysplastic syndrome). FN risk factors defined in the EORTC guidelines were tested by univariate analyzes and were also included in a logistic regression model. A search of the age at which pts in the NEXT study were significantly more likely to have a FN was also conducted. **Results:** Overall, the NEXT study analyzed 2102 pts but only 1838 pts who received primary prophylaxis (PP) with biosimilar filgrastim were included in this subanalysis. Apart from CT-related FN risk, other factors that may increase the FN risk are in order of importance: age > 65 years, advanced disease, history of prior FN, no antibiotic prophylaxis, no G-CSF use, poor performance and/or nutritional status, female gender, Hemoglobin < 12 g/dL, liver, renal or cardiovascular disease. The analysis of age distribution of pts with FN, who received PP in NEXT study, shows a threshold at 62 years. The only factor statistically significantly associated with FN occurrence among those included in the logistic regression is age > 62 years, confirming the age-related high risk of FN. Indeed, patients older than 62 years are more likely to have a FN than younger patients (OR [95% CI]: 2.1 [1.1 - 4.0]). The limit to 65 years stated in the EORTC guidelines is not significant in our analysis. **Conclusions:** According with the EORTC guidelines, this analysis confirms the age-related high risk of FN. Caution is required even before the 65 years stated in these guidelines. Indeed, we might wonder about the need for G-CSF prophylactic use in > 62-years patients with a CT-related FN risk 10-20%. Clinical trial information: NCT01574235.

9604 Poster Session (Board #263), Sat, 1:15 PM-4:45 PM

Pilot trial assessing the efficacy and safety of a supplemental B vitamin complex to reduce the onset and severity of chemotherapy-induced peripheral neuropathy. *First Author: Janet Margaret Schloss, The University of Queensland, Woolloongabba, Australia*

Background: Chemotherapy induced peripheral neuropathy [CIPN] is a debilitating side effect resulting from the administration of neurotoxic chemotherapy agents. It is estimated that a third of all patients undergoing chemotherapy experience CIPN, with a third of those progressing to a permanent neuropathy. Patients experiencing moderate to severe CIPN report reduced quality of life, chronic discomfort and disruption of physical abilities for general life activities which can be temporary or permanent. Moreover, CIPN can lead to a dose reduction or possible cessation of treatment, which may adversely impact disease outcomes. **Methods:** In a randomised placebo-controlled trial, newly diagnosed patients undergoing chemotherapy treatment with paclitaxel, oxaliplatin or vincristine were assessed for the safety and efficacy of an oral B group vitamin to reduce the incidence of CIPN. The primary outcome was the TNS and secondary outcomes included B vitamin pathology, EORTC QoL, Brief Pain Inventory and PNQ. **Results:** A total of 71 subjects were randomised from 121 evaluable patients (B vitamin n = 38; placebo n = 33). Participants between groups were matched for gender, chemotherapy agents, age and BMI. No statistical significance was found for the prevention of CIPN from vitamin B supplementation through total TNS score (p = 0.73). Statistical significance was recorded for sensory peripheral neuropathy in the PNQ (12 weeks p = 0.03; 24 weeks p = 0.005; 36 weeks p = 0.021). The risk estimate for the PNQ was also statistically significant with an OR = 5.78, 95% CI = [1.63-20.5]. **Conclusions:** B vitamin supplementation throughout chemotherapy administration was not superior to placebo ($p > 0.05$) for the prevention of CIPN. Patient perception of reduced sensory peripheral neuropathy with B vitamin supplementation over placebo was statistically significant. Although not significant a trend was observed for the prevention of the onset and severity of CIPN throughout chemotherapy with B vitamins supplementation over placebo. Furthermore, patients with moderate to severe CIPN may have a vitamin B12 deficiency that may lead to a worse symptomatic presentation. Clinical trial information: 12611000078954.

9605 Poster Session (Board #264), Sat, 1:15 PM-4:45 PM

Prospective multicenter study evaluating adrenal suppression after dexamethasone therapy as an antiemetic in cancer patients: a KSWOG (Korean South West Oncology Group) study. *First Author: Hye Sook Han, Chungbuk National University Hospital, Cheongju, South Korea*

Background: Dexamethasone has a high therapeutic index for the prevention of chemotherapy-induced nausea and vomiting; however, the chronic use of high-dose glucocorticoids is associated with adrenal insufficiency. The objective of the present study was to assess the prevalence and associated factors of adrenal suppression after antiemetic dexamethasone therapy in cancer patients receiving chemotherapy. **Methods:** Patients who were scheduled to receive at least three cycles of highly or moderately emetogenic chemotherapy with dexamethasone as one of antiemetics were enrolled. Patients with a suppressed baseline adrenal response before chemotherapy and those administrated corticosteroids within 6 months of study commencement were excluded. **Results:** Between October 2010 and August 2014, 481 patients receiving chemotherapy underwent the rapid ACTH stimulation test to assess eligibility; 350 of these patients were included in the final analysis. Fifty-six patients (16.0%) showed a suppressed adrenal response in the rapid ACTH stimulation test at 3 or 6 months after the first chemotherapy with dexamethasone as an antiemetic. Multivariate analysis revealed that the incidence of adrenal suppression was significantly associated with the duration of megestrol acetate use ($P < 0.001$). Adrenal suppression did not correlate with age, sex, performance status, primary tumor site, tumor stage, intent of first chemotherapy, emetic risk of first chemotherapy, chemotherapeutic agents used, or the dose and duration of dexamethasone. **Conclusions:** This large prospective study indicates that approximately 15% of cancer patients with a normal adrenal response showed suppressed adrenal responses after antiemetic dexamethasone therapy; this was particularly significant for patients co-treated with megestrol acetate.

9606 Poster Session (Board #265), Sat, 1:15 PM-4:45 PM

Patient self-evaluation of side-effects related to adjuvant chemotherapy in breast cancer: A prospective study. *First Author: Filippo Montemurro, Fondazione del Piemonte per l'Oncologia, Candiolo Cancer Institute, Candiolo, Italy*

Background: There is a growing interest in patient-reported outcomes (PRO) in cancer treatment. We evaluated a Common-toxicity criteria (CTC) v4.02-based, self-administered questionnaire to collect 10 common chemotherapy-related side effects (CSE) in patients (pts) undergoing standard adjuvant chemotherapy (ACT) for operable breast cancer. **Methods:** In this prospective study, 610 pts at 11 sites were administered the questionnaire after the first and the third cycle of ACT. For each item (nausea, vomiting, constipation, anorexia, taste alterations, diarrhea, fatigue, pain, neuropathy and dyspnea) the CTC v4.02 definitions of grade of severity were translated into Italian and rephrased. Pts were asked to choose the definition that best represented the worst CSE experienced after ACT. At each time/point, information on CSE was extracted from the medical charts to compare pts- vs doctors (drs)-reported CSE. **Results:** 596 and 581 questionnaires were collected after cycle 1 and cycle 3 of ACT. A median of 82% of the fields was completely filled-in. 594 and 573 pts-questionnaires had a corresponding drs-questionnaire. The frequency of $G \geq 1$ CSE was systematically higher in pts than in drs questionnaires, as was the grade of severity. For example, Constipation (any grade), Anorexia (any grade) and Dysgeusia (any grade) were reported by pts almost twice as frequently as by drs. Notably, Paresthesia and Dyspnea (any grade) were rarely reported by drs (4% for both), but were reported by 24% and 27% of the pts, respectively, reaching grade 2 or higher in 6% and 11% of the pts respectively. Finally, we found a significant positive correlation between the magnitude of the discrepancy in the frequency of CSE reporting and the number of patients enrolled at each site, suggesting an influence of workload on discrepancy. **Conclusions:** Self-evaluation of adjuvant chemotherapy-related toxic effects according to the CTC system is feasible in the clinical practice and potentially time saving. Whether the observed discrepancy is due to pts overestimating or drs underreporting CSE needs to be clarified, but our results suggest a potential effect of the patient workload on this phenomenon.

9607 Poster Session (Board #266), Sat, 1:15 PM-4:45 PM

Identifying predictors of taxane-induced peripheral neuropathy using shotgun proteomics technology. *First Author: Meghna S. Trivedi, Columbia University Medical Center, New York, NY*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of taxanes. Advances in proteomic technologies incorporating mass spectrometry (MS) for biomarker discovery show great promise in providing molecular profiles from complex biological samples. We evaluated the association between protein cargos in serum exosomes and severity of CIPN. **Methods:** We conducted a nested case-control study within a prospective cohort of women with early stage breast cancer receiving adjuvant taxane chemotherapy. Neuropathy was assessed at baseline, completion of taxane, and 6 and 12 months after taxane completion using the Functional Assessment of Cancer Therapy-GOG-Neurotoxicity (FACT-Ntx) score (range 0-44). Blood samples were collected at baseline, completion of taxane, and 12 months. The changes in FACT-Ntx score from baseline to follow-up time points were used to identify 2 groups of subjects: those with no change in FACT-Ntx score (N = 8) and those with a $\geq$ 20% worsening in FACT-Ntx score (N = 8). MS-based proteomics technology was used to identify proteins present in serum exosomes and potential biomarkers for CIPN. One-way ANOVA analysis with $p < 0.05$ as the threshold cutoff for statistical significance was applied using the Qlucore Omics Explorer to identify biomarkers predictive of developing CIPN. **Results:** From the serum exosomes derived from this cohort, MS-based proteomics technology identified over 700 proteins known to be in different subcellular locations (*e.g.,* 32% cytoplasm and 19% nucleus) and have different functions (*e.g.,*15% enzymes, 6.8% transcription regulators, and 5% kinases). We found a 12-protein signature from the baseline serum samples that can be used to distinguish between patients with or without CIPN after taxane treatment ($p < 0.05$) suggesting that the baseline samples can predict subsequent neurotoxicity. **Conclusions:** We were able to identify a serum exosomal profile that is associated with taxane-induced peripheral neuropathy. We believe that this new panel of biomarkers could be used to identify patients at high risk of developing severe CIPN. We plan to validate the 12-protein profile in a larger cohort of patients who have received taxane therapy.

9608 Poster Session (Board #267), Sat, 1:15 PM-4:45 PM

A randomized trial of vitamin D_3 in aromatase inhibitor-associated musculoskeletal symptoms. *First Author: Alice C. Shapiro, Frauenshuh Cancer Center and Park Nicollet Institute, Minneapolis, MN*

Background: Vitamin D_3 supplementation (D_3) has been suggested as a treatment for aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS), but efficacy and safety are unclear. **Methods:** We randomly assigned 113 post-menopausal women ($\geq$ 18 years; stage I-IIIA breast cancer; taking an AI and experiencing AIMSS), to either 600 IU D_3 (control: n = 56) or 4,000 IU D_3 (experimental: n = 57), daily for 6 months (6 mos). The primary study endpoint was change in musculoskeletal symptoms (MS) from baseline to 6 mos, measured by: The Breast Cancer Prevention Trial Symptom Scales-MS subscale (BCPT-MS), the Australian/Canadian Osteoarthritis Hand Index (AUSCAN), the Western Ontario and McMaster Osteoarthritis Index (WOMAC) and hand grip strength (Dynamometer). Plasma AI pharmacokinetics (AI-PK) were estimated using non-linear mixed-effects modeling. Effects of D_3 on AI-PK were tested by likelihood ratio test. Serum 25(OH)D was quantified by chemiluminescent immunoassay (DiaSorin, Stillwater, MN). Sample size was calculated on a change of 0.62 in BCPT-MS score. Assuming a two-tailed test with $\alpha = 0.05$ and power = 80%, adequate sample size was 116 (58 per group). Primary endpoint analyses were based on intent-to-treat and determined using a General Linear Model controlling for possible effect modifiers. **Results**: The groups did not differ on demographic or clinical characteristics nor on AIMSS measures. After 6 mos, serum 25(OH)D was 33$\pm$8 ng/mL vs. 46$\pm$11 (mean$\pm$sd; control vs experimental; $p < 0.001$). There were no statistically significant differences between groups (control vs exp) in mean change in AIMSS scales from baseline to 6 mos: BCPT-MS: -0.45 vs. -0.24; WOMAC function: -1.23 vs -3.96; WOMAC pain: -0.56 vs. -1.18; WOMAC stiffness: -0.47 vs -0.54; AUSCAN function: -0.75 vs -1.12; AUSCAN pain: -0.24 vs. -0.90; AUSCAN stiffness: -0.11 vs. -0.08; hand grip: 1.06 vs 1.78 (all $p > 0.1$). AI clearance did not differ significantly between groups (baseline vs 6 mos; $p > 0.5$). **Conclusions**: Women randomly assigned to higher dose D_3 (4,000 IU) showed no improvement in AIMSS over usual dose D_3 (600 IU). While D_3 does not appear to adversely affect AI drug metabolism, it may have other health effects in this population. Clinical trial information: NCT01509079.

9609 Poster Session (Board #268), Sat, 1:15 PM-4:45 PM

Usefulness of denosumab to nonsquamous non-small cell lung cancer patients with bone metastases. *First Author: Hibiki Udagawa, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Denosumab reduces the incidence of the skeletal-related events (SRE) in patients with bone metastases (BM) from solid tumors. However, there have been no detailed reports about the efficacy of Denosumab to the untreated non-squamous non-small cell lung cancer (NSCLC) patients with BM. **Methods:** The medical records of patients less than 75 years of age, with BM from non-squamous NSCLC and treated with platinum-doublet or EGFR-TKI as 1st-line systemic chemotherapy at our institution from May 2010 to April 2014 were retrospectively reviewed. The overall survival (OS), progression-free survival (PFS) of platinum-based chemotherapy and/or EGFR-TKI and time to SRE (radiation or surgery to bone, spinal cord compression or pathologic fracture) were analyzed according to the treatment for the BM (Denosumab, Zoledronic Acid or no treatment). **Results:** A total of 149 patients were eligible. Fifty-two patients received Denosumab (Dmab-group), 51 received Zoledronic Acid (ZA-group) and 46 did not receive the treatment for the BM (Non-group). The frequency of the prior SRE in the Non-group was lower than the Dmab-Group and ZA-group (21.7%, 44.2% and 43.1%, respectively), but there was no difference of other clinicopathological characteristics among 3 groups. The OS in the Dmab-group was significantly longer than that in the ZA-group or Non-group (25.4 months vs 13.9 months, 11.2 months, respectively; $p = 0.01$). In the multivariate analysis, Dmab-group was significantly associated with a favorable survival [vs ZA-group; $p < 0.01$, HR 0.365 (95 %CI, 0.209-0.621). vs Non-group; $p < 0.01$, HR 0.388 (95%CI, 0.213-0.691)]. The Dmab-group showed significantly longer PFS for patients treated with platinum-based chemotherapy than the ZA-group or Non-group (5.1 months vs 3.3 months, 4.3 months, respectively; $p = 0.046$). No significant difference in the PFS for patients treated with EGFR-TKI or time to SRE was observed among 3 groups. **Conclusions:** Our results suggest that Denosumab may improve overall survival compared with Zoledronic Acid or no treatment for BM in patients with non-squamous NSCLC and BM.

9610 Poster Session (Board #269), Sat, 1:15 PM-4:45 PM

Phase II study of preventive effect of topical menthol for chemotherapy-induced peripheral neurotoxicity. *First Author: Kumi Nakamura, Aizawa Hospital, Matsumoto, Japan*

Background: Chemotherapy-Induced Peripheral Neurotoxicity (CIPN) is a major dose-limiting toxicity of many commonly used chemotherapeutic agents that not only negatively affects quality of life, but also can limit successful disease control in cancer care. Menthol is a compound derived from mint leaves that functions as an agonist of Transient Receptor Potential Melastatin-8 (TRPM-8). TRPM-8 is distributed in peripheral nerves and has been shown to be associated with cold hypersensitivity, noxious cold and sensory disturbance. It is also related to the occurrence of CIPN. We previously reported that applying topical menthol reduced existing CIPN in 75% of patients in a phase II study. As the next step, we conducted a phase II study about the preventive effect of menthol for CIPN. **Methods:** Patients who were to start regimens containing oxaliplatin (l-OHP) were included in this study. l-OHP is widely used for colorectal cancer (CRC), and is reported to cause grade 2+ CIPN (45-54% at the cumulative dose of 500mg/m2). Participants applied 1% topical menthol twice daily to their hands and feet from the start of l-OHP treatment. CIPN symptoms were assessed using the FACT&GOG-Ntx and Visual Analog Scale (VAS). The primary endpoint was the frequency of Grade 2{CIPN at the cumulative l-OHP dose of 500 mg/m^2. **Results:** Thirty-two CRC patients who were to start regimens containing l-OHP were enrolled in this study. Twenty-two patients were in adjuvant setting and 10 were in metastatic setting.Treatment regimens were capecitabine and l-OHP (CapeOx) (n = 22), CapeOx plus bevacizumab (n = 9) and FOLFOX plus cetuximab (n = 1). Of the 32 registered patients, 8 terminated or changed their chemotherapy regimens before reaching a cumulative l-OHP dose of 500 mg/m^2 and were excluded from analysis. The frequency of Grade 2{CIPN was 12.5% (95% CI: 2.7-32.4%) at the cumulative l-OHP dose of 500 mg/m^2. This was significantly lower than the expectation value (25%). The means of the FACT/GOG-Ntx score and the VAS scale were 3.6 (0-14) and 2.5 (0-8.8), respectively. There were no adverse events reported from menthol application. **Conclusions:** This phase II study showed preventive menthol application significantly reduced l-OHP-induced CIPN. Clinical trial information: UMIN000009655.

9611 Poster Session (Board #270), Sat, 1:15 PM-4:45 PM

Longitudinal study of pneumonitis and esophagitis-related symptoms in patients receiving concurrent chemoradiation for NSCLC. *First Author: Xin Shelley Wang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Clinical practice and research often solely rely on clinician ratings of treatment toxicities, where a simple "symptomatic/not symptomatic" question to the patient is typically used in addition to clinical signs as evidence of toxicity. Prospective, patient-reported outcome (PRO)-based studies that quantify symptom development and major toxicity levels related to concurrent chemoradiation therapy (CXRT) are lacking. We longitudinally examined the relationship between PROs and clinician-rated toxicities in patients with locally advanced non-small cell lung cancer (NSCLC) treated with CXRT. **Methods:** 155 patients repeatedly reported symptoms on a 0-10 scale via the MD Anderson Symptom Inventory (MDASI-Lung Cancer), from pre-CXRT for up to 6 months. Clinicians rated toxicity using the CTCAE 4.0. Patient factors (age, sex, comorbidities), worst CTCAE score of each toxicity during the study, radiation dose/volume variables, and days from start of CXRT were included in the longitudinal mixed modeling. **Results:** We observed a significant linear increase in coughing and shortness of breath over time during the study (both $P < .0001$), whereas the most-severe symptoms overall (fatigue, lack of appetite, disturbed sleep) exhibited a decrease by the end of treatment. Post-CXRT, patients with grade 2+ radiation pneumonitis (RP) had significantly more-severe cough and shortness of breath, compared with those with grade $\leq$ 1 RP ($P < .0001$). Mean lung dose was predictive of grade 2+ RP (OR, 1.27 (1.09-1.49), P = .0023). Gross tumor volume was significantly related to increased cough severity ($P < .01$). Pain, sore throat, and difficulty swallowing peaked by the end of CXRT, and all were significantly worse for patients with grade 2+ esophagitis vs. grade 0-1 (all $P < .0001$). There was no difference in symptom severity pre-CXRT by toxicity group. **Conclusions:** Longitudinal analysis identified temporal associations between clinician-rated toxicity and emerging patient-reported symptom burden from CXRT for NSCLC. Further investigation of the benefits of routine symptom assessment for clinical management and early prevention of RP and esophagitis is warranted.

9612 Poster Session (Board #271), Sat, 1:15 PM-4:45 PM

The conversion ratio (CR) for opioid rotation (OR) from strong opioids to transdermal fentanyl (TDF) in cancer patients. *First Author: Akhila Sunkepally Reddy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cancer patients frequently undergo OR for uncontrolled pain or opioid induced neurotoxicity (OIN). TDF is one of the most common opioids prescribed to cancer patients. However, the accurate CR for OR from other opioids to TDF is unknown and various currently used methods result in a wide variation of CRs. Our aim was to determine the CR of morphine equivalent daily dose (MEDD) to TDF when correcting for MEDD of breakthrough opioids (net MEDD) in cancer outpatients. **Methods:** We reviewed records of 22,532 consecutive patient visits at our Supportive Care Center in 2010-13 for OR from other opioids to TDF. Data regarding Edmonton Symptom Assessment Scale (ESAS) and MEDD were collected in patients who returned for follow up within 5 weeks. Linear regression analysis was used to estimate the CR between TDF dose and net MEDD (MEDD prior to OR minus MEDD of breakthrough opioid used along with TDF after OR). Successful OR was defined as 2-point or 30% reduction in pain score and continuation of the new opioid at follow up. **Results:** 129 patients underwent OR from other opioids to TDF. The mean age was 56 years, 59% male, and 88% had advanced cancer. The median time between OR and follow up was 14 days. Uncontrolled pain (80%) was the most frequent reason for OR and 59% had a successful OR with significant improvement in ESAS pain, constipation, and symptom distress scores. In 101 patients with OR and no worsening of pain at follow up, the median CR (range) from net MEDD to TDF mg/day was .01 (-0.02-0.04) and correlation of TDF dose to net MEDD was .77 ($P < .0001$). The CR was not significantly impacted by variables such as mucositis, serum albumin, and body mass index (BMI). The CR of .01 suggests that MEDD of 100mg is equivalent to 1mg TDF/day or 40mcg/hour TDF patch (1000mcg/24hours). **Conclusions:** The median CR from MEDD to TDF mg/day is .01 and the CR from MEDD to TDF mcg/hour patch is 0.4. Further validation studies are needed.

Comparison of Fentanyl (mg/day)/ Net MEDD Ratio

Variables	Level	N	Median CR	Min-Max	p-value
All		101	.01	-0.02-0.04	
Mucositis	No	49	.01	0 -0.03	.67
	Yes	52	.01	-0.02-0.04	.
BMI	≤ 20	13	.01	0-0.02	.43
	20-30	62	.01	-0.02-0.04	.
	> 30	26	.01	0-0.03	.
Albumin g/dl	< 3	4	.01	0-0.02	.41
	3-3.5	17	.01	0-0.02	.
	> 3.5	78	.01	-0.02-0.04	

9613 Poster Session (Board #272), Sat, 1:15 PM-4:45 PM

Association of high symptom burden with oral oncolytic agents. *First Author: Jane Alcyne Severson, University of Michigain Health System, Ann Arbor, MI*

Background: Increasing numbers of cancer patients are being treated with oral oncolytics. This change represents a shift from frequent direct observation during intravenous therapy to periodic observation and self-management. Despite this shift, patients are still at risk for many of the same chemotherapy-associated symptoms and toxicities. We sought to characterize the symptom burden experienced by patients prescribed oral oncolytics. **Methods:** Michigan Oncology Quality Consortium (MOQC) sponsored a collaborative focused on improving oral oncolytic care. Eight oncology practices participated. Patient symptoms were assessed with a modified Edmonton Symptom Assessment System (ESAS) prior to each outpatient visit. 13 symptoms were categorized as mild (0 to 3), moderate (4 to 6), and severe (7 to 10). A total of 1196 surveys were analyzed. **Results:** Overall, the average ESAS symptom score was mild in 83% of patients, moderate in 12% of patients, and severe in 5% of patients. These composite scores, however, obscure the significant symptom burden in select ESAS domains. For example, 34% of patients categorized their overall well-being as being moderate/severely affected; 35% of patients felt they were moderate/severely fatigued, and 20% indicated moderate/severe pain symptoms. Notably, 271/1196 (23%) of the assessments had 4 or more symptoms reported moderate to severe. (See table). **Conclusions:** Whether due to underlying disease or medication side effects, patients taking oral oncolytics experience significant symptom burden that impacts quality of life. Intolerance of oral oncolytics may lead to adherence issues, potentially affecting expected outcomes. Given the prevalence of symptoms and potential for toxicity, self-management strategies to improve early recognition and treatment of symptoms by patients taking oral oncolytics are necessary.

Oral oncolytic symptom burden profile.

	Mild (0-3)	Moderate (4-6)	Severe (7-10)
Pain	80%	15%	5%
Tiredness	65%	21%	14%
Drowsiness	76%	16%	8%
Nausea	92%	6%	2%
Appetite	79%	13%	8%
Shortness of Breath	88%	9%	3%
Depression	87%	11%	2%
Anxiety	87%	10%	3%
Well Being	66%	21%	13%
Constipation	88%	9%	3%
Diarrhea	92%	5%	3%
Tingling/ Numbness	82%	12%	6%
Mouth Sores	96%	3%	1%
Overall Symptom Burden (n = 1196)	83%	12%	5%

9614 Poster Session (Board #273), Sat, 1:15 PM-4:45 PM

Randomized pilot study comparing high-dose (HD) influenza vaccine to standard-dose (SD) influenza vaccine in adult oncology patients younger than 65 receiving chemotherapy. *First Author: Saad Jamshed, Rochester General Hospital, Rochester, NY*

Background: Pts on chemotherapy often fail to develop a robust response to influenza vaccine. Compared to SD influenza vaccine, HD vaccine has shown improved immunogenicity & protection against influenza illness in adults ≥65 yrs. This study compared the immunogenicity & tolerability of HD to SD vaccine in pts <65 yrs receiving chemotherapy. **Methods:** 105 pts were randomized to receive either SD or HD (51 vs 54) vaccine on day1 of chemotherapy during 2012-2013 & 2013-2014 seasons. HAI titers were measured prior to & 4-wks after vaccination. HAI were summarized as GMT, seroconversion & seroprotection rates. Sample size calculation was based on 30-50% effect size on GMTs. Equal numbers were expected in each group & assumed 80% power. GMTs for each strain were transformed to log 2, t-test was performed on log-transformed HAI titer. χ^2 was used for seroconversion rate. A p-value > 0.05 was considered significant. **Results:** 5 pts were excluded, 1 received the vaccine twice. 4 pts who enrolled both yrs, were included only once (yr 1). Mean age (52.9 vs 53.9 yrs) and baseline HAI titers were equivalent; 90% in both arms had solid tumors & 58 vs 50% were receiving curative therapy in SD vs HD arms, respectively. Both vaccines were well tolerated with no SAEs. Seroprotection was excellent for all antigens in both arms. Seroconversion rate for all 3 influenza antigens & post vaccination GMTs for H3N2 & B strains were significantly improved with HD vaccine (Table). **Conclusions:** Trivalent HD influenza vaccine can be safely administered to chemotherapy pts with improved immunogenicity over SD vaccine. A larger study is needed to show clinical benefits with HD vaccine. Clinical trial information: NCT01666782.

Vaccine Antigen	SD (n = 50) Post HAI GMT (95% CI)	HD (n = 50) Post HAI GMT (95% CI)	(*t*-test)
H1N1	979.1 (609.1-1349.0)	1350.1 (819.8-1880.4)	$p = 0.106$
H3N2	811.2 (401.2-1221.3)	1143.4 (739.6-1547.3)	$p = 0.005$
B	228.0 (129.9-326.2)	351.6 (215.6-487.7)	$p = 0.02$
Seroconversion Rate (%) (≥ 4 fold change)			(χ^2)
H1N1	46.0	72.0	$p = 0.014$
H3N2	58.0	80.0	$p = 0.029$
B	44.0	80.0	$p = 0.0004$

9615 Poster Session (Board #274), Sat, 1:15 PM-4:45 PM

Impact of rolapitant on quality of life (QoL) in patients (pts) receiving highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). *First Author: Martin Chasen, Palliative Care, at The Ottawa Hospital Cancer Centre and the Medical Director of the Palliative Rehabilitation Program at the Élisabeth Bruyère Hospital, Ottawa, Ottawa, ON, Canada*

Background: Rolapitant is a novel NK-1 receptor antagonist with a half-life of 180h, and does not inhibit CYP3A4 as other drugs do in the class, and therefore requires no dose modifications of concomitant steroids. Rolapitant demonstrated efficacy for prevention of CINV in phase 3 trials (HEC1, HEC2, and MEC). This pooled analysis examined the effect of rolapitant on QoL. **Methods**: In 3 double-blind, active-controlled studies, pts were randomized to oral rolapitant 200 mg or placebo 1–2 h before chemotherapy. All pts received active control: granisetron 2 mg oral or 10 mcg/kg IV and oral dexamethasone 20 mg. In the MEC study, granisetron was continued on Days 2 and 3. QoLwas assessed on Day 6 using the Functional Living Index-Emesis (FLIE) Questionnaire, and reported as a total score and by nausea and vomiting domains. Pts with a valid questionnaire from the MITT population (all randomized pts who received at least 1 dose of study drug) in the 2 pooled HEC studies and one MEC study were analyzed. **Results**: Baseline characteristics were comparable across treatment groups. Most common cancers were breast for MEC and lung for HEC studies. At Day 6, significant improvements ($P < 0.05$) were observed with rolapitant vs. active control for FLIE total, nausea, and vomiting domain scores (Table). **Conclusions**: Rolapitant improved QoLin pts receiving both HEC and MEC compared with active control, in addition to providing significant protection from CINV. Clinical trial information: NCT01500213; NCT01499849; NCT01500226.

	HEC		MEC	
	Rolapitant	Active Control	Rolapitant	Active Control
Total Score, n	491	479	605	607
Mean (SD)	114.5 (17.3)	109.3 (24.5)	112.7 (19.7)	108.6 (23.5)
Mean difference (95% CI)	5.2 (2.6, 7.9)		4.1 (1.7, 6.5)	
p-value*	< 0.001		< 0.001	
Nausea Domain, n	493	480	606	608
Mean (SD)	55.3 (11.3)	53.5 (13.5)	54.1 (12.4)	52.3 (13.8)
Mean difference (95% CI)	1.8 (0.2, 3.4)		1.8 (0.3, 3.3)	
p-value*	0.020		0.019	
Vomiting Domain, n	491	479	605	607
Mean (SD)	59.2 (8.1)	55.8 (12.3)	58.6 (9.2)	56.3 (11.3)
Mean difference (95% CI)	3.4 (2.1, 4.7)		2.3 (1.1, 3.4)	
p-value*	< 0.001		< 0.001	
No impact on daily life n/N (%)**	371/491 (75.6)	339/479 (70.8)	443/605 (73.2)	409/607 (67.4)
p-value	0.082		0.027	

*ANCOVA with study and gender as covariates; **FLIE total score >108

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9616 Poster Session (Board #275), Sat, 1:15 PM-4:45 PM

Evaluation of brain-derived neurotrophic factor (BDNF) genetic polymorphism (rs6265) on chemotherapy-associated cognitive impairment in early-stage breast cancer (ESBC) patients. *First Author: Terence NG, National University of Singapore, Singapore, Singapore*

Background: BDNF is a neurotrophin that regulates neuronal function and development, which is implicated in several neurodegenerative conditions. There is preliminary data to suggest that the reduction of BDNF concentrations may lead to post-chemotherapy cognitive impairment. We hypothesized that a single nucleotide polymorphism (rs6265) of the *BDNF* gene may down-regulate BDNF levels, predisposing certain patients with cognitive impairment. This study was designed to evaluate the impact of *BDNF* gene polymorphism on chemotherapy-associated cognitive impairment. **Methods:** Overall, 145 chemotherapy receiving ESBC patients (mean age: 50.8 ± 8.8 years; 82.1% Chinese) were recruited between 2011 and 2014. Patients' self-perceived cognitive function were assessed longitudinally over three time points, using the validated FACT-Cog (v.3) to examine six cognitive domains: concentration, functional interference, memory, mental acuity, multitasking ability and verbal fluency. Genotyping was performed using Sanger sequencing. Logistic regression was used to evaluate the association between *BDNF* Val66Met polymorphism and cognition, adjusting for ethnicity and clinically important covariates. **Results:** 54 (37%) patients reported cognitive impairment post-chemotherapy. 38 (26.2%) patients were homozygous for Val/Val, 74 (51.0%) were heterozygous for Val/Met, and 33 (22.8%) were homozygous for Met/Met without deviation from the *Hardy-Weinberg equilibrium ($p > 0.05$)*. The *BDNF* Met/Met genotype was associated with statistically significantly lower odds of developing cognitive impairment (OR = 0.26, 95% CI: 0.08-0.92, $p = 0.036$). Furthermore, the Met-carriers were less likely to experience impairment in the verbal fluency (OR = 0.34, 95% CI: 0.12-0.90, $p = 0.031$) and multitasking ability (OR = 0.37, 95% CI: 0.15-0.91, $p = 0.030$) domains, comparing to the Val/Val homozygote. **Conclusions:** This is the first study to provide evidence that carriers of the *BDNF* Met allele are protective against chemotherapy-associated cognitive impairment. Further validation studies are required to confirm the findings.

9617 Poster Session (Board #276), Sat, 1:15 PM-4:45 PM

Development and validation of a Clinical Index of Severe Febrile Neutropenia: A prospective multicenter study. *First Author: Juan Virizuela Echaburu, Hospital Universitario Virgen Macarena, Seville, Spain*

Background: To develop and validate a prognostic score for serious neutropenic events based on characteristics available prior to starting chemotherapy **Methods:** FINITE is a prospective, multicenter study to assess prognostic factors and patterns of care in adult cancer patients with seemingly stable febrile neutropenia. For this analysis, we used only those clinical variables that are routinely available on Day 1 of chemotherapy in all solid tumor patients. The main outcome measure was occurrence of serious complications. A logistic regression with Penalized Maximum Likelihood Estimations (PMLE) was applied; to build an additive score, estimates were rounded as integers. To validate the model, the bootstrap bias-corrected c-index was calculated as a measure of prediction performance. A separate dataset with 216 patients was used for external validation. **Results:** We enrolled 1238 patients from 25 centers. The primary end point (serious complications) ensued in 161 patients (13%; 95% CI, 11.1%-14.9%) and 21 patients died (1.7%; 95% CI, 1.1%-2.6%). We developed a *Clinical Index of Severe Febrile Neutropenia*-(CISFN) with six baseline explanatory covariates associated with serious complications: Eastern Cooperative Oncology Group Performance Status ≥ 2 (2 points), chronic obstructive pulmonary disease (1 point), chronic cardiovascular disease (1 point), protein-energy malnutrition (1 point), chronic corticoids (1 point), and inoperable locally advanced or metastatic cancer (1 point). We integrated these predictors into a score from 0 to 7, which classifies patients into three risk groups: low (0 points), intermediate (1-2 points), and high risk (≥ 3 points). Complications rates were 4.1% in low, 8.7% in intermediate, and 38% in high risk groups ($p < 0.001$). Mortality within each class was 0.2%, 1.4%, and 4.9%, respectively ($p < 0.001$). This model was well calibrated (Hosmer-Lemeshow test, $p > 0.1$) and resulted in an optimism-corrected c-index of 0.762 (95% CI, 0.759-0.763). The validation in a separate dataset yielded a c-index of 0.745 (95% CI, 0.665-0.825). **Conclusions:** This study identified predictive factors for serious neutropenic events with potential implications for G-CSF prophylaxis.

9618 Poster Session (Board #277), Sat, 1:15 PM-4:45 PM

Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients (pts) receiving anthracycline-cyclophosphamide (AC)-based chemotherapy. *First Author: Ian D. Schnadig, Compass Onc, Tualatin, OR*

Background: Rolapitant, a novel NK-1 receptor antagonist, demonstrated efficacy in the prevention of CINV in pts receiving moderately- or highly emetogenic chemotherapy (MEC; HEC). In this post-hoc analysis, we evaluated safety and efficacy outcomes in pts receiving AC-based therapy, now considered HEC. **Methods**: This double-blind, active-controlled study randomized pts to oral rolapitant 200 mg plus granisetron 2 mg and dexamethasone 20 mg or granisetron and dexamethasone alone (active control). Complete response (CR=no emesis and no use of rescue medication), no emesis, no significant nausea, and time to emesis or rescue medication during overall, acute, and delayed phases and treatment-emergent adverse events (AEs) are presented. **Results**: 703 pts received AC-based therapy, of which 97% had breast cancer. CR was significantly higher for rolapitant vs. active control for delayed and overall phases in pts receiving AC-based therapy (Table). Time to first emesis or use of rescue medication was significantly longer with rolapitant vs. active control (between-group comparison, p = 0.032); median was not reached in either treatment arm. A significantly greater proportion of pts on rolapitant (73.0%) vs. active control (60.2%) had no emesis during the overall phase ($p < 0.001$). Rates of no significant nausea were similar for rolapitant (63.7%) and active control (62.4%) in the overall phase (p = 0.728). Treatment-related AEs (TRAEs) during Cycle 1 occurred in 8.7% and 8.8% of pts on rolapitant vs. active control,. Most frequent TRAEs were constipation (2.9% vs. 2.7%), fatigue (2.3% vs. 2.2%), and headache (2.3% vs. 3.3%). **Conclusions**: Rolapitant was superior to active control in preventing CINV during delayed and overall phases after AC-based chemotherapy. There were no differences in the safety profile of rolapitant in the pt groups. These results are consistent with the overall pt population in this study. Clinical trial information: NCT01500213; NCT01499849; NCT01500226.

	Rolapitant	Active Control	
Phase	N=344	N=359	p-value*
Overall (0–120 h)	216 (62.8%)	197 (54.9%)	0.033
Delayed (>24–120 h)	230 (66.9%)	214 (59.6%)	0.047
Acute (0–24 h)	264 (76.7%)	276 (76.9%)	0.966

* unstratified CMH test

9619 Poster Session (Board #278), Sat, 1:15 PM-4:45 PM

Evaluating the effect of neutropenic diet on infection and mortality rate in cancer patients: A meta-analysis. *First Author: Mohamad Bassam Sonbol, Georgia Regents University, Augusta, GA*

Background: Dietary manipulation for patients undergoing chemotherapy has been proposed as a method to reduce the risk of infection. These diets, referred to as "neutropenic diets (ND)" usually restrict fresh raw fruits, raw vegetables, raw meat or soft cheeses. Regular diets (RD) generally include foods restricted in ND and are prepared within standardized FDA food safety guidelines. ND are used in transplant centers and hospital wards where cancer patients are being treated. The goal of this meta-analysis was to determine the effectiveness of ND over RD at preventing infection **Methods:** We searched the medical literature to identify studies comparing ND with RD in patients with cancer. Primary outcomes were mortality of any cause, major infections (pneumonia, bacteremia, or fungemia, or pneumonia accompanied with bacteremia or fungemia), and the composite outcome of neutropenic fever or infection (major infections as defined above, minor infections, or fever). The overall effect was calculated by use of a random effects model. A sensitivity analysis was conducted to evaluate influence of the included observational trials on outcomes. **Results:** Four studies were identified, 3 randomized trials and 1 observational study, encompassing 918 patients with cancer or stem cell transplant. Patients randomized to ND had no difference in major infection rate compared to the RD group (RR = 1.08, CI 0.72 to 1.61). ND patients also had a comparable mortality rate to the RD group (RR = 1.08, CI 0.78 to 1. 50). These results persisted after omitting the observational study from analysis. When analyzing for the overall composite outcome of any infection or fever, the hazard was significantly higher in ND arm compared to RD arm (RR 1.18, CI 1.05 to 1.34). **Conclusions:** This study shows no superiority or advantage with respect to mortality or infection of using neutropenic diet over a regular diet in neutropenic cancer patients. Larger randomized controlled studies are needed to further study this important dietary issue for patients. In the meantime, it may be time to relax the restrictions of ND in order to attain better nutrition.

9620 Poster Session (Board #279), Sat, 1:15 PM-4:45 PM

Risk assessment of anticancer treatments beyond performance status: A prospective study in 277 cancer patients. *First Author: Anne Jouinot, Medical Oncology, Paris Descartes University, Cochin - Port Royal Hospital, AP-HP, Paris, France*

Background: Alterations of performance status (PS) and of nutritional status are predictors of acute toxicity following anticancer treatment. Resting energy expenditure (REE) is often increased in cancer patients and may be a major determinant for the alteration of nutritional status and the development of precachexia and cachexia. We investigated whether abnormal metabolism could predict early acute toxicity (EAT). **Methods:** In this prospective observational monocentric study, REE was measured by indirect calorimetry before anticancer treatment initiation. C-Reactive Protein (CRP), albumin, transthyretin and PS were collected. Measured REE was compared with predicted REE as defined by the Harris-Benedict formula. Patients were classified as hypometabolic (REE $<$ 90%), normometabolic (90-110%) or hypermetabolic ($>$ 110%). Toxicity was assessed after the first cycle of treatment. An EAT was defined as any event leading to unplanned hospital admission, dose reduction, treatment delay ($>$ 7 days) or discontinuation. **Results:** A total of 277 patients (pts) with solid tumors (gastro-intestinal 25%, genitourinary 23%, thoracic 22%) were included. Sex ratio: 1.25; median age: 63 years (20-91). Most of the pts (211; 76%) had locally advanced or metastatic disease and were treated with chemotherapy (246; 89%) or tyrosine-kinase inhibitor (30; 11%). Calorimetry revealed pts with either normo- (29%), hyper- (51%) or hypometabolism (20%). A subset of 59 pts (21%) experienced an EAT. The occurrence of EAT was associated with poor PS (2-3 vs 0-1: OR = 2.04 [1.12-3.73], p = 0.029), low albumin ($<$ 35 vs $\geq$ 35g/l: OR = 2.39 [1.03-5.54], p = 0.048), inflammation (CRP $\geq$ 10 vs $<$ 10mg/l: OR = 2.43 [1.35-4.37], p = 0.004) and abnormal metabolism (abnormal vs normal: OR = 2.36 [1.13-4.95], p = 0.023). In multivariate analysis, elevated CRP was an independent predictor of EAT (p = 0.047). The REE was associated with higher sensitivity (83%) than CRP (55%), PS (41%) and albumin (17%) to predict EAT. **Conclusions:** Pts with abnormal metabolism experience more early acute toxicity. The measurement of resting energy expenditure might improve the detection of patients at risk for toxicity and missed with the standard clinical evaluation.

9621 Poster Session (Board #280), Sat, 1:15 PM-4:45 PM

Clinical predictors of recurrent venous thromboembolism (VTE) in cancer patients from a randomized trial of long-term tinzaparin versus warfarin for treatment: The CATCH study. *First Author: Alok A. Khorana, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH*

Background: Cancer patients with VTE continue to remain at high risk for recurrent VTE even with adequate anticoagulation. We determined baseline clinical predictors of recurrent VTE, including the previously developed Ottawa Score, in a pre-specified analysis of the CATCH study. **Methods:** The CATCH study was a randomized, open-label, multicenter, Phase III trial (NCT01130025) comparing tinzaparin 175 IU/kg once daily for 6 months with initial tinzaparin transitioning to dose-adjusted warfarin (target INR 2–3) for 6 months in patients with active cancer and acute, symptomatic proximal deep vein thrombosis and/or pulmonary embolism. Clinical predictors of recurrent events were identified using Fisher's exact test; competing risk regression analysis was then conducted accounting for multiple variables. **Results:** We evaluated multiple clinical variables present at or prior to randomization. Of 900 randomized patients, 492 (54.7%) had metastatic disease, 288 (32.0%) were on chemotherapy, 286 (31.8%) had recent hospitalization, 209 (23.2%) had ECOG performance status 2, 129 (14.3%) had venous compression from mass or adenopathy and 92 (10.2%) had recent radiation therapy; VTE occurred in 6.9% of the tinzaparin arm versus 10.0% of the warfarin arm (HR 0.65; 95% CI 0.41–1.03), as reported. In multivariate analysis, risk factors associated with recurrent VTE included venous compression (HR 2.96; 95% CI 1.8–4.86; $P<$ 0.001) and diagnosis of hepatobiliary cancer (HR 2.91; 95% CI 1.2–7.02; $P=$ 0.018). Ottawa score did not predict for recurrence risk, with recurrent VTE rates of 3.4, 9.7 and 8.2% in low-, intermediate- and high-risk groups, respectively. **Conclusions:** Cancer patients with acute VTE are at significant risk for recurrent events, despite anticoagulation. Major clinical predictors of recurrence include tumor venous compression and a diagnosis of hepatobiliary cancer. More intense treatment strategies for higher-risk patients should be considered. Clinical trial information: NCT01130025.

9622 Poster Session (Board #281), Sat, 1:15 PM-4:45 PM

Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting (CINV) in moderately emetogenic therapy (MEC). *First Author: Paul Joseph Hesketh, Lahey Hosp and Med Ctr, Burlington, MA*

Background: Rolapitant, a novel NK-1 receptor antagonist, showed efficacy for prevention of CINV in patients (pts) receiving MEC (anthracycline/cyclophosphamide (A/C) and other regimens) in a global phase 3 trial. Recent anti-emetic guidelines consider A/C based regimens to be highly emetogenic. In this post hoc analysis, the efficacy and safety of rolapitant was assessed during Cycle 1 in pts receiving non-AC MEC. **Methods**: In a double-blind, active-controlled study, pts were randomized to oral rolapitant 200 mg or placebo 1–2 hours before MEC. All pts received granisetron 2 mg oral on days 1-3 and oral dexamethasone 20 mg on day 1. Pt subgroups were carboplatin-based MEC and Other MEC (OM; non-AC, non-carboplatin). Complete response (CR=no emesis and no use of rescue medication), no emesis, and no nausea were assessed during overall (0-120 h), acute (0-24 h), and delayed (>24-120 h) phases. **Results**: CR was significantly (P<0.05) higher with rolapitant than active control for overall and delayed phases in the carboplatin subset and for acute and overall phases in the OM subset (Table). No emesis rates were significantly (p<0.05) higher with rolapitant in carboplatin and OM subsets in the overall phase. No nausea rates were significantly higher with rolapitant during the overall (p= 0.023) and delayed (p=0.034) phases in carboplatin-based MEC. Incidences of treatment-related AEs in Cycle 1 with rolapitant vs. active control were 11.3% vs. 6.7% in carboplatin-based and 9.2% vs. 6.0% in OM-based therapy. Most common AEs with rolapitant and active control were constipation, fatigue, and headache. **Conclusions**: Rolapitant was superior to active control in preventing CINV in pt subgroups receiving either carboplatin or other non-AC MEC regimens. Rolapitant was well tolerated with low incidence of AEs. Clinical trial information: NCT01500226.

	Carboplatin (N = 401)		Other MEC (OM) (N = 228)	
Complete response rates (%)	Rolapitant (N = 192)	Active control (N = 209)	Rolapitant (N = 130)	Active control (N = 98)
Delayed phase (>24–120 h)	82.3%	65.6%	66.9%	60.2%
p-value[a]		<0.001		0.296
Acute phase (0–24 h)	91.7%	88.0%	89.2%	76.5%
p-value[a]		0.231		0.010
Overall phase (0–120 h)	80.2%	64.6%	66.9%	54.1%
p-value[a]		<0.001		0.049

[a]unstratified CMH test.

9623 Poster Session (Board #282), Sat, 1:15 PM-4:45 PM

Establishing a new quality of life (QL) / patient reported outcome (PRO) / symptom scale in advanced cancer: Content validity for the "CSS" based on input from 3860 patients. *First Author: Julia Chia-Ying Shih, Albert Einstein College of Medicine - Jacobi Medical Center, Bronx, NY*

Background: Preserving or improving QL while managing symptoms are major goals in cancer care. To achieve these ends, the input of patients (pts) is mandatory as these are true PROs. The CSS (Cancer Symptom Scale) is a measure for pts with advanced cancer based on issues common to most malignancies; additionally, the CSS is designed to enhance patient input in late in life care settings such as hospice. While other measures exist, few if any are used in these settings routinely. The CSS is based on the model of the well-validated LCSS, and is planned to be a feasible and acceptable measure appropriate for use on an ePRO platform to minimize patient and caregiver burden. **Methods:** 50 cancer health care providers (HCPs) developed an initial list of issues to be evaluated by pts. This anonymous web-based survey used the resources of Nexcura.com and was then sent to pts to rate 18 to 21 issues on a 5 point scale ranging from "not important at all" to "very important (VI)." **Results:** Responses were given by 3,860 pts with: lung (660), breast (1072) and prostate (2128) cancer. 299 pts with advanced cancer had low performance status (KPS ≤60%) / stage IV extent. Results based on the top 2 categories (VI + important) of the leading 15 issues are listed below in the Table. **Conclusions:** 1) Responses from all 3860 pts are similar to those of the 299 with advanced disease, except for greater concern for pain and appetite in those with advanced cancer, and less importance for body image; 2) HCPs often rated items similarly to pts, but underestimated pt concern with concentration; and 3) the 5 items of greatest importance to patients are not symptoms but are items of global concern, and must be included in validated PRO measures. We believe this content validity survey for the CSS is the largest obtaining PROs from pts with cancer.

	% of All Patients (N max = 3860)	% of Stage IV Patients (N max = 299)
Quality of life	97	97
Concentration*	97	100
Independence	96	96
Ability to perform normal activities	95	93
Sleep	93	92
Fatigue	90	91
Dyspnea	83	80
Depression	82	78
Anxiety	78	74
Pain	77	83
Symptom distress	76	73
Diarrhea	69	66
Constipation	66	67
Appetite	66	76
Body image	65	44

* only tested in breast ca, and in 25 pts with advanced cancer.

9624 Poster Session (Board #283), Sat, 1:15 PM-4:45 PM

Sleep quality and its association with fatigue, symptom burden, and mood in patients with advanced cancer in a phase 1 clinic. *First Author: Goldy George, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Limited data exist about sleep quality (SQ) in patients (pts) on phase 1 clinical trials. Poor SQ is often not captured as an adverse event (AE) and its association with fatigue, one of the most frequently reported AEs, is not documented routinely. Here, we describe SQ and the relation between SQ and fatigue, symptoms, and mood in pts in the MD Anderson phase 1 clinical trials clinic. **Methods:** Sleep, fatigue, symptom severity/interference and mood were assessed using the validated Pittsburgh Sleep Quality Index (PSQI), Brief Fatigue Inventory, MD Anderson Symptom Inventory, and Profile of Mood States, respectively; ECOG was from medical records. Statistics included multivariable regression models. **Results:** The sample (N = 262) was 52% female, 80% ECOG 0-1, mean age 58.4 ± 0.7y. The % of "poor" sleepers (global PSQI score > 5) was 64%. In contrast, pts' subjective self-assessment of SQ was: 27% as "bad" or "fairly bad", 59% as "fairly good" and 14% as "very good". Among pts, 28% took medicines for sleep; 15% slept < 6 hours at night; 20% had sleep latency > 30 minutes for ≥ 3 nights per week; and 42% reported poor sleep efficiency (< 85% time in bed spent sleeping). The % of pts reporting fatigue were 35% as "severe", 14% as "moderate", 39% as "mild", and 12% "none". In an adjusted multivariable regression model, poor overall SQ was associated with greater fatigue ($P < 0.001$). Interestingly, SQ (PSQI) sub-components associated with greater fatigue were sleep disturbance (OR = 2.6, 95% CI = 1.3, 5.1, $P < 0.007$) and daytime dysfunction (OR = 4.1, 95% CI = 2.3, 7.6, $P < 0.001$), but sleep latency, and sleep efficiency were not related to fatigue. Poor overall SQ also was associated with higher symptom severity (Pearson's r = 0.6, $P < 0.001$), mood disturbance (Pearson's r = 0.5, $P < 0.001$), and greater fatigue-(Pearson's r = 0.4, P < 0.001) and symptom-related interference (Pearson's r = 0.5, P < 0.001) with activity, walking ability, relationships with others, and enjoyment of life. **Conclusions:** Poor SQ is a significant problem (64% pts) and associated with greater fatigue, symptom severity, symptom interference, and greater mood disturbance. Deciphering SQ should be routine practice in phase 1 clinical assessments.

9625 Poster Session (Board #284), Sat, 1:15 PM-4:45 PM

Patient-reported experience combining complementary and alternative medicine (CAM) with conventional oncology treatment (COT). *First Author: Alvaro G. Menendez, Roger Williams Medical Center/ Boston University School of Medicine, Providence, RI*

Background: CAM encompasses a diverse group of interventions not generally considered to be part of COT. The objective of this study is to describe the characteristics, factors and patient reported experiences associated with the use of CAM by patients (pts) receiving COT. **Methods:** An IRB approved, 14 item questionnaire was offered to all pts receiving COT at a single institution cancer center over a defined 2 mo interval. Demographics, prevalence and type of CAM used; as well as specific questions to define oncologist endorsement of CAM in combination with COT were collected. **Results:** 198/215 (92%) questionnaires were completed and analyzed. Utilization of CAM before the diagnosis (dx) of cancer was seen in 21/198(11%) pts. Following a cancer dx, 114/198(58%) reported the use of CAM. Dietary supplements were the most commonly used 57/108(52%); 41/108(38%) used massage and other mind-body techniques; while 10/108(9%) used multiple types of CAM. The source of CAM information was the oncologist in 42/138(30%), TV in 26/138(19%) and friends/family in 23/138(17%). Analysis demonstrated no significant difference in the use of CAM by gender, age, level of education or family income; however Hispanic ethnicity was a statistically significant variable (p = 0.027) in reported quality of life improvement with CAM. 141/198(71%) of pts reported a desire to discuss CAM integration into their COT, however only 95/198(48%) did so. After discussion with their oncologist, 30/45(66%) of pts reported receiving additional information about CAM, 11/45(24%) reported that CAM use was acceptable but did not receive additional information and 4/45(9%) were discouraged from CAM use. **Conclusions:** This study reveals that routine CAM use is not uncommon, but is four times more frequent after a dx of cancer. The majority of pts do not address CAM with their oncologist, despite a reported interest in doing so. About 1/3 of oncologists were reported not to provide additional information and actually discouraged CAM. This study identifies that the majority of pts with cancer use CAM, however potential barriers between patients and oncologists exist for the effective integration of CAM with COT.

9626 Poster Session (Board #285), Sat, 1:15 PM-4:45 PM

Interpreting the febrile neutropenia rates from randomized controlled trials for consideration of primary prophylaxis in the real world: A systematic review and meta-analysis. *First Author: Judy Truong, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Guidelines recommend primary prophylaxis (PP) with granulocyte colony stimulating factors (G-CSF) for patients above a febrile neutropenia (FN) risk threshold of 20%. When considering the role of PP with G-CSF, practitioners often use FN rates of regimens based on data from randomized controlled trials (RCTs), which are often comprised of highly selected patients. Patients who received these regimens in the real world may be at higher risk of FN. **Methods:** A systematic literature search was conducted using MEDLINE, EMBASE, and CENTRAL databases for full-length articles reporting FN rates for breast cancer-related chemotherapies between Jan/96 and Feb/14. A regimen was included if there was at least 1 RCT and 1 observational study (ObS). Any pilot, dose-finding, feasibility, phase I, or phase II studies were excluded. Meta-regression using logistic regression with fixed-effects and random-effects was used to model the odds ratio (OR) of FN with 95% confidence intervals (CI). **Results:** 128 studies involving 29 regimens and 50,069 patients were identified. 65 ObS (n = 7,812) and 110 RCT (n = 42,257) cohorts were included. The unadjusted FN rate was 11.7% in ObS and 7.9% in RCT cohorts. The univariable fixed effects OR for FN in the ObS compared to RCT cohorts was 1.58 (CI: 1.09-2.28; p= 0.017). The FN rates remained significantly higher in the ObS compared to RCT cohorts (OR = 1.74; CI: 1.15-2.62; p =0.012) in the multivariable mixed effects model adjusted for age, chemotherapy intent, chemotherapy regimen and accounted for random effects of study and chemotherapy regimen. This meant that a 13% FN rate in RCT would translate into 20% FN rate in ObS study. The unadjusted FN rates were higher in taxane regimens than non-taxane regimens in both the ObS (16.5% vs. 6.4%) and RCT (10.0% vs. 4.7%) cohorts. **Conclusions:** FN rates in ObS are significantly higher than suggested by RCTs in many breast cancer-related chemotherapy regimens. A 13% FN rate in RCT appeared to correspond to the 20% FN rates in the real world. Large population-based studies are needed to confirm FN rates of different regimens in the real world to ensure optimal utilization of G-CSF.

9627 Poster Session (Board #286), Sat, 1:15 PM-4:45 PM

Can a homeopathic medicine complex reduce hot flashes induced by adjuvant endocrine therapy in localized breast cancer patients? Results of a randomized placebo-controlled phase III trial. *First Author: Pierre-Etienne Heudel, CENTRE LEON BERARD, Lyon, France*

Background: Homeopathy is already used for the management of menopausal hot flashes (HF) and could reduce this frequent endocrine therapy's (ET) side effect. **Methods:** Localized breast cancer patients (pts), treated for at least one month with adjuvant ET and complaining of HF were included in a multicentric randomized double-blind phase III study. Primary endpoint, analyzed in an intent-to-treat basis, was the variation of HF score (HFS) between pre and 4 weeks (w) post randomization. HFS was calculated (over 1 w) as the mean of HF frequency, weighted by a 4-level intensity scale. After a run-in period of placebo (2-4 w to exclude pts with strong placebo effect), only pts maintaining a HFS ≥ 10 were randomized to receive Actheane (a homeopathic medicine complex BRN-01) (A) vs Placebo (P) during 2 months. The trial was powered (90% power, two-sided alpha of 5%) to detect a 5-point (± 8.6) difference of HFS variation between arms; 138 randomized pts were needed. Secondary endpoints were HFS variation after 8 w of treatment, compliance, tolerance, quality of life (QoL) and satisfaction of pts. **Results:** From February 2010 to April 2014, 299 pts were included and 138 (46.2%) randomized (65 to A and 73 to P). Patients' characteristics were well balanced between groups. Median age was 51 years [range 36-72], 82 pts were postmenopausal, 79 were treated by tamoxifen and 59 by aromatase inhibitor. No statistical difference was observed in HFS variation after 4 w (median of -2.9 points for A vs -2.5 for P; p = 0.76, corresponding to a median decrease of 17.2% vs 15.4% of HFS). However, HFS decreased for 75.4% of pts in A arm vs 67.6% in P. QoL score after 4 w was stable or improved for respectively 71.7% vs 73.9% of pts. Compliance to study treatment was similar between the 2 arms (82% for A vs 85% for P, p = 0.61). None of the 3 grade 3 adverse events declared (1 cholecystitis and 2 joint pains) were related to treatment. **Conclusions:** Although efficacy hypothesis was not reached, the management of HF globally decreased HFS, with positive impact on QoL. Because HF are a disabling symptom without validated treatment, Actheane could be a well-tolerated therapeutic option. Clinical trial information: NCT01246427.

9628 Poster Session (Board #287), Sat, 1:15 PM-4:45 PM

A randomised, open-label trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) plus standard care versus standard care alone to prevent / attenuate cachexia in advanced cancer patients undergoing chemotherapy. *First Author: Stein Kaasa, Trondheim University Hospital, Trondheim, Norway*

Background: The pathophysiology of cancer cachexia is multi-factorial consisting of muscle wasting, negative protein and energy balance, and systemic inflammation. There is no established treatment for cachexia, paradoxical to the importance of this condition in limiting oncology treatment. New approaches are needed to address the complexity of the syndrome and to challenge the accepted therapeutic nihilism. To treat cachexia optimally it has been argued that a multimodal intervention is necessary to enable the multi factorial pathophysiology to be targeted. Integral to this is targeting inflammation as the main driver of cachexia. **Methods:** An international, multicentre randomised phase II study was conducted. Eligible patients had advanced lung cancer or pancreatic cancer and were due to start palliative chemotherapy. Patients were randomised (1:1 ratio) to receive either a multimodal intervention (exercise, anti-inflammatories, energy dense nutritional supplements combined with dietary advice) or standard cancer care. Primary outcome measures were feasibility of the intervention assessed by compliance and enrolment. Secondary outcomes examined weight, physical activity (using ActivPAL) and CT based muscle mass. Means and standard deviations (SD) are reported. **Results:** Forty-six patients were recruited from three regional cancer center's (Glascow (UK), Trondheim and Oslo (Norway). Overall compliance was $>$ 54% in all components of the intervention. Patients' in the treatment arm weight increased (0.91% (SD 2.46)), whilst those in the control arm lost weight (-2.12% (SD 2.50)), $p < 0.001$ ($N = 41$). Patients in the control arm lost 2.2% more muscle than the treatment arm, $p =$ 0,69. There were no statistical significant differences in physical activity in the patients that had repeated measurements of physical activity with ActivPal ($n = 22$). **Conclusions:** A multimodal cachexia intervention is feasible and improves weight in patients with incurable lung or pancreatic cancer. Based on these exciting findings, a definitive phase III study is now underway. Clinical trial information: NCT01419145.

9629 Poster Session (Board #288), Sat, 1:15 PM-4:45 PM

A phase III, randomized, double-blind study of single-dose intravenous fosaprepitant in preventing chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy. *First Author: Bernardo Leon Rapoport, The Medical Oncology Center of Rosebank, Johannesburg, South Africa*

Background: This is the first study performed to directly evaluate the efficacy and safety of a single dose of intravenous (IV) fosaprepitant (FA), an NK1 receptor antagonist, used with a 5-HT3 antagonist and corticosteroid in subjects receiving moderately emetogenic chemotherapy (MEC). **Methods:** This was a global, phase 3, randomized, double-blind, parallel-group study in adult subjects naive to MEC and highly emetogenic chemotherapy (HEC) scheduled to receive an IV dose of ≥ 1 MEC agents on treatment day 1. Subjects were randomly assigned 1:1 to a control or FA regimen. Those in the control regimen received 8 mg oral ondansetron, 20 mg dexamethasone, and IV saline as placebo before the first dose of MEC on day 1, and 8 mg oral ondansetron 8 hours after the first dose, followed by 8 mg oral ondansetron every 12 hours on days 2 and 3. Those in the FA regimen received the same dose of oral ondansetron on day 1, along with 12 mg dexamethasone and a single dose of 150 mg IV FA before the first dose of MEC on day 1, with no additional prophylactic antiemetic beyond day 1. Primary outcomes were the proportion of subjects with a complete response (CR: no vomiting and no rescue medication use) during the delayed phase (25 to 120 hours after MEC) and FA safety/tolerability. **Results:** Baseline characteristics were generally balanced among the 1000 subjects in the primary efficacy population (502 FA, 498 control). The majority were white, $\geq$ 50 years of age, and female. CR was achieved in 396 (78.9%) subjects in the FA regimen and 341 (68.5%) in the control regimen during the delayed phase (treatment difference of 10.4%, $P <$ 0.001). Safety profiles were comparable between the treatment groups; drug-related adverse events occurred in 8.5% (FA) vs 9.1% (control). There were no cases of severe infusion-site pain, erythema, or induration reported; 3 cases of infusion-site thrombophlebitis were observed in the FA regimen compared with 0 in the control regimen. **Conclusions:** Single-dose 150-mg IV FA regimen is generally safe and well tolerated and provides superior control of CINV associated with MEC as measured by the proportion of subjects with CR in the delayed phase. Clinical trial information: NCT01594749.

9630 Poster Session (Board #289), Sat, 1:15 PM-4:45 PM

Effective complementary ASCO policy and day to day decision support strategies optimize anti-emetic choices. *First Author: Anmol Baranwal, Oncology Analytics, Inc., Plantation, FL*

Background: Emetogenicity is a common reason for patients forgoing effective chemotherapy. ASCO, in its 2013 Top Five list, recommends against overuse of antiemetics and for the use of cost-effective agents. Oncology Analytics (OA) is a cancer care decision-support entity comprised of oncologists, PharmDs and oncology RNs, interacting with some 5000 oncologists and promoting high quality cost-effective cancer treatment based on level I data and national guidelines. We hypothesize that on-patent antiemetics are overused in comparison to equally effective generics; that this misuse/overuse induces financial toxicity; and that these ill effects can be offset by ASCO policy initiatives and OA decision support activities. **Methods:** We analyzed antiemetic requests in 2013 & 2014 in Georgia and Florida. Linear regression and chi-squared were utilized to determine time trends for the ratio of palonosetron vs. generic antiemetic regimens (ondansetron and granisetron) across these 7 quarters. We contrasted prescribing behavior concurrent with ongoing OA interaction, before and after the release of ASCO recommendations against unnecessary expensive anti-emetics. **Results:** 12,116 antiemetic requests were assessed in a pre-approval setting. After the 2013 ASCO policy recommendation, there was an immediate increase in the likelihood of requests for cost-effective regimens compared to more expensive "on -patent" choices (chi-squared $p = 0.004$). Over a thousand (1164/5341, 22%) of the requests for branded medications were inappropriate according to ASCO and/or NCCN guidelines, and discouraged by OA. Over this time span, there is a clear trend toward cost-effective generic choices, decreasing extrapolated costs by about $300,000 annually. **Conclusions:** The ASCO-defined overuse of expensive antiemetics in Florida and Georgia is substantial. ASCO national Policy, supported by daily OA interventions, diminishes the unnecessary use of expensive anti-emetics, increases the use of cost-effective antiemetic alternatives, and diminishes financial toxicity while enhancing cancer care quality. ASCO guidelines, when supported by a decision support program, result in significant cost savings.

9631 Poster Session (Board #290), Sat, 1:15 PM-4:45 PM

Do cancer patients present with subclinical peripheral neuropathy prior to initiating neurotoxic chemotherapy? *First Author: Sabrina Ramnarine, Edinburgh Cancer Research UK Centre, University of Edinburgh, Edinburgh, United Kingdom*

Background: Chemotherapy-induced peripheral neuropathy (CIPN), is a common dose-limiting toxicity which may compromise patient survival, leaving many with chronic pain, disability and a negative impact on quality of life. The natural history and underlying pathophysiological mechanisms are unclear. Clinical management is challenging, therefore, early identification and prediction of patients who will develop CIPN is critical. Using a translational approach, this study aims to investigate and characterise the presence of subclinical peripheral neuropathy in gynaecological, colorectal and lung cancer patients. **Methods:** Quantitative Sensory Testing (QST) was conducted on 21 patients with the above cancers prior to starting neurotoxic chemotherapy and compared with 21 age and gender matched healthy controls, to characterise somatosensory profile. Skin temperature, thresholds for thermal, mechanical and sharpness detection along with sensorimotor function (grooved pegboard test) were assessed. Resting heart rate was measured as a marker of autonomic function. **Results:** Heart rate differed significantly between the two groups (healthy, mean 72.3 vs 87.9 in patients; $p < 0.0001$). Detection of painful thermal thresholds (lower limb) were also significantly different in the healthy group compared to patients (hot: 47.4°C vs 45.4°C; $p = 0.005$: cold: 9.7°C vs 16.2°C; $p =$ 0.04) with evidence of variance in the upper limb for hot (42.0°C vs 39.4°C; $p = 0.03$). Although not statistically significant, large differences existed between the groups in the pegboard test: dominant hand 75.6secs vs 83.2secs ($p = 0.15$), non-dominant hand, 79.0secs vs 88.4secs ($p =$ 0.06). **Conclusions:** This cohort of patients exhibited signs suggestive of subclinical autonomic and sensory nerve dysfunction prior to initiating chemotherapy manifested as: increased resting heart rate, hot and cold hyperalgesia and evidence of some sensorimotor impairment. This indicates a cancer-mediated process potentially contributing to CIPN and may provide insight into the complexities of the underlying pathophysiological mechanisms.

9632 Poster Session (Board #291), Sat, 1:15 PM-4:45 PM

Cost communication preferences, financial burden, and health-related quality-of-life (HRQoL). *First Author: Jonas A. De Souza, University of Chicago Medicine, Chicago, IL*

Background: Care team- patient communication regarding costs has been suggested as a means of minimizing patients' financial burden (FB) in oncology. However, it is unknown how cost communication preferences are related to FB or HRQoL. **Methods:** Patients with advanced cancers who had completed at least 3 months of chemotherapy were asked whether they agreed or disagreed with the following communication preference items: (1) willingness to discuss costs; (2) willingness to know the costs before treatment; (3) willingness to allow costs to be incorporated into shared-decision making (SDM); (4) wishing costs had been discussed in the past; (5) and whether costs were actually discussed. FB was assessed by the COST (COmprehensive Score for financial Toxicity), as well as by the EORTC financial impact (FI). Demographics, resource utilization, and HRQoL, measured by the FACT-G and EORTC QLQ-C30, were collected. Linear regression and chi-square tests were performed. **Results:** 233 patients were assessed. Most of the patients (n = 190, 82%) had never discussed costs with their care team. There was no association between preferences and HRQoL. Patients with FB by either instrument were more likely to report item (4) (COST, $p < .01$; FI, $p < .001$). Out of the 43 (18%) patients who agreed with this item, 34 (79%) had FB by COST, and 37 (86%) by the FI. There was no significant association between items (1), (2), (3), (5) and FB. Factors associated with communication preferences included age (item 4), race (2 and 4), employment (4), income (4) and education (1), as listed in the table below. **Conclusions:** HRQoL is not significantly associated with cost communication preferences. An opportunity for intervention was identified, as most of the patients who wished to have discussed costs in the past were now experiencing FB. The knowledge of these preferences may indicate the best timing and population with whom costs should be discussed.

Willingness to:	A%	D%	U%	Age	Race	Employment	Income	Education
(1) to discuss	45	29	26	NS	NS	NS	NS	*
(2) to know	68	15	17	NS	*	NS	NS	NS
(3) to use in SDM	41	37	22	NS	NS	NS	NS	NS
(4) Wished had discussed	18	54	27	*	*	**	**	NS
(5) Costs discussed	18	82	0	NS	NS	NS	NS	NS

A%, agree; D%, disagree; U%, unsure; NS, not significant; * $p < .05$; ** $p < .005$

9633 Poster Session (Board #292), Sat, 1:15 PM-4:45 PM

Randomized trial of a home-based exercise intervention for patients with advanced colorectal cancer: Effects on physical functioning and activity levels. *First Author: Karen Basen-Engquist, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Considerable evidence demonstrates the benefits of exercise for cancer survivors, but few studies focus on those living with advanced disease. We conducted a randomized trial of a home-based exercise intervention for patients with advanced colorectal cancer (CRC), and investigated the effects on physical functioning (primary) and physical activity. **Methods:** 152 patients with advanced CRC were recruited through the Community Clinical Oncology Program, and were randomized to: 1) a 4 month home-based exercise intervention (EX), or 2) a relaxation control group (R). Both groups received telephone coaching/prompts, instructional materials, and brief coaching and letters from their provider. The EX arm received pedometers and resistance bands. Participants completed self-reports of physical functioning and activity, and performance tasks (2-min step test, 8-ft up and go, arm curl test, 30-sec sit–to-stand test) at baseline and end of study (EOS). Linear mixed model analysis tested intervention arm effects on EOS outcomes, adjusting for baseline and accounting for random effects of study site and physician. **Results:** Of the 152 randomized patients, 55 (72%) in EX and 57 (75%) in R completed the study. No serious adverse events were attributable to the interventions. At EOS, the EX arm reported more light and moderate activity at EOS than the R arm ($p = 0.003$ and 0.002, respectively), and performed better on the 30-sec sit-to-stand than R group participants ($p = 0.05$), with a trend toward better performance on the 8-ft up-and-go ($p = .12$). There were no significant group differences in SF-36 physical functioning, step test, or arm curl test. **Conclusions:** In one of the first trials to test home-based exercise for patients with advanced CRC, EX effectively increased activity levels and improved select aspects of physical functioning, suggesting it may be a safe and useful intervention in this population. Clinical trial information: NCT00985400.

Estimated effects of EX on physical functioning.

Outcome	Effect estimate (SE)	p
30-sec sit-to-stand	1.1 (0.6)	0.05
8-ft Up-and-Go	-0.9 (0.6)	0.12
2-min step	4.5 (4.7)	0.33
Arm curl	0.5 (0.7)	0.53
SF-36 Physical Functioning	3.2 (4.6)	0.49

TPS9634 Poster Session (Board #293a), Sat, 1:15 PM-4:45 PM

A feasibility trial of geriatric assessment and integrated care plan for older cancer patients. *First Author: Martine Puts, University of Toronto, Toronto, ON, Canada*

Background: The majority of persons diagnosed with cancer are older adults. A comprehensive geriatric assessment (CGA) can identify current health care issues, start interventions to prevent/postpone adverse outcomes and maintain/improve the functional status and well-being of older adults. However, there is limited and conflicting evidence to support the effectiveness of CGA in oncology settings. Here, we explore the impact of a CGA and integrated care plan in optimizing outcomes in older patients with advanced breast (BC), gastrointestinal (GI) or genitourinary (GU) cancer **Methods:** A two-group parallel single-blind phase II RCT is enrolling 60 patients aged 70 years and over, diagnosed with GI, GU or BC, referred for first line chemotherapy or having received < 2cycles (< 6weeks) of chemotherapy at Princess Margaret Cancer Centre. Patients need to be fluent in English, have a life expectancy > 6 months, ECOG PS 0-2 and able to provide informed consent. Randomization to intervention and control group is 1:1 and stratified by treatment intent (adjuvant vs. palliative). The intervention includes a full CGA by a multidisciplinary geriatric team followed by an integrated care plan to address the issues identified. Based on the CGA and discussion with the patient, tailored evidence-based interventions will be carried out by the team using a standardized intervention protocol. Participants in the intervention group are seen by the intervention team at baseline for the CGA and development of the integrated care plan; and at 3 and 6 months to assess intervention fidelity and measure outcomes. The co-primary outcomes are: 1) Maintaining/improving quality of life (EORTC QLQ-C30); 2) Modification of the cancer treatment plan. The secondary outcomes are: 1) Functional status (OARS Instrumental Activities of Daily Living); and 2) Feasibility of the study by tumor site. 15 of 60 planned patients have been enrolled to date. This will be one of the first RCTs of CGA in geriatric oncology to show feasibility and provide estimates of impact on relevant outcomes to inform the design of a phase 3 trial. Clinical trial information: NCT02222259.

TPS9635 Poster Session (Board #293b), Sat, 1:15 PM-4:45 PM

VOTRAGE study pazopanib in vulnerable elderly patients after geriatric assessment—A phase I study with geriatric criteria. *First Author: Loic Mourey, Institut Universitaire du Cancer - Oncopole, Toulouse, France*

Background: Efficacy and toxicity of targeted therapies don't seem to vary considerably with age, but the impact of side effects in elderly patients is a major concern for clinicians. Our study aims to find the maximum tolerated dose (MTD) of Pazopanib (P) in a population of elderly patients, classified as "vulnerable" after comprehensive geriatric assessment (CGA), with a phase I methodology, integrating a geriatric criterion (2 points drop in ADL). Pharmacokinetic and pharmacogenomic studies are also planned. **Methods:** Open-label, multicenter (4), non-randomized, phase 1 dose escalation study to determine MTD and DLT (dose-limiting toxicity) of P in a population of vulnerable elderly patients, selected after CGA.Eligible patients will be enrolled into a standard 3+3 design with a dose of P of 400, 600 and 800 mg daily. DLT will be assessed during the first month. Patients will receive P until progression or untolerable toxicities (30 pts max). **Main inclusion criteria:** Age ≥ 75; metastatic cancer (kidney, lung, neuroendocrine pancreatic, sarcoma, ovary, thyroid, bladder, breast); No geriatric syndrome, no ADL impairment; Geriatric disorders (and/or); CIRSG: ≤2 gr 3 comorbidities; IADL: <8; SPPB: 6-9; MNA: 17-23; MMSE: < 24; GDS 15: >5 **Geriatric assessment:** G8 ADL: Activities Daily Living, IADL: Instrumental ADL MMSE: Mini-Mental State Examination SPPB: Short Physical Performance Battery MNA: Mini-Nutritional Assessment CAM: Confusion Assessment Method GDS-15: Geriatric Depression Scale CIRS-G: Cumulative Illness Rating Scale for Geriatrics **DLT definition:** The MTD is defined as the highest dose level for which 6 patients were treated with a maximum of one patient (~20%) presenting a DLT during the first month of treatment. DLT is defined as follow: -geriatric criteria: drop ≥2 points in ADL -classical hematologic and non hematologic criteria. **Status of the study**: 11 patients included (2^{nd} cohort of 2^{nd}level - 600 mg daily) **Conclusions:** This study is an attempt to adapt a phase I methodology to vulnerable elderly patients. The results will help clinicians to prescribe Pazopanib in this particular but numerous population, relying on geriatric assessment. Study funded by GSK Clinical trial information: NCT01642017.

TPS9636 Poster Session (Board #294a), Sat, 1:15 PM-4:45 PM

Cancer-related cognitive dysfunction (CRCD) and psychosocial development in young adult cancer survivors. *First Author: Kim Edelstein, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Chemotherapy is associated with long-lasting neurocognitive sequelae and structural and functional brain imaging changes in about 25% of older adults who do not receive central nervous system (CNS) directed treatment. This suggests that cancer or its treatment affects the brain regardless of primary tumor site. Because the brain continues to develop into the 3rd decade of life, younger adults (YA; age 18-39 yrs) may be vulnerable to CRCD. Cancer also disrupts acquisition of developmental milestones in YA. CRCD may exacerbate those disruptions, but this has never been studied. Study aims are to characterize CRCD in YA, explore its relation to psychosocial development, and identify subgroups at risk of adverse outcomes. **Methods:** In this prospective, inception-cohort study, we are recruiting YA who do not require CNS-directed therapy from ambulatory clinics at the Princess Margaret Cancer Centre (leukemia, lymphoma, breast, gynecology, gastrointestinal, genitourinary, sarcoma) and the YA Oncology clinic at the Jewish General Hospital: 200 YA with cancer who require chemotherapy, 100 YA with cancer who do not require it, and 100 healthy YA with no cancer history. As of Jan 30 2015, 113 participants were enrolled. Chemotherapy patients are assessed prior to treatment, and then 6 and 12 months later. The other groups are assessed at similar time intervals. The 2-hr test battery consists of standardized neurocognitive tests sensitive to CRCD and validated self-report psychosocial measures. Repeated measures mixed effects models will be used to examine longitudinal changes in each of the neurocognitive domains and each of the psychosocial development scores, using the predicted residual sum of squares method to avoid interpretation problems associated with repeated testing. Relationships between CRCD, psychosocial development, treatment, cancer type, and individual characteristics will be examined using regression. Exploratory analyses will investigate whether demographic, disease, or treatment factors contribute to longitudinal changes. Results will provide the basis for interventions that alleviate the psychosocial and cognitive sequelae in this underserved population.

TPS9637 Poster Session (Board #294b), Sat, 1:15 PM-4:45 PM

Rehabilitation of cognitive dysfunction in brain tumor patients. *First Author: Nadine M. Richard, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Quality of life is increasingly recognized as important to comprehensive cancer care. Individuals with brain tumors face the particular challenge of cognitive impairment from their disease and/or treatment effects. Prevalent deficits in processing speed, memory, attention and executive functions interfere with patients' interpersonal relationships, occupational activities and functional independence. Standard medical care typically provides minimal education or intervention for cognitive symptoms. Cognitive rehabilitation is a relatively new field, with very few well-controlled studies in cancer patients. As a result, oncology and supportive care teams lack accessible, reliable tools to address cognitive dysfunction. **Methods:** Building on research in other cognitively-impaired populations, we designed two behavioural interventions for brain tumor patients. Each offers a structured yet client-centered program through 8 weekly individual treatment sessions and between-session exercises. Goal Management Training (GMT) is a neuroscience-based intervention combining mindfulness practice and strategy training. The Brain Health Workshop (BHW) is a supportive psycho-educational program about the brain, cognition, and living with effects of a brain tumor. Using a prospective randomized controlled design, 54 brain tumor patients (with chronic cognitive dysfunction, $\geq$ 3 months post-radiation or surgery) are being enrolled in one of three study arms: GMT, BHW, or standard care (wait-list control). Patients complete a battery of tests assessing cognitive functioning, daily functioning, and quality of life (1) prior to intervention, (2) after the 8-week behavioural intervention (or wait-list) period, and (3) after an additional 4 months to evaluate longer-term outcomes. Analyses of variance will examine treatment effects, with regression analyses to explore moderating effects of participant demographics, severity of baseline cognitive impairment, and tumor and treatment factors (e.g., tumor location, radiation dose and distribution). Results of this trial will lay the groundwork for implementation of evidence-based cognitive interventions for brain tumor and cancer patients across other disease sites.

TPS9638 Poster Session (Board #295a), Sat, 1:15 PM-4:45 PM

A phase III randomized double-blind study of prophylactic topical dapsone 5% versus moisturizer for cetuximab-induced papulopustular (acneiform) rash. *First Author: Mario E. Lacouture, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Epidermal growth factor receptor inhibitors (EGFRI) such as cetuximab, are associated with an acneiform rash that can affect up to 90% of treated patients, and can lead to interruptions and discontinuation of treatment by 76% and 32% of oncologists, respectively. Affected patients experience significant impairment in their quality of life (QoL) and psychosocial well-being. Prophylactic therapies include topical corticosteroids in combination with oral antibiotics, or the latter as single agents. No nonsteroidal topical agent has hitherto been investigated for the prevention of rash. Dapsone, a sulfone anti-microbial agent with known anti-inflammatory properties, is approved for the topical treatment of acne vulgaris. It suppresses neutrophil recruitment (interferes with migration and β-2 integrin-mediated adherence), inhibits release of prostaglandins and leukotrienes, IL-8 (from keratinocytes), and generation of toxic, oxygen-derived free radicals. While the exact pathogenesis of the acneiform rash to EGFRIs is not known, neutrophil recruitment and activation appear to play a key role. Therefore, we hypothesized that topical dapsone may be a safe and effective preventative strategy. **Methods**: We designed a prospective, randomized double-blind controlled trial to measure the ability of twice daily split-face and chest application of topical dapsone 5% gel versus moisturizer, to reduce the total lesion count (of the acneiform rash) by 20% at day 28, in conjunction with oral antibiotics. Up to 40 subjects (80 sides) with metastatic colorectal cancer or head and neck squamous cell carcinoma will be randomized and monitored for 6 weeks. Secondary objectives include evaluation of the difference in dermatologic QoL between the side of the face/ chest treated with dapsone versus the contralateral side treated with moisturizer, using the Skindex-16/FACT-EGFRI-18 questionnaires. The difference in global severity of rash between the two application sides will also be evaluated by measuring the agreement of blinded independent dermatologists' review of day-28 standardized photography of both sides. ClinicalTrials.gov: NCT01931150. Clinical trial information: NCT01931150.

TPS9639 Poster Session (Board #295b), Sat, 1:15 PM-4:45 PM

Efficacy and safety of olanzapine combined with aprepitant, palonosetron, and dexamethasone for the prevention of cisplatin-based chemotherapy-induced nausea and vomiting for gynecological cancer: KCOG G-1301 phase II trial. *First Author: Masakazu Abe, Department of Gynecologic Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: Olanzapine is proved to be effective for chemotherapy-induced nausea and vomiting (CINV). But its preventive efficacy in combination with standard antiemetic therapy (palonosetron, aprepitant, and dexamethasone) is unknown. The purpose of this study is to prove the preventive effect of olanzapine for the prevention of CINV caused by highly emetogenic chemotherapy (HEC) when used with standard antiemetic therapy. We started a prospective multicenter phase II study at six facilities related to Kansai Clinical Oncology Group (KCOG) since September 2013. **Methods:** Chemo-naïve patients aged 20-79 years old is enrolled. They are gynecologic cancer patients who are treated with HEC regimen containing cisplatin (more than 50 mg/m2). Target sample size is 40. Since olanzapine is contraindicated in patients with diabetes mellitus, their blood sugar level and HbA1c are checked to confirm that they do not have glucose intolerance before treatment. All patients are informed of drug information and the consent of using olanzapine are obtained. Aprepitant is administered at a dose of 125 mg before chemotherapy on day 1 and at 80 mg on days 2 and 3. Palonosetron (0.75 mg) is given before chemotherapy on day 1. Dexamethasone is administered at a dose of 9.9 mg before chemotherapy on day 1 and at 6.6 mg on days 2–4. 5mg oral olanzapine is administered for 6 days from the day before chemotherapy. All of patients record the self-evaluation diary about their emesis every 24 h throughout the overall phase (0–120 h after cisplatin). The primary endpoint is the proportion of patients with a complete response (no vomiting and no rescue therapy) throughout the overall phase. The secondary endpoints are the proportion of patients with complete response in the acute phase (0–24 h after cisplatin) and in the delayed phase (24–120 h after cisplatin) of the study, as well as the proportion of patients with complete control (no vomiting, no rescue therapy, no significant nausea (numeric rating scale 0-2)) and total control (no vomiting, no rescue, no nausea) throughout the study and in the acute and delayed phases. Clinical trial information: UMIN000011857.

TPS9640 Poster Session (Board #296a), Sat, 1:15 PM-4:45 PM

TabPRO trial: Tablet-based real-time detection of patient-reported outcomes during adjuvant outpatient chemotherapy for breast cancer. *First Author: Michael R. Mallmann, Department of Obstetrics & Gynecology, University Hospital of Bonn, Bonn, Germany*

Background: Current symptom inquiry during adjuvant chemotherapy is based on symptom reporting at regular intervals, usually at the start of the subsequent cycle of chemotherapy or by telephone interviews during chemotherapy cycles. Consequently there exists a time lag between occurrence of symptoms, reporting by the patient and initiation of side-effect directed therapy. In contrast, a real-time reporting of symptoms might fasten reaction towards side effects and thus improve patient care. **Methods:** This prospective multicenter trial determines the feasibility of an App-based query system to collect patient-reported outcomes (PRO) during outpatient adjuvant chemotherapy for breast cancer and to treat side effects during chemotherapy in real-time. The system includes an App-based symptoms assessment software for patients and an either Tablet- or computer-based symptoms-control software for physicians and health-care professionals offering a daily checkup of symptoms using a visual and intuitive App-based symptom assessment. Thus far, all 57 anticipated patients that are treated with adjuvant therapy for breast cancer in the participating trial centers have been enrolled. We evaluate all chemotherapy-related symptoms in terms of frequency, severity, both association with chemotherapy cycles or patient characteristics and course during chemotherapy on at least a daily basis. Moreover, we evaluate time of reaction between reporting of PRO by the patient and both assessment and contacting by the physician. We evaluate the frequency of intervention as well as satisfaction with such a system by both patients and physicians. Electronic tablet-based PRO might increase efficiency of data collection and transmission, the patient-physician communication and consecutively patient compliance. Due to early intervention this type of outcome-monitoring might help to minimize chemotherapy-induced side effects by a rapid reaction to the reported symptoms. Consequently the TabPRO trial with its daily reporting of PRO has the potential to change the current assessment of chemotherapy-related side effects and to optimize patient care during outpatient chemotherapy. Clinical trial information: NCT01991691.

TPS9641 Poster Session (Board #296b), Sat, 1:15 PM-4:45 PM

Three-arm randomized trial of sodium alginate, orally administered mucoprotective agent, for preventing radiation esophagitis in pts with locally advanced non-small-cell lung cancer (LA-NSCLC) receiving concurrent chemoradiotherapy (CRT): Okayama Lung Cancer Study Group 1401. *First Author: Katsuyuki Hotta, Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan*

Background: Concurrent CRT is the standard treatment in LA-NSCLC. Our phase 3 trial also showed a favorable efficacy of cisplatin-docetaxel and concurrent thoracic radiotherapy (JCO 2010). However, this intensive therapy can cause G3 or worse severe esophagitis of around 14%~27%, which would deteriorate pt's QOL and then lead to poor treatment compliance. Unfortunately, various types of supportive therapy including amifostine have failed to demonstrate the prevention of this toxicity. Sodium Alginate, already approved in Japan for gastritis, is highly viscous enough to stay long on the esophageal mucosa, leading to a mucosal protective effect in esophagus. To investigate if the agent indeed has a preventive effect for severe esophagitis in pts receiving concurrent CRT, we started three-arm randomized trial of sodium alginate with two different schedules vs. water. **Methods:** Pts have to meet the followings: untreated LA-NSCLC; suitable for receiving CRT; PS of 0 or 1; age $>$ 20 yrs. The primary endpoint is set as proportion of $\geq$ G3 esophagitis by CTCAE ver.4.0. With the stratification by institute, PS and esophagus V35 (Technol Cancer Res Treat. 2013), pts will be randomly assigned centrally to one of the followings; sodium alginate initiated concomitantly with CRT (A), sodium alginate initiated soon after developing extremely mild esophagitis during CRT (B), or water administered through CRT (C). Sodium alginate is administered at a dose of 60 ml per day. Assuming the proportion of $\geq$ G3 esophagitis would be 8% each in arms A and B and 27% in arm C, the required sample size is 200 pts (1-β: .7, α: .05). The secondary endpoint includes QOL, the frequency of additional prescription of analgesics, response and survival. Enrollment began in 2014, and will complete by 2017. UMIN registration number of 000013113 Clinical trial information: 000013113.

TPS9642 Poster Session (Board #297a), Sat, 1:15 PM-4:45 PM

Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism. *First Author: Annie Young, University of Warwick, Coventry, United Kingdom*

Background: Venous thromboembolism (VTE) in cancer patients is an important and increasingly frequent clinical problem. The impact of VTE on cancer patients can be considerable. Targeted patient selection by identifying patients with clinically relevant recurrent VTE may have wider health economic benefits whilst reducing patient risk through over-treatment. In the UK, dalteparin is the licensed anticoagulant for the extended treatment and prevention of recurrence of VTE in cancer patients and thus, the gold standard. Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability. **Methods:** Select-d is a prospective, randomised, open label, multicentre pilot trial comparing dalteparin (200 IU/kg daily subcutaneously for 1 month and 150 IU/kg months 2-6); and rivaroxaban (15 mg orally twice daily for 3 weeks and 20mg once daily for 6 months in total) for cancer patients with VTE, with a second placebo-controlled randomisation (rivaroxaban vs placebo) comparing the duration of therapy (6 vs 12 months) in residual vein thrombosis (RVT) positive patients. 70% of patients are estimated to be RVT positive after initial treatment. 530 patients are being recruited toprovide reliable estimates of the primary outcome (VTE recurrence rates) to within the 95% confidence interval of 8% assuming VTE rates are 10% at six months. The secondary objectives include safety, acceptability, biomarker identification and health economics. The select-d trial is amongst the first randomised trials of the new oral anticoagulants in patients with cancer, following recommendations from the UK National Institute of Health and Care Excellence. The select-d trial will recruit for two years with a minimum of one year follow up. The results will support optimal treatment for this key patient group. The independent TSC and DSMC fully support this important trial. Clinical trial information: ISRCTN86712308.

TPS9643 Poster Session (Board #297b), Sat, 1:15 PM-4:45 PM

Phase 3 randomized double blind placebo controlled trial evaluating Omega-3 in the prevention of Taxane or Platinum Induced Peripheral Sensory Neuropathy. *First Author: Ralph Maroun, Department of Oncology, McGill University Health Center, Montreal, QC, Canada*

Background: Chemotherapy induced peripheral neurotoxicity (CIPN) is a common and feared side effect of taxanes and platinum based chemotherapy. CIPN often leads to a decrease in dose intensity and or premature discontinuation of chemotherapy. Omega-3 fatty acids (OFA) have beneficial effects on neurological disorders including diabetic neuropathy, primarily by inhibition of the formation of proinflammatory cytokines involved in peripheral neuropathy (PN). A small study by Ghoreishi et al. has shown benefit of OFA in the prevention of taxane induced neuropathy. We hypothesize that the supplementation of OFA should diminish and or delay platinum or taxane induced PN. **Methods:** Randomized double blind placebo controlled trial to investigate the efficacy of OFA in reducing incidence and severity of taxane or platinum-induced PN. Eligible patients with breast cancer randomly assigned to take mammalian OFA with Vit D3 (provided by Auum Inc) 5cc sublingual tid vs placebo tid for 6 months. Clinical and electrophysiological studies were performed before the onset of chemotherapy and one month after cessation of therapy to evaluate CIPN based on "reduced Total Neuropathy Score"(rTNS). Eligibility criteria: Age 18-75, ECOG $<$ 2, receiving taxane or platinum based chemotherapy Endpoints:The primary endpoint was the incidence of grade 2+ CIPN (CTCAE v 3.0) in each treatment arm, analyzed by chi-square testing. Planned sample size was 100 patients per arm to provide 80% power to detect a difference in incidence of grade 2+ CIPN from 25% in the placebo group to 10% in the OFA group. Secondary endpoints: 1. rTNS to evaluate the existence and severity of CIPN (rTNS consists of subjective sensory symptoms and objective measured by nerve conduction studies). The patients receive an rTNS score ranging from 0 to 28. The severity of CIPN then is graded as follows:1.mild (total score 1–10), moderate (total score 11-19); and severe (total score 20–28).) 2.Brief pain inventory and 3.The 11-item FACT/GOG-Ntx, version 4 (questionnaires validated to assess neuropathy due to chemotherapy). Conduct to Date: Study activation: Dec 2014. Enrollment: 15 subjects. Clinical trial information: NCT02294149.

10000 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Morbidity and mortality associated with subsequent meningiomas among childhood cancer survivors exposed to cranial radiotherapy: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Daniel C. Bowers, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Survivors of childhood cancer who were exposed to cranial radiotherapy (CRT) are at increased risk of subsequent meningiomas. However, incidence rates, neurological sequelae and impact on mortality are not well defined. **Methods:** Among 4,221 survivors exposed to CRT, subsequent meningiomas were self-reported and confirmed by pathology, medical records or death certificate. Age of onset of specific neurologic conditions was self-reported and proxy-reported. Standardized incidence ratios (SIRs) and absolute excess risk (AER) were estimated using expected age-, gender-, and calendar-year specific rates from SEER. Hazard ratios (HRs) for neurological sequelae and mortality were estimated using Cox proportional regression. **Results:** 199 meningiomas were identified among 169 survivors. The median age at meningioma diagnosis was 28 years (range, 7 – 50 years); median age at last follow-up was 32 years of age (range, 9 – 56 years). Median interval from primary cancer to first meningioma diagnosis was 22 years (range, 5 – 37 years). The cumulative incidence of a subsequent meningioma by age 40 years was 5.6% (95% CI: 4.7% – 6.7%). The SIR for a subsequent meningioma was 619.4 (95% CI: 532.7 – 720.2) and the AER was 21.8 per 10,000 person-years (95% CI: 18.5 – 25.1). Within 12 months of diagnosis of a subsequent meningioma, 13.6% of participants reported new-onset seizures, 10.7% auditory-vestibular-visual deficits, 11.8% focal neurological dysfunction and 6.5% severe headaches. With a median follow-up of 72 months following subsequent meningioma diagnosis, 22 (13%) participants died (6 deaths attributed to meningioma). Adjusting for cranial radiotherapy dose, a diagnosis of subsequent meningioma was independently associated with increased all-cause mortality (HR = 2.3; 95% CI: 1.5 – 3.5; $p < 0.01$). **Conclusions:** CRT-exposed childhood cancer survivors with subsequent meningiomas experience considerable new-onset neurological morbidity and increased all-cause mortality. Effective screening methods for subsequent meningiomas may reduce neurological morbidity.

10001 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Chemotherapy and brain function in long-term survivors of childhood acute lymphoblastic leukemia (ALL). *First Author: Yin Ting Cheung, St. Jude Children's Research Hospital, Memphis, TN*

Background: Limited data are available on associations among chemotherapy treatment and brain function in long-term survivors of childhood ALL. This study evaluated associations between treatment exposure, neurocognitive testing, and functional magnetic resonance imaging (fMRI) in children treated on an institutional protocol, which featured chemotherapy without cranial irradiation. **Methods:** Long-term survivors of ALL (n = 213; 51.2% male; mean[SD] age 14.8[4.8]; 7.7[1.7] years post-diagnosis), completed neurocognitive testing and brain fMRI during an executive function/attention task. During chemotherapy, serum concentrations of high-dose intravenous methotrexate (HD-MTX), plasma homocysteine (HYC) following HD-MTX, and dexamethasone (DEX) were quantified as area under the curve (AUC). Serum cortisol level was also measured following oral DEX. These variables, along with number of triple intrathecal therapy doses, were analyzed with general linear modeling as predictors of neurocognitive and fMRI outcomes. fMRI analysis was performed using SPM8. **Results:** Survivors performed below normative data on two standard measures of executive function: cognitive flexibility (mean[SD] Z-score = -0.55[1.2]) and fluency (-0.38[0.9]), both *p's* < 0.0001. After adjustment for demographic factors, poorer cognitive flexibility was associated with higher MTX AUC (Est. -0.024; $p = 0.015$) and higher HYC AUC (Est. -0.011; $p = 0.049$). Poorer fluency was also associated with higher MTX AUC (Est. -0.023; $p = 0.007$). Survivors diagnosed at younger ages performed poorly on fluency at any level of MTX AUC, while those diagnosed at older ages performed poorly only if exposed to high MTX AUC ($p = 0.063$). Brain activation was positively correlated with MTX AUC in bilateral frontal and caudate nuclei, and left putamen and anterior cingulate cortex. Of note, these brain regions are associated with cognitive flexibility and fluency, as well as other executive functions. **Conclusions:** Higher serum concentrations of MTX and plasma HYC following HD-MTX for childhood ALL may predict those at greatest risk for neurocognitive problems, particularly executive dysfunction, and altered brain activity during long-term survivorship.

10002 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Neurocognitive function of children treated for high-risk B-acute lymphoblastic leukemia (HR-ALL) randomized to Capizzi (CMTX) versus high-dose methotrexate (HDMTX): A report from the Children's Oncology Group (COG). *First Author: Naomi J. Winick, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Survivors of childhood HR-ALL are at risk for neurocognitive deficits. The causes are multifactorial including treatment, host and environmental factors. This study evaluated the relative impact of two different approaches to methotrexate delivery while simultaneously examining associations with demographic and treatment factors, in the absence of cranial radiation, on neurocognitive functioning after completion of therapy. **Methods:** Patients with HR-ALL, treated on COG AALL0232, were randomized to receive HD-MTX with leucovorin rescue versus lower dose, escalating CMTX with asparaginase. Intellectual functioning (IQ), working memory, and processing speed (PS) of participants was evaluated 8 - 24 months following completion of therapy. **Results:** Two-hundred thirty-seven participants were eligible and enrolled on study, with 195 (54% female) submitting valid data. Mean age at diagnosis was 8.9 years (SD = 5), with 46% (n = 90) under age 10 at diagnosis. Method of methotrexate delivery was unrelated to differences in neuropsychological outcomes. Survivors younger than 10 at diagnosis, however, had an 11.8 point decrement (SE = 2.1) in estimated IQ ($p < .01$), and a 5.3 (SE = 2.2) point estimated decrease in PS scores ($p < .05$), compared to older participants, after controlling for ethnicity, race, gender, insurance status and time off treatment [(raw IQ: 94.9 + 15 vs. 107.2 + 15), (PS: 94.9 + 15 vs. 98.7 + 16)]. Additionally, participants covered by US public insurers had adjusted IQs that were 12.0 points lower (SE = 2.8, $p < .01$), than participants with private insurance (raw IQ: 93.1 + 15 vs. 106.1 + 15). **Conclusions:** Even in the absence of cranial radiation, young survivors of HR-ALL are at risk for deficits in global intellectual functioning and processing speed. Critically, insurance status was also strongly associated with neurocognitive outcomes. These data may serve as a basis for developing screening protocols and potential interventions to both identify children with deficits and to ameliorate the impact of therapy on their neurocognitive outcomes. Clinical trial information: NCT00437060.

10003 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Langerhans cell histiocytosis in children: Correlation of *BRAF* status with clinical characteristic. *First Author: Sébastien Héritier, Versaille University & APHP, Trousseau hospital, Paris, France*

Background: In 2010, *BRAF* mutations were reported in patients with Langerhans cell histiocytosis (LCH). We have shown that $BRAF^{V600E}$ mutations are also present in more than half of Erdheim Chester disease (EDC), and that lesions of both ECD and LCH are responsive to treatment with vemurafenib. This study aims to define the clinical features of LCH children with or without *BRAF* mutations. **Methods:** 319 children (age < 18 years) were included in the French nationwide GeneHistio study. This study was approved by an ethical comity, and signed informed consent was obtained for all patients. LCH diagnosis was validated by pathological central review, and detection of $BRAF^{V600E}$mutation was performed by pyrosequencing. **Results:** 240 (80%) patients were informative for *BRAF* mutation. This cohort was similar to the 1423 patients of the French LCH cohort who were not analyzed for *BRAF*, except for the frequency of hematologic involvement (15% versus 10%, $P = 0.044$). Median age at diagnosis was 5.0 years [range, 0-17 yr], mean follow-up was 4.7 years, and sex ratio was 1.2. LCH was a single-system disease (SS) in 55%, and multisystemic disease without (MSRO-) or with (MSRO+) risk organ in 20% and 25% of cases respectively. Affected organs were bone (82%), skin (33%), pituitary (17%), hematological involvement (15%), liver (14%), spleen (13%), lung (13%) and central nervous system (CNS) (7%). The 5 years relapse free survival was 58%, and 7 death occurred. $BRAF^{V600E}$ mutation was detected in 125 cases (52%). Univariate analysis showed that $BRAF^{V600E}$ was associated with skin or liver or spleen involvement, or with hematological dysfunction ($P < 0.05$). Furthermore the frequency of $BRAF^{V600E}$ was different in children with SS, MSRO- and MSRO+ disease ($P < 0.005$). Multivariate analysis showed that skin and hematologic involvement had a higher frequency of $BRAF^{V600E}$ with Odds ratio of 3.6 (95%CI [1.6-8.5] and 8.3 (95%CI [1.7-39.9] respectively. Sequelae of LCH were detected in 24% and 12% of patients with or without $BRAF^{V600E}$ ($P = 0.02$). **Conclusions:** In children with LCH, $BRAF^{V600E}$ mutation is associated with features commonly found in more aggressive forms of the disease.

10004 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Phase 1 study of dabrafenib in pediatric patients (pts) with relapsed or refractory *BRAF* V600E high- and low-grade gliomas (HGG, LGG), Langerhans cell histiocytosis (LCH), and other solid tumors (OST). *First Author: Mark W. Kieran, Dana-Farber Cancer Inst-PND, Boston, MA*

Background: Dabrafenib is an orally available, selective ATP-competitive inhibitor of BRAF V600E kinase, approved in unresectable or metastatic melanoma pts with the V600E mutation. This international study was designed to determine the recommended phase 2 dose (RP2D) in pts < 18yrs based on maximum tolerated dose, or systemic exposure similar to that seen in adult pts (AUC, 4000–5500 ng*h/mL), whichever came first. **Methods:** Dabrafenib was given orally twice daily, beginning at 3.0mg/kg/day. Toxicity, pharmacokinetics, and response were assessed by disease-appropriate criteria at each dose for pts > 12yrs and ≤ 12yrs. Doses of 3.0, 3.75, 4.5, and 5.25mg/kg/day were assessed by a rolling six design. When a dose level was filled and under assessment, additional pts could join the previous dose level deemed tolerable. **Results:** Enrollment for phase 1 completed at 27 pts, 15 male, median age 9yrs (range 1–17), with HGG n = 8, LGG n = 15, LCH n = 2, and OST n = 2. One pt had a dose-limiting toxicity (DLT) of grade 3 maculopapular rash (MR) at 4.5mg/kg/day, but is on study ≈9mths after restarting dabrafenib at 3.75mg/kg/day. Serious adverse events judged related to dabrafenib included MR (1 pt); hypotension, disseminated intravascular coagulation, fever (1 pt, outside DLT period); and arthralgia (1 pt). Duration on study ranged from 9wks to 19mo (ongoing); 20 pts remain on treatment. The RP2D for pts > 12yrs is 4.5mg/kg/day (median AUC 5285) and 5.25mg/kg/day (median AUC 4384) for ≤ 12yrs. Investigator-assessed best radiographic responses included 3 complete response (CR), 3 partial response (PR) and 2 progressive disease (PD) in HGG; 8 PR, 6 stable disease (SD) and 1 PD in LGG; 2 CR in LCH; 1 SD and 1 PD in OST (source data verification ongoing). **Conclusions:** The RP2D of dabrafenib for children > 12yrs and for those ≤ 12 was determined based on the target AUC when taken twice daily. The drug was well-tolerated with manageable toxicity. A high proportion of pts demonstrated radiographic responses in this phase 1 trial in different *BRAF* V600E-positive tumors. The disease stratified phase 2 component of the study is underway (NCT01677741). Clinical trial information: NCT01677741.

10005 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Phase I study of ceritinib in pediatric patients (Pts) with malignancies harboring a genetic alteration in ALK (ALK+): Safety, pharmacokinetic (PK), and efficacy results. *First Author: Birgit Geoerger, Institut Gustave Roussy, Paris, France*

Background: Ceritinib is a potent ALK inhibitor with durable efficacy in adult pts with *ALK*-translocated non-small cell lung cancer. This report describes the results of a phase I study (NCT01742286) in pediatric pts with ALK-aberrant malignancies: anaplastic large cell lymphoma (ALCL); myofibroblastic tumor (MT)/inflammatory (IMT) rhabdomyosarcoma (RMS) and neuroblastoma (NB). In these tumors *ALK* aberrations differ: ALCL and IMT carry gene translocations, NB amplifications or mutations, and RMS copy number gain or no change. **Methods:** This trial enrolled pediatric pts ≥ 1 to <18 yrs. ALK gene aberration was required, except in ALCL and RMS, where ALK+ by immunohistochemistry was sufficient. In a fasted, dose-escalation phase, pts received ceritinib at 300–560 mg/m^2/day to determine the recommended dose for expansion (RDE). Pts were assessed for safety, PK and efficacy. **Results:** Twenty-two pts were enrolled (22 centers in 10 countries) over 13 months including: 2 ALCL, 6 IMT, 1 MT, 7 NB, 6 RMS. Median age was 10 years (range 2-17), 14 were male and 3 were crizotinib-pretreated (1 NB, 2 IMT). Completion of the fasted escalation phase established a RDE of 510 mg/m^2. Common adverse events (% Any Grade [G]; G3/4) were diarrhea (86.4; 9.1), vomiting (81.8; 0), nausea (54.4; 0), elevated ALT (45.5; 18.2), abdominal pain (40.9; 9.1), decreased appetite (40.9; 0), elevated AST (36.4; 18.2), pyrexia (36.4; 0), and fatigue (31.8; 0). Two pts had dose limiting toxicity at 560 mg/m^2: G3 elevated ALT and persistent G2 abdominal pain. PK at the RDE (AUC and CL/F) was comparable to that reported for adults at this dose. Early data show responses in 2 of 2 pts with ALCL and 4 of 7 pts with MT/IMT (2 CR: 1 in a crizotinib-pretreated pt). To date, one pt with ALK F1174L mutated NB had shrinkage of a retroperitoneal mass; disease progressed in the brain, where lower ceritinib exposure is expected. Dose escalation with food is ongoing. **Conclusions:** The RDE in children is 510 mg/m^2/day without food. The toxicity profile is similar to that in adults. Food may reduce gastrointestinal symptoms and allow further dose escalation. Ceritinib showed efficacy in pediatric pts with ALCL and MT/IMT. Clinical trial information: NCT01742286.

10006 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Outcomes of dasatinib plus intensive chemotherapy or stem cell transplant (SCT) for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph$^+$ ALL) on Children's Oncology Group AALL0622. *First Author: William Birdsall Slayton, Shands At the Univ of Florida, Gainesville, FL*

Background: Children, adolescents and young adults with Ph$^+$ALL treated on COG AALL0031 had an outstanding 70% 5-year disease-free survival (DFS) rate with intensive chemotherapy plus imatinib given continuously. We hypothesized that dasatinib would improve outcomes compared to imatinib due to increased potency, better CNS penetration, and activity against imatinib-resistant clones. **Methods:** AALL0622 tested the safety and feasibility of adding dasatinib 60 mg/m^2 daily to AALL0031 chemotherapy in newly diagnosed Ph$^+$ALL subjects (1-30 yrs). Cohort 1 subjects received dasatinib 2 wks out of each 3-4 wk block, whereas Cohort 2 subjects received dasatinib continuously. SCT was recommended for subjects with a sibling donor and those with high risk (HR) disease based on rate of response measured by flow cytometry at end induction and consolidation. The remaining standard risk (SR) subjects were treated with chemotherapy plus dasatinib. While all AALL0031 subjects received cranial XRT, only CNS3 cases on AALL0622 received the same. **Results:** Sixty eligible subjects were enrolled from 7/2008 to 2/2012 (39 Cohort 1 and 21 Cohort 2); 33 completed protocol therapy; 18 came off therapy to have SCT, 2 were inevaluable for cohort based analysis, and 7 were dropouts. Dasatinib plus chemo was well tolerated with no toxic deaths. For the 51 evaluable subjects, 3 yr event-free (EFS) and overall (OS) survival were 79±6% and 93±3%, respectively. SR subjects (n = 48, 19% underwent SCT) had a 3-yr EFS/OS of 83±6%/96±3% and HR subjects (n = 9, 78% underwent SCT) had an EFS/OS of 63±19%/88±13%. Ten percent (6/60) had an isolated or combined CNS relapse on AALL0622 vs 6% (3/54; p = 0.50) on AALL0031. No difference in DFS was seen between AALL0031 subjects receiving imatinib continuously and AALL0622 whole cohort (3-yr DFS of 79 ±6% for both studies, p = 0.39). **Conclusions:** Dasatinib with intensive chemotherapy was well tolerated. Subjects with rapid response had excellent outcomes without SCT. Further follow-up and additional trials are necessary to define the relative role of dasatinib and imatinib in promoting long-term survival in pediatric Ph$^+$ ALL. Clinical trial information: NCT00720109.

10007 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Feasibility of intensive post-Induction therapy incorporating clofarabine (CLOF) in the very high risk (VHR) stratum of patients with newly diagnosed high risk B-lymphoblastic leukemia (HR B-ALL): Children's Oncology Group AALL1131. *First Author: Michael Burke, Medical College of Wisconsin, Milwaukee, WI*

Background: Four-year disease free survival (DFS) for patients with B-ALL classified as VHR is approximately 70%. Strategies to improve DFS with intensive post-Induction therapy using fractionated cyclophosphamide (CPM), etoposide (ETOP) and CLOF were evaluated on AALL1131. **Methods:** AALL1131 enrolled patients 1-30 years old with newly diagnosed HR B-ALL. The VHR subset was randomly assigned post-Induction to the Control Arm (CA) with modified BFM CPM + fractionated cytarabine + mercaptopurine, Experimental Arm 1 (Exp1) with CPM + ETOP, or Experimental Arm 2 (Exp2) with CLOF (30 mg/m^{2}x 5 days) + CPM + ETOP during Part 2 of Consolidation (CON) and Delayed Intensification. All arms included identical doses of vincristine and pegaspargase. **Results:** The rates of Grade 4/5 infection and Grade 3/4 pancreatitis were significantly increased in Exp2 compared to CA and Exp1 (Table). The dose of CLOF was subsequently reduced from 30 to 20 mg/m^{2}x 5 days and myeloid growth factor was required following CLOF administration. Despite these changes, 3/39 patients developed Grade 4 infections and one of these patients later developed a Grade 5 toxicity [acute kidney injury (AKI)] attributed to CLOF versus no Grade 4/5 infections on CA (n = 20) or Exp1 (n = 47). Four patients on Exp2 had prolonged cytopenias > 60 days during the 28 day CON Part 2 versus none on CA or Exp1. Two of the Exp2 patients failed to recover counts, one had Grade 5 AKI on day 92 and one was removed from protocol therapy on day 92. **Conclusions:** CLOF as administered with CPM/ETOP on Exp2 showed greater toxicity and was not considered feasible due to infectious toxicities and prolonged cytopenias. Exp2 was permanently closed to accrual in September 2014. Clinical trial information: NCT01406756.

Toxicities: CON part 2

CLOF (30 mg/m^2 x 5 days)

Toxicity	CA (N = 26)	Exp 1 (N = 49)	Exp 2 (N = 50)	p
Gr4/5 Infection	1 Gr 4	1 Gr 4	12 Gr 4 (11) Gr 5 (1)	0.0017
Gr3/4 Pancreatitis	0	0	5	0.0238
Gr3/4 AKI	0	0	2	0.3517

CLOF (20 mg/m^2 x 5 days)

Toxicity	CA (N = 20)	Exp 1 (N = 47)	Exp 2 (N = 39)	p
Gr4/5 Infection	0	0	3 (7.7%)	0.14
Gr3/4 Pancreatitis	0 (0%)	1 (2.1%)	1 (2.6%)	1.00
Gr3/4/5 AKI	0 (0%)	0 (0%)	1 (2.6%)*	0.56

*Also listed as a Gr 4 infection.

10008 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Gemtuzumab ozogamycin (GO) and toxic mortality (TM) in children and adolescents with acute myeloid leukemia (AML) enrolled on Children's Oncology Group (COG) trial AAML0531. *First Author: Jaszianne A. Tolbert, Childrens Mercy Hosp, Kansas City, MO*

Background: Survival benefit in children with AML using GO was seen in COG AAML0531, though with greater TM. This retrospective analysis examines the overall causes of mortality focusing on the impact of GO and other potential risk factors of TM. **Methods:** Patients with *de novo*AML were randomized to chemotherapy with (GO) or without GO (noGO). Low risk and intermediate risk patients without a matched sib donor received 5 chemotherapy courses while all others received 3 chemotherapy courses and stem cell transplant (SCT). GO included a 3mg/m2/dose on day 6 of Induction I and, if not receiving SCT, on day 7 of Intensification II. Induction death (ID) was defined as any death during the two induction courses. Treatment-related mortality (TRM) was defined as death in the intensification cycles while in complete remission. ID and TRM risk factoring in patient, disease and treatment factors were analyzed. SCT recipients were censored after Intensification I. **Results:** 1,022 patients (511 per arm) age 0-29 yrs enrolled; 49 experienced first event death during therapy. 22 (2%) died in induction and 29(3%) died while in remission. ID was identical between arms (n = 11), with most deaths in Induction I. TRM occurred more frequently among GO recipients (NoGO 9[2%] v GO 18[4%]; p = 0.096). The majority of TRM occurred in Intensification II and III (NoGO 9[100%] v GO 16[89%]). Infection-related complications were the main cause of all TM (NoGO 13[65%] v GO 19[65%]). ID was proportionately greater in infants < 1yo (p = .01) yet no infant experienced TRM. Multivariate analysis excluding infants showed that WBC > / = 100,000 (OR 3.67, p = 0.013) and non-white race (OR 3.45, p = 0.018) were risk factors for ID. The only significant negative impact upon TRM was obesity (OR 3.33, p = 0.01). **Conclusions:** GO did not increase ID, but did non-significantly increase TRM during intensification in those not going to SCT. Excluding infants, high WBC and non-white race were significant risk factors for ID whereas obesity was the primary risk factor for TRM. As infection was the primary cause of all TM, continued focus on preventing and treating infection in these identified risk groups is imperative. Clinical trial information: NCT00372593.

10009 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Augmentation of therapy for favorable-histology Wilms Tumor with combined loss of heterozygosity of chromosomes 1p and 16q: A report from the Children's Oncology Group studies AREN0532 and AREN0533. *First Author: David B. Dix, British Columbia Childrens Hosp, Vancouver, BC, Canada*

Background: In National Wilms Tumor Study-5, tumor-specific combined loss of heterozygosity (LOH) of chromosomes 1p and 16q was associated with adverse outcome in patients with favorable histology Wilms Tumor (FHWT): stage I/II patients treated with Regimen EE4A (vincristine (VCR)/ dactinomycin (DACT)) had 4-year EFS of 91.2% without LOH and 74.9% with LOH; stage III/IV patients treated with Regimen DD4A (VCR/ DACT/ doxorubicin(DOX)) and radiotherapy (RT) had 4-year EFS of 83% without LOH and 65.9% with LOH. The AREN0533/AREN0532 studies assessed whether augmenting therapy would improve EFS for FHWT with combined 1p/16q LOH. Stage I/II patients were treated with the addition of DOX (Regimen DD4A) but no RT. Stage III/IV patients were treated with Regimen M (VCR/DACT/DOX alternating with cyclophosphamide/etoposide) and RT. **Methods:** Patients were enrolled through the AREN03B2 Biology and Classification study between10/2006 and 7/2013. All patients underwent central review of pathology, surgical reports and diagnostic imaging. Tumor tissue was evaluated for LOH 1p and 16q by microsatellite testing. Descriptive statistics were used to compare the EFS/OS between NWTS-5 and the current studies. **Results:** Median follow up for 1,134 patients enrolled on AREN0532/0533 was 3.6 years (0.1 to 8.1 years). Combined LOH 1p and 16q was detected in 35 evaluable stage I/II patients and 52 stage III/IV patients. At analysis in December 2014 the number of events was 6 observed versus 9 expected for stage I/II, and 4 observed versus 18 expected for stage III/IV. The 4 year EFS for the stage I/II LOH patients and stage III/IV LOH patients was 83.9% (95%CI: 64.9%, 93.1%) and 91.5% (95%CI: 78.5%, 96.8%) respectively. Grade 3 or higher hematological toxicity was the most common toxicity observed with Regimen M, affecting 60% of patients. There were no unexpected toxicities. **Conclusions:** Regimen M therapy improved EFS for patients with stage III/IV FHWT with LOH at 1p/16q as compared to the historical comparison group treated with Regimen DD4A. The benefit of using Regimen DD4A instead of Regimen EE4A for stage I/II FHWT with LOH is less clear. Clinical trial information: NCT00379340; NCT00352534.

10010 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Outcome and prognostic factors in stage III favorable histology Wilms tumor (FHWT): A report from the Children's Oncology Group (COG) study AREN0532. *First Author: Conrad Vincent Fernandez, IWK Health Centre, Halifax, NS, Canada*

Background: National Wilms Tumor Study 5 showed an inferior outcome for stage III FHWT patients with combined Loss of Heterozygosity (LOH) at chromosomes 1p and 16q when treated with Regimen DD4A (vincristine/dactinomycin/ doxorubicin/radiation therapy (RT)). Patients with combined LOH were thus treated with increased therapy on COG study AREN0533. We evaluated the outcomes and prognostic utility of clinical and biological variables for the remaining stage III FHWT patients. **Methods:** From October 2006 to August 2013, 583 eligible patients met COG stage III criteria on central review of pathology, diagnostic imaging and surgical reports. Forty patients found to have combined LOH 1p and 16q were excluded from the survival analysis. All patients received DD4A; those with anaplasia at delayed nephrectomy were removed from protocol therapy. Tumor 1p and 16q LOH status was determined by microsatellite analysis. **Results:** Median follow up was 42 months (1.5-90). Median age at diagnosis was 45 months (range 1.4-220); 381 (70%) were white. Median tumor weight was 550 grams (22-3140). The 4-year event-free survival (EFS) and OS estimates were 88% (95%CI: 85-91%) and 96% (95%CI 93-98%), respectively. Fifty-eight out of 62 events occurred in the first 2 years. Site of relapse: lung +/- other (n = 35), abdomen or pelvis (n = 5), liver (n = 5), other (n = 15). Causes of death: relapse (n = 12), toxicity (n = 2), second malignancy (n = 1), non-cancer death (n = 1), other (n = 1). 123/543 (23%) had delayed nephrectomy. Submitted delayed nephrectomy histology showed: Anaplasia (n = 8); Low Risk/completely necrotic (n = 5; 0 relapses), Intermediate risk (n = 54; 6 relapses), High-Risk/Blastemal Type (n = 4; 4 relapses) and Indeterminate (n = 2; 2 relapses). Other prognostic variables examined in the table below. **Conclusions**: Most stage III FHWT patients had very good EFS and OS with DD4A and RT. Lymph node status, post-chemotherapy histology, and LOH were predictive of EFS. Future trials should consider modifying therapy based on identified prognostic markers. Clinical trial information: NCT00352534.

		n	EFS	P value	OS	P value
Lymph Nodes	Negative	237	95%	< 0.01	98%	0.18
	Positive	152	83%		95%	
Gross residual disease	Negative	394	89%	0.14	97%	0.39
	Positive	134	85%		93%	
LOH	Neither	382	92%	< 0.01	97%	0.55
	16q only	99	83%		97%	
	1p only	56	74%		93%	

10011 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Omission of lung radiation in patients with stage IV favorable histology Wilms Tumor (FHWT) showing complete lung nodule response after chemotherapy: A report from Children's Oncology Group study AREN0533. *First Author: David B. Dix, British Columbia Childrens Hosp, Vancouver, BC, Canada*

Background: In National Wilms Tumor Study-5, patients with stage IV FHWT with metastases limited to the lung had 5-year EFS of 74% in the setting of incomplete lung nodule response by Day 70 versus 85% with complete lung nodule response (CR). All patients were treated with Regimen DD4A (vincristine/dactinomycin/doxorubicin) and whole lung irradiation (RT). To decrease the risk of long-term toxicities associated with RT, the AREN0533 study sought to determine whether patients with lung nodule CR after 6 weeks of chemotherapy would maintain excellent EFS without the use of lung RT. **Methods:** Patients were enrolled between February 2007 and February 2013 after undergoing central review of surgical reports, pathology slides and chest CT scans on the AREN03B2 Biology and Classification Study. Lung nodule response after 6 weeks of chemotherapy was determined by central radiology review. The null hypothesis was that 4-year EFS for CR when treated with DD4A therapy and pulmonary RT is 85%. The study was designed to have 90% power (testing at 10% 1-sided) to detect an increase in the risk of failure corresponding to 4-year EFS of 75%. **Results:** Among 391 patients enrolled, 296 had lung-only metastases, of which 105 (39%) had CR. At interim analysis in June 2014, 20 events were observed, compared to 14.5 expected under the null hypothesis (p = 0.15). 19 of the 20 events were recurrences and 1 was a second malignancy. Among the 19 recurrences, there were 2 deaths with a median follow-up of 2.3 years from recurrence. Recurrences were in the lung only (17), lung and liver (1) and abdomen (1). The 4-year EFS and OS estimates for the CR patients were 78% (95% CI: 68%, 86%) and 95% (95% CI: 83%, 98%). **Conclusions:** Patients with FHWT with week 6 lung nodule CR treated without lung RT had EFS somewhat less than the historical standard treated with lung RT, though this difference was not statistically significant. The excellent OS suggests that omission of lung RT may provide an acceptable treatment approach for this patient subgroup. Clinicians should balance the benefit of avoidance of lung RT against the possibility of a modest increase in relapse risk. Clinical trial information: NCT00379340.

10012 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Risk-based treatment for synovial sarcoma in patients under 30 years of age: Children's Oncology Group study ARST0332. *First Author: Rajkumar Venkatramani, Baylor College of Medicine, Houston, TX*

Background: Synovial sarcoma (SS) is the second most common soft tissue sarcoma in children. ARST0332 evaluated a risk-based treatment strategy for young soft tissue sarcoma patients designed to limit therapy for low-risk disease and to test neoadjuvant chemoradiotherapy for unresected high-risk disease. **Methods:** Newly diagnosed SS patients < 30 years old were assigned to 4 treatment arms based on disease features including POG grade: A (surgery only): grossly excised intermediate-grade and ≤ 5 cm widely excised high-grade tumor; B (55.8 Gy radiotherapy [RT]): ≤ 5 cm marginally resected high-grade tumor; C (ifosfamide/doxorubicin chemotherapy + 55.8 Gy RT): > 5 cm grossly resected high-grade tumor ± metastases; D (neoadjuvant ifosfamide/doxorubicin chemotherapy and 45 Gy RT, then surgery and RT boost based on margins): > 5cm unresected tumor ± metastases. Patients treated in Arm A and B were considered *low-risk* (LR), Arm C and D without metastases as *intermediate-risk* (IR) and those with metastases as *high-risk* (HR). **Results:** Of the 149 SS patients enrolled, 129 were eligible for analysis: LR (43), IR (66) and HR (20). Most (74%) were 10-19 years of age and 52% were female. Tumors were 79% extremity, 71% > 5 cm, 30% intermediate-grade, 70% high-grade, 63% invasive, 96% deep, and 16% metastatic. Thirty-nine patients (30%) did not receive RT. There were no toxic deaths and only 5 unexpected grade 4 adverse events. By risk group, at a median follow-up of 2.6 years, estimated 3-year event-free survival was: LR 83%, IR 79%, HR 16% and overall survival was: LR 97%, IR 93%, HR 29%. After accounting for risk category, none of the other patient or disease characteristics (age, gender, tumor site, neurovascular invasiveness, depth) were statistically significantly associated with outcome. **Conclusions:** The novel risk-based treatment strategy used in ARST0332 produced favorable outcomes in non-metastatic SS patients relative to historical controls using RT less frequently and at lower doses. The outcome for metastatic SS remains unsatisfactory and new therapies are urgently needed. Besides risk group, no other factors predictive of outcome were identified. Clinical trial information: NCT00346164.

10013 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Long-term risks for chronic medical conditions and premature mortality in survivors of pediatric soft tissue sarcoma: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Emily L Mueller, Indiana University, Indianapolis, IN*

Background: Approximately 67% of children with soft tissue sarcoma (STS) survive 5+ years. Late mortality, subsequent malignant neoplasms (SMN), and frequency or severity of chronic medical conditions (CMC) have not been extensively assessed. **Methods:** The CCSS, a multi-institutional retrospective cohort study of 5+ year survivors of childhood cancer, assessed outcomes for 1,246 STS survivors and 4,023 siblings with up to five questionnaires over 14 years. Self-reported CMCs were graded using CTCAE v4.03. Cox proportional hazards models provided hazard ratios (HR) and associated 95% confidence intervals (CI) for CMC. SMNs ≥ 5 years from primary cancer diagnosis were confirmed by pathology report, medical record, or death certificate. Standardized incidence ratios (SIR) and standardized mortality ratios (SMR) were generated using SEER and US mortality rates, respectively. **Results:** Median age at diagnosis was 8 years (range 0-20); median follow-up was 20 years (1.5-33.9). 243 survivors died, with SMR 5.3 (95% CI 4.7-6.0) and cumulative incidence 17.1% at 35 years from diagnosis. Compared with siblings, 42% of survivors reported ≥ 1 severe, disabling or life-threatening (grade 3-4) CMC (HR 3.5; 95% CI 2.9-4.2). Hearing, vision, and/or speech were the most prevalent severe chronic morbidities at 35 years post diagnosis (cumulative incidence at 35 years 17.0%, CI 14.7-19.3%), with survivors 2.6 times more likely to have experienced this CMC as compared to siblings (CI 1.8-3.8). Survivors who received radiation to the brain, head or neck (HR = 3.3, CI 1.8-6.4), pelvis (HR = 4.2, CI 2.2-7.8), or extremities (HR = 4.2, CI 2.2-8.1) were at particular risk for multiple (≥ 2) severe to life-threatening CMCs. The SIR of SMN was 5.6 (CI 4.6-7.0). The most frequent SMN was new (non-recurrent) soft tissue sarcoma (n = 22, SIR 22.6, CI 14.9-34.3), but risk was highest for the development of a secondary osteosarcoma (n = 12, SIR = 55.0, CI. 31.3-96.9). **Conclusions:** Survivors of pediatric STS, especially those exposed to radiation, experience significant long-term sequelae. This observation should guide long-term surveillance and inform the evolution of new therapies.

10014 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Association of recurrent or progressive p of form types II and III pleuropulmonary blastoma (PPB) with poor outcome: A report from the international PPB registry. *First Author: Kris Ann Pinekenstein Schultz, Childrens Hosps and Clinics - Minnesota, Minneapolis, MN*

Background: Pleuropulmonary blastoma (PPB) is a rare malignancy of the lung presenting in young children. PPB is the sentinel disease of the PPB-*DICER1*familial syndrome. The International PPB Registry (IPBBR) has pathologically confirmed 425 cases of PPB. Three pathologic subtypes correlate with outcome: Type I/Ir, purely cystic; Type II, combined cystic solid; Type III, purely solid. Five-year survival rates for Types I/Ir, II and III PPB are 91%, 71% and 53%, respectively. The outcome of Type II and III PPB after a relapse (recurrence or progression) is unknown. **Methods:** Yearly follow-up is requested for all patients by the IPPBR. All PPB was confirmed by central pathology review. Reports of relapse and second malignancies were obtained by the IPPBR from the local institution. In most cases, the pathology of relapse or second malignancy was available for additional central review. **Results:** A total of 107 PPB patients relapsed, of them 35 (33%) were alive at a median of 15 months (range 0-61) and 72 (67%) had died at a median of 10 months (range 0-60). Twenty-nine (27%) relapsed with isolated CNS metastasis, 51 (48%) with isolated chest relapse, and 27 (25%) with other relapse; of them 66%, 53% and 96% respectively have died. Of the survivors, 34/35 (97%) had isolated disease either in the chest or CNS. In addition to the patients with recurrence, 6 patients had secondary malignancies believed to be related to prior therapy and 5 had a metachronous *DICER1*-related tumor; of these 83% and 100% respectively, were alive. **Conclusions:** In this cohort of centrally-reviewed relapsed PPB only one-third were alive at last follow-up. Patients with isolated CNS or chest maybe sometimes survive, but patients with bone metastasis rarely survive. Novel treatment regimens for relapsed PPB are urgently needed.

	Alive	Dead	Total
Relapse			
-Isolated CNS	10 (34%)	19 (66%)	29
-Isolated chest	24 (47%)	27 (53%)	51
-Other (combined chest + CNS or systemic)	1 (4%)	26 (96%)	27
Total Relapse	35 (33%)	72 (67%)	107
Secondary malignancy	5 (83%)	1 (17%)	6
DICER1*-related metachronous malignancies	5 (100%)	0 (0%)	5

*Thyroid carcinoma, Sertoli-Leydig cell tumor, cervical embryonal rhabdomyosarcoma.

10015 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Early results from Children's Oncology Group (COG) ARST08P1: Pilot studies of cixutumumab or temozolomide with intensive multiagent chemotherapy for patients with metastatic rhabdomyosarcoma (RMS). *First Author: Suman Malempati, Oregon Health and Science University, Portland, OR*

Background: Data from a previous COG study (ARST0431) showed an early FFS improvement but no long-term survival benefit with intensive interval-compressed chemotherapy in metastatic RMS. ARST08P1 aimed to determine the feasibility of adding cixutumumab (insulin-like growth factor-1 receptor (IGF-1R) monoclonal antibody) or temozolomide to an intensive chemotherapy backbone. **Methods**: A series of non-randomized single-arm pilot studies were conducted. After determining feasibility, pilots were expanded to assess efficacy. Eligible patients were < 50yrs with metastatic RMS. Backbone therapy consisted of blocks of vincristine/irinotecan (weeks 1-6, 20-25, 47-51), interval-compressed vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide/etoposide (weeks 7-9 and 26-34), and vincristine/actinomycin-D/cyclophosphamide (weeks 38-46). In Pilot 1, patients received cixutumumab (3, 6, or 9 mg/kg) IV once weekly throughout therapy. In Pilot 2, patients received oral temozolomide (100mg/m2) daily x 5 days with irinotecan. Patients received radiation therapy (RT) at weeks 20-25. RT was also permitted at weeks 1-6 or 47-51. **Results**: 168 eligible patients were enrolled (1/2010 - 7/2013). 71 patients received temozolomide and 97 patients received cixutumumab (19 at 3 mg/kg, 18 at 6 mg/kg, and 60 at 9 mg/kg). Most patients were ≥ 10 yrs old (73%) with alveolar histology (70%) and with bone and/or bone marrow metastases (59%). Two cases of Grade 4 and one grade 5 sinusoidal obstructive syndrome (SOS) occurred with cixutumumab at 9 mg/kg in combination with the chemotherapy backbone. Otherwise, toxicities were similar to ARST0431. With a median follow-up of 1.6 yrs, 18-month EFS was 68% with cixutumumab and 39% with temozolomide (log rank p-value < 0.001). **Conclusions**: Addition of cixutumumab or temozolomide to intensive multi-agent chemotherapy for metastatic RMS was safe and feasible. SOS may be a concern with higher doses of cixutumumab combined with intensive chemotherapy. Early FFS was better with cixutumumab than temozolomide. Overall outcome for metastatic RMS remained poor. Clinical trial information: NCT01055314.

10016 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Banked EBV-specific T-cells from HLA-partially matched normal donors to induce durable remissions of rituximab refractory EBV$^+$ B-cell lymphomas post hematopoietic and organ allografts. *First Author: Susan Prockop, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: EBV-LPD complicating allogeneic hematopoietic cell transplant (alloHCT) most frequently present as malignant, high grade, diffuse large B cell lymphomas (DLBCL) that do not respond to reduction in immune suppression. Rituximab induces remissions in about 55% of those with radiographic evidence of disease. Survival of rituximab-refractory EBV-LPD patients (pts) is 16 – 56 days. There are few other treatment options. We evaluated the efficacy and safety of EBV-CTLs in 2 clinical trials in alloHCT recipients with EBV+ disease. **Methods:** As part of 2 ongoing clinical trials (95-024 and 11-130) 57 pts received EBV-CTLs derived from unrelated third-party donors (13 on 95-024 and 18 on 11-130) or primary stem cell donors (26 on 95-024). Fifty-one pts were treated for monomorphic DLBCL, 3 polymorphic, 1 NK/T cell lymphoma and 2 for viremia alone. Subjects on 11-130 had all failed prior rituximab. On 95-024 28 of 39 pts had failed prior rituximab. Subjects in both studies received up to 5 cycles of EBV-CTL infusions; each cycle 1 or 2×10^6 cells/kg weekly for 3 weeks. **Results:** Of the 18 recipients of 3rd party EBV-CTLs on 11-130, 9 had complete response (CR), 3 partial response (PR) and 1 stable disease (SD) for a response rate of 67% and non-progression rate of 72%. The median duration of CR+PR was 318d. Kaplan-Meier (KM) overall survival (OS) was 71.8% at 1 and 2y. KM progression-free survival was 66.7% at 1y. Of 39 pts on 95-024, 23 had CR, 1 PR, and 3 SD, for a response rate of 62%. Strikingly, the 1y OS for rituximab-refractory pts in both studies was 50% and 49% for pts treated with 3rd party and transplant donor-derived EBV-CTLs respectively. Four patients on 11-130 and 6 patients on 95-024 died soon after the first EBV-CTL infusion; no death was considered related to treatment. EBV-CTLs had low toxicity: no pts developed cytokine release syndrome or required therapy for EBV-CTL-related GvHD. **Conclusions:** EBV-CTLs produce high response rates that are durable; pts who achieved CR had no relapses of EBV LPD. The OS in both studies far exceeded the survival reported for this patient population. EBV-CTLs had a favorable safety profile and were well tolerated. Clinical trial information: NCT01498484.

10017 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A feasibility and phase II study of the hu14.18-IL2 immunocytokine in combination with GM-CSF and isotretinoin in patients with recurrent or refractory neuroblastoma: A Children's Oncology Group study. *First Author: Suzanne Shusterman, Dana Farber Cancer Inst, Boston, MA*

Background: Combining anti-GD2 (disialoganglioside) monoclonal antibody with GM-CSF, IL2 and isotretinoin is now standard of care for high-risk neuroblastoma (NB) minimal residual disease (MRD) therapy. The humanized anti-GD2 antibody conjugated to IL2 (hu14.18-IL2) has clinical activity in NB and is more effective in NB-bearing mice than antibody and cytokine given separately. We therefore evaluated the safety, tolerability and anti-tumor activity of hu14.18-IL2 given with GM-CSF and isotretinoin in a schedule similar to current MRD therapy. **Methods:** Hu14.18-IL2 was given at the phase II dose (12 mg/m^2) on days 4-6 of a 28 day cycle with GM-CSF (250 μg/m^2/dose, days 1-2, 8-14) and isotretinoin (160 mg/m^2/day, days 11-25). Tolerability was determined based on the number of patients who developed an unacceptable toxicity (required pressor support or intubation). Response was evaluated every 2 cycles for patients with disease measurable by standard radiologic criteria (stratum 1), and for patients with disease evaluable only by MIBG and/or bone marrow histology (stratum 2). Disease burden was described in stratum 2 patients based on Curie scoring. **Results:** Fifty-two patients were enrolled on study; 51 were evaluable for toxicity and 44 were evaluable for response. Four patients had unacceptable toxicities, well below the protocol-defined rule for safety. Other grade 3 and 4 non-hematologic toxicities were reversible and expected based on prior trials. No responses were seen in stratum 1 (n = 14). In stratum 2 (n = 30), 7 responses were confirmed by central review (5 CRs and 2 PRs). The median baseline Curie score of the responders was 2 compared to 10 for non-responders (Wilcoxon rank-sum two-sided p-value = 0.0345). **Conclusions:** Hu14.18-IL2 given with GM-CSF and isotretinoin is safe and tolerable. Patients with only MIBG and/or bone marrow disease had a 23% response rate, confirming activity of the combination. Responders had a significantly lower disease burden than non-responders at study entry. These data support further study of hu14.18-IL2 in high-risk NB patients with MRD or a relatively low disease burden. Clinical trial information: NCT01334515.

10018 Poster Discussion Session; Displayed in Poster Session (Board #88), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Pulmonary function in adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort Study (SJLIFE). *First Author: Daniel M. Green, St. Jude Children's Research Hospital, Memphis, TN*

Background: The relationship between treatment exposures and long-term pulmonary function of childhood cancer survivors (CCS) treated with pulmonary toxic therapies has not been well studied. **Methods:** 606 of 989 SJLIFE CCS treated with pulmonary toxic therapy underwent assessment of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), single breath diffusion capacity for carbon monoxide corrected for hemoglobin ($DLCO_{corr}$) and total lung capacity (TLC) according to American Thoracic Society standards. Results were expressed as percent of race-, age-, and sex predicted values. Lung radiation dose was estimated using the patients' actual treatment ports and a CT dosimetry phantom. Associations were assessed using logistic regression. Variables significant at $p < 0.1$ on univariate analysis were entered into the multivariable models. **Results:** Median age at evaluation was 34.2 years [interquartile range (IQR), 28.7 to 40.1] and median time from diagnosis 21.9 years (IQR 16.6 to 27.8). Among survivors, 50.7% had $FEV_1 < 80\%$ of predicted, 47.2% FVC < 80%, 31.2% TLC < 75%, and 44.6% $DLCO_{corr} <$ 75%. Only 0.8% of survivors had obstructive ($FEV_1/FVC < 0.7$), but 31.2% had restrictive (TLC < 75%) lung defects. Risk factors are shown in the Table. **Conclusions:** These risk factors identified CCS who may benefit from interventions to improve pulmonary function.

	Odds Ratio (95% Confidence Interval)		
Risk factor	$DLCO_{corr}$ < 75% predicted	FEV1 < 80% predicted	TLC < 75% predicted
Age at diagnosis (years)			
5 – 9	0.81 (0.44, 1.50)	0.41 (0.21, 0.81)	0.71 (0.38, 1.35)
10 – 14	0.55 (0.31, 1.00)	0.53 (0.28, 0.99)	0.32 (0.17, 0.60)
15 – 22	0.39 (0.21, 0.71)	0.38 (0.20, 0.72)	0.25 (0.13, 0.47)
Elapsed time after diagnosis	1.04 (1.01, 1.06)	1.08 (1.05, 1.11)	1.08 (1.05, 1.11)
Lobectomy, metastectomy, wedge resection	*	2.18 (1.30, 3.63)	2.35 (1.36, 4.05)
Other chest surgery	*	4.95 (1.30, 18.92)	*
Current smoker	*	*	0.56 (0.34, 0.93)
Bleomycin (per 40 mg/m^2)	0.93 (0.75, 1.16)	*	0.93 (0.72, 1.20)
Cyclophosphamide (per 1000 mg/m^2)	1.04 (1.01, 1.08)	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)
V10 (per 10% increase)	1.14 (1.08, 1.21)	1.18 (1.11, 1.25)	1.19 (1.11, 1.27)

*-Did not satisfy criterion for inclusion in multivariable model.

10019 Poster Discussion Session; Displayed in Poster Session (Board #89), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Second malignancies in neuroblastoma patients: A report from the International Neuroblastoma Risk Group. *First Author: Mark A. Applebaum, University of Chicago, Chicago, IL*

Background: Exposures to radiation and chemotherapy are associated with increased risk of second malignant neoplasms (SMN) in neuroblastoma survivors. However, it remains unclear if modifications in risk-based treatment strategies during the past 25 years have changed SMN rates. **Methods:** The International Neuroblastoma Risk Group (INRG) Task Force created a database of neuroblastoma patients diagnosed from 1974-2013. SMN risk was measured by cumulative incidence, standardized incidence ratios (SIR) and absolute excess risk (AER) per 10,000 person-years relative to a matched United States population. Poisson regression compared rates of SMN between different groups. **Results:** Of the 16,520 patients in the INRG database, 9,261 enrolled on Children's Oncology Group protocols had SMN data available. 79 (0.85%) patients developed SMN, including hematologic malignancies (n = 38), sarcomas (n = 19), carcinomas (n = 10), CNS tumors (n = 10), hepatoblastoma (n = 1), and nephroblastoma (n = 1). The incidence of SMN of the entire cohort was almost 9-fold higher than expected (SIR 8.9 (95% CI: 7.1-11.1), AER 13.3). High-risk patients had more than a 20-fold higher incidence of SMN than expected (SIR 20.1 (95% CI: 14.7-26.9), AER 32.5). Intermediate-risk patients showed a 6-fold rise in SMN (SIR 6.2 (95% CI: 3.3-10), AER 8.3), and low-risk patients trended toward higher than expected SMN rates (SIR = 2.6 (95% CI: 0.95-5.7), AER 2.8). High-risk patients had a significantly higher cumulative incidence of SMN compared to intermediate- or low-risk patients (1.6% vs. 0.98% vs. 0.37%; p = 0.01). The cumulative incidence of SMN for two treatment eras (1: 1990-1996; 2: 1997-2009), corresponding to intensification of treatment regimens for high-risk disease, showed a higher frequency of SMN for those treated in Era 2 compared to Era 1 (1.4% vs. 0.39% at 10-years, p = 0.012). **Conclusions:** The incidence of SMN is higher than expected in high and intermediate-risk neuroblastoma survivors. The exposure to more intensive treatment likely contributes to the higher incidence of SMN observed in high-risk patients diagnosed after 1996. Genome-wide association studies (n = 5,188) to identify modifiers of SMN susceptibility are ongoing.

10020 Poster Discussion Session; Displayed in Poster Session (Board #90), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Temporal trends in health status among adults in the Childhood Cancer Survivor Study (CCSS). *First Author: Kirsten K. Ness, St. Jude Children's Research Hospital, Memphis, TN*

Background: The impact of temporal changes in childhood cancer therapy on long-term health status has not been evaluated. With expansion of CCSS, information about health status is available for 5+ year survivors diagnosed from 1970-1999. **Methods:** We estimated prevalence of poor general and mental health, functional impairment, activity limitation and cancer-related anxiety and pain at baseline evaluation among 15,830 survivors of childhood cancer. Outcomes were compared among treatment decades using log-binomial regression to calculate relative risk (RR) and 95% confidence interval (CI), adjusted for age, sex, race and diagnosis. **Results:** Proportions of survivors treated with radiation and amputation decreased; proportions treated with anthracyclines or alkylating agents increased over time. Survivors diagnosed more recently were more likely to report poor general health, pain and anxiety, and less likely to report functional impairment. Diagnoses with large increases ($p < 0.001$) in prevalence of adverse outcomes from 1970-79 to 1990-99 were leukemia (9.8 to 12.6% poor general health), bone tumor (23.2 to 30.7% pain) and Hodgkin lymphoma (15.7 to 19.2% anxiety). CNS tumor survivors had the largest decrease in functional impairment prevalence (37.7 to 19.7%). **Conclusions:** While the proportion of childhood cancer survivors reporting functional impairment in the most recent era decreased, particularly among CNS tumor survivors, proportions reporting poor general health, pain and anxiety increased slightly from 1970 to 1999.

	1970-79	1980-89	1990-99
		Median (Range)	
Diagnosis age (years)	8 (0-21)	11 (0-21)	10 (0-21)
Age at evaluation	28 (18-48)	26 (18-48)	26 (18-42)
		%	
Male	52.4	53.4	50.6
White	89.0	83.9	76.2
Cranial radiation	33.1	24.4	12.4
Chest radiation	24.2	20.0	9.9
Amputation	5.4	4.5	1.7
Alkylating agent	27.4	59.9	58.4
Anthracycline	30.7	51.4	59.3
Mean dose (mg/m^2)	335 ± 284	271 ± 144	214 ± 118
		RR (95% CI)	
Poor general health	1.0	1.1 (1.0-1.2)	1.2 (1.1-1.3)
Functional impairment		1.0 (0.9-1.1)	0.8 (0.7-0.9)
Activity limitation		0.9 (0.8-1.0)	0.9 (0.8-1.0)
Poor mental health		1.0 (0.9-1.1)	1.0 (0.9-1.1)
Pain		1.1 (1.0-1.2)	1.2 (1.1-1.4)
Anxiety		1.1 (1.0-1.3)	1.2 (1.1-1.3)

*p-values for trend < 0.001.

10021 Poster Discussion Session; Displayed in Poster Session (Board #91), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Survival and late effects in the risk-stratified hepatoblastoma patients treated by JPLT-2 protocol. *First Author: Eiso Hiyama, Hiroshima University, Hiroshima-Shi, Japan*

Background: The Japanese Study Group for Pediatric Liver Tumor (JPLT) has conducted cooperative treatment studies on hepatoblastoma (HB) since 1991. The main aim in JPLT-2 study launched in 1999 and closed in 2012 to evaluate the efficacy of cisplatin/pirarubicin in risk-stratified HB. This protocol was launched in 1999 and closed in 2012 to evaluate the cure rate of risk-stratified HB: standard risk HB (a tumor involving three or fewer sectors of the liver), intermediate risk HB (a tumor involving all sectors of the liver or invasion into portal or hepatic vein) and high risk HB (a tumor involving all sectors of the liver or with metastasis). **Methods:** Until 2012, 385 HB children who were younger than 15 years of age were eligible for inclusion in the JPLT2 study in which the cisplatin/pirarubicin regimen (CITA) is kept as the first line. In this study, we examined the outcome and late effects of the HB patients by the risk-stratified three groups (standard, intermediate and high risk groups). **Results:** Among 385 cases, PRETEXT I was 31, II was 120, III was 145, and IV was 89 including 86 cases (18%) with metastatic tumors. The 3-year EFS/OS of the cases with standard risk HB were 94/82%, while those of the cases with Intermediate and high risk HB was 64/49% and 34/28%, respectively. Except for 40 cases who underwent primary resection, complete resection of primary after CITA was performed 86% of standard risk, 66% of intermediate risk and 56% of high risk patients. And the late phase complications were 5 cases with maldevelopment, 17 with cardiac complications, 26 with ototoxicity and 5 with second malignancies. **Conclusions:** As compared with other multicenter cooperative protocols, CITA regimens achieved similar rates of survival and resectability in standard risk patients. More promising strategies including adequate liver transplantation and new targeting drugs should be developed for intermediate and high risk HBs. Clinical trial information: UMIN000001116.

10022 Poster Discussion Session; Displayed in Poster Session (Board #92), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

The *DICER1* syndrome: Genotype-phenotype correlation in PPB patients. *First Author: Leslie Ann Doros, Childrens Natl Med Ctr, Arlington, VA*

Background: Mutations in *DICER1* were first described in 2009 from individuals diagnosed with pleuropulmonary blastoma (PPB). Since then, *DICER1* mutations have been found in individuals with other tumor types. Collectively, mutations in this gene and associated tumors make up the *DICER1* Syndrome. About 40% of PPB patients or first/second-degree relatives exhibit ≥ 1 feature of the syndrome. Through a multi-institutional study, we aim to better understand the *DICER1*syndrome disease spectrum and genotype-phenotype correlations. **Methods:** Informed consent was obtained from participants or legal guardians. Use of Sanger and Next-Gen sequencing, and targeted aCGH on blood, saliva and tumor tissue was performed. Phenotypes were abstracted from the International PPB Registry (IPPBR) records. **Results:** To date, 409 PPB patients have enrolled in the IPPBR. More than 150 individuals with PPB have undergone genetic testing; 111 have a deleterious mutation. About 43% of PPB mutation positive individuals were found to have additional related conditions: benign lung cysts (22%), cystic nephroma(CN)/renal cysts (16%), thyroid hyperplasia/cancer (20%), embryonal rhabdomyosarcoma (5%), nasal chondromesenchymal hamartoma (6%), ovarian Sertoli-Leydig cell tumor (4%), ciliary body medulloepithelioma (2%), and rarely Wilms tumor, Hodgkin's lymphoma, neuroblastoma, and brain tumors. Twelve (30%) mutation negative PPB patients were found to have additional related conditions with the most common being CN and thyroid disease. Patients with mosaic RNase IIIb mutations had the greatest number of disease foci. **Conclusions:** The germline mutation detection rate among this cohort is ~67% via Sanger sequencing. Use of Next-Gen sequencing and targeted aCGH increased detection to 75%. Deletions and mosaicism have been identified through these means. *DICER1* mutation positive PPB patients are at significant risk for other conditions. Sanger and Next-Gen sequencing mutation negative patients with multiple conditions require further molecular analysis. Understanding the *DICER1* syndrome spectrum of conditions and specific genotype-phenotype correlations will improve surveillance recommendations.

10023 Poster Discussion Session; Displayed in Poster Session (Board #93), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Clinical outcome and biological predictors of relapse following nephrectomy only for very low risk Wilms tumor (VLR WT): A report from Children's Oncology Group AREN0532. *First Author: Conrad Vincent Fernandez, IWK Health Centre, Halifax, NS, Canada*

Background: An earlier study of observation only following nephrectomy for VLR WT defined as stage I, age < 2 years, favorable histology with a weight<550 grams was suspended for excess relapse. Follow up revealed a higher salvage rate than originally predicted and suggested novel prognostic biomarkers. In this study, we sought to determine if 1) an observation alone strategy in centrally reviewed VLR WT demonstrates an Event Free Survival (EFS) of > 85% and Overall Survival (OS) of > 95%, and 2) to validate prognostic biomarkers. **Methods:** From 10/30/2006-8/12/2013, 116 eligible patients were enrolled with VLR WT; negative lymph node sampling was required and predisposition syndromes were excluded. All cases had central review of pathology, diagnostic imaging and surgical reports on the AREN03B2 biology and classification study. Evaluable tumors were analyzed for mutation of *WT1,* 1p and 16q loss of heterozygosity (LOH) using microsatellite analysis, 1q gain, 1p and 16q loss by MLPA, and 11p15 loss or retention of imprinting (LOI, ROI) using methylation restriction sites analysis. **Results:** Median follow up was 80 months (5-97). Median age was 11.5 months (0.1-23). 12 patients relapsed with no deaths. Estimated 4-year EFS was 89.7% (95% CI 84.1-95.2%) and OS was 100%. 1 patient is alive with disease after 4 relapses. First site of relapse was lung (n=5), tumor bed (n=4), abdomen (n=2), contralateral kidney (n=1). Median time to first relapse was 4.2 months (2.2-43). The presence of intralobar (p=0.46) or perilobar rests (p=1.0) was not associated with relapse, nor was histological subtype (p=0.16). 1q gain, 1p loss and/or 16q loss did not predict relapse, nor did *WT1* mutation (but 13/14 with *WT1* mutations also had 11p15 LOH). 11p15 methylation status predicted relapse. **Conclusions:** Most patients meeting VLR criteria can be safely managed by nephrectomy alone. 11p15 LOH/LOI predicts relapse. Future trials considering expansion of an observation alone strategy for low risk WT should incorporate these biomarkers. Clinical trial information: NCT00352534.

	Relapse No	Relapse Yes	Total	P value
11p15 LOH	32 (80%)	8 (20%)	40	0.0106
11p15 ROI	58 (97%)	2 (3%)	60	
11p15 LOI	6 (75%)	2 (25%)	8	
Total	96 (89%)	12 (11%)	108	

10024 Poster Discussion Session; Displayed in Poster Session (Board #94), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Loss of STAG2 expression and prognosis in Ewing sarcoma family of tumors. *First Author: Armita Bahrami, St. Jude Children's Research Hospital, Memphis, TN*

Background: The Ewing sarcoma family of tumors (ESFTs) is an aggressive primitive sarcoma of bone and soft tissue. Although several clinical factors are associated with patient outcomes, few biomarkers have prognostic relevance. Recurrent inactivating mutations or deletions in the cohesin complex subunit *STAG2* have been recently described in 15-20% of ESFTs, but their prognostic significance is uncertain. We previously reported that concurrent *STAG2* and *TP53* mutations in ESFTs predict clinical aggressiveness. In this study of an independent cohort, we evaluated the prognostic significance of STAG2 deficiency on clinical outcomes in correlation with established clinical risk markers. **Methods:** Immunohistochemical (IHC) analysis for STAG2 was performed on 143 ESFT samples from 111 patients (90 osseous; 21 extraosseous). The Cox regression model was used to study the association between overall survival (OS) and potential risk factors [age at diagnosis (< 15 vs. ≥ 15 years), gender, primary tumor site (axial vs. extremities), metastatic disease at diagnosis, and STAG2 status]. p53 IHC was performed on STAG2-deficient ESFTs to determine the frequency of coexisting *TP53* missense mutations (*TP53mut*). **Results:** ESFTs occurred in 68 (66%) male and 43 (34%) female patients with a median age of 12.9 years (range, 5 months to 22 years). Tumors involved extremities in 47 (42%) patients and axial/pelvis in 64 (58%) patients. Metastatic disease at diagnosis was seen in 27 (24%) patients. Of the 111 patients, 38 were alive (median follow-up, 16.1 years), 64 died of disease, and 9 died of other causes (median time to death, 2.8 years). STAG2 was expressed in 95 (86%) tumors and not in 16 (14%) tumors. Of the 16 STAG2-negative tumors, 4(25%) harbored concurrent *TP53mut*. Cox regression analysis identified metastatic disease at diagnosis as the most significant adverse prognostic indicator for OS ($P = 0.0005$). Axial location and STAG2 deficiency were associated with a lower OS, but neither reached statistical significance ($P = 0.053$ and $P = 0.059$, respectively). **Conclusions:** Our findings do not support using STAG2 loss as single predictor of outcome. The effects of STAG2 deficiency in ESFTs may be mediated by coexisting genetic modifiers such as *TP53* alterations.

10025 Poster Discussion Session; Displayed in Poster Session (Board #95), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Activity of Hsp90-inhibitor drug conjugate (HDC) STA-12-8666 in preclinical models of pediatric sarcoma. *First Author: Christine Heske, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD*

Background: Long-term survival in patients with metastatic relapsed or recurrent Ewing sarcoma (ES) and rhabdomyosarcoma (RMS) is poor. Early phase studies have shown encouraging responses in these patients using irinotecan. However, limitations of irinotecan, including a low conversion rate to its active metabolite (SN38) and a high excretion rate of the inactive form, diminish delivery of this drug to tumors and hinder efficacy. In addition, systemic toxicity limits dose escalation in the clinical setting, especially in drug combinations. Hsp90 is widely expressed in cancer cells, and Hsp90 inhibitors display favorable pharmacokinetics for anticancer use as they remain in tumors for a prolonged period of time and at higher levels, compared to normal tissue. This property makes them ideal intracellular delivery vehicles for chemotherapeutic drugs, allowing for high tumor exposure and low systemic toxicity. STA-12-8666 (Synta Pharmaceuticals) is an HDC conjugated to SN38. The purpose of this study was to test this HDC in xenograft models of pediatric sarcoma. **Methods:** To test therapeutic efficacy of this HDC, female SCID mice underwent orthotopic injection of ES or RMS cells. When tumors reached between 100 and 500 mm3 (ES) or 50 and 90 mm3 (RMS), mice were randomized and then treated weekly with STA-12-8666, vehicle, irinotecan or ganetespib (an Hsp90 inhibitor). Tumors were measured twice per week with calipers, and mice were weighed weekly to determine drug tolerability. Tumors were harvested at midpoints and at study endpoint for biology studies. **Results:** In xenograft models of both ES and RMS, treatment with STA-12-8666 produced superior antitumor efficacy compared to controls. All tumors underwent complete regression with tumor eradication persisting for greater than 11 weeks. Additional early data has shown regression of larger tumors up to 1000 mm3. Studies are ongoing and will be reported. Tolerability was excellent with no toxicity-related deaths or significant weight loss in treated mice. Dose titration arms and pharmacodynamic studies of tumors are ongoing. **Conclusions:** Preclinical data suggest that STA-12-8666 may be a promising anticancer agent for ES and RMS patients.

10026 Poster Discussion Session; Displayed in Poster Session (Board #96), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

RNA helicase DDX3 is a novel therapeutic target for Ewing sarcoma. *First Author: David Mark Loeb, Johns Hopkins Univ, Baltimore, MD*

Background: There is growing interest in RNA and DNA helicases as therapeutic targets in a variety of sarcomas. We investigated the expression and function of RNA helicase DDX3 in Ewing sarcoma and have begun to explore the effect of a novel DDX3 inhibitor, RK-33. **Methods:** We determined DDX3 expression in Ewing sarcoma cell lines, xenografts, and tissue microarrays by quantitative RT-PCR, western blotting, immunohistochemistry and quantitative proteomics using isobaric mass tags (tandem mass tags, TMTs). Stable DDX3-knockdown cell lines were created and evaluated. Proliferation, clonogenic activity in soft agar, sphere formation, and growth in immunodeficient mice were assayed. The effect of RK-33 on Ewing sarcoma was evaluated in cell lines and xenografts. **Results:** RNA helicase mRNA and protein are expressed at high level in Ewing sarcoma cell lines and patient-derived xenografts, and immunohistochemical staining is seen in 22 of 25 biopsy samples. Knockdown of DDX3 impairs proliferation, soft agar clonogenic activity, and sarcosphere formation and increases radiation sensitivity by slowing DNA damage repair in Ewing sarcoma cell lines, and impairs tumor growth in xenografts. Proteomic analysis implicates DDX3 in the translation of proteins important for numerous cellular pathways, including DNA damage repair and resistance to apoptosis. The DDX3 inhibitor, RK-33, is cytotoxic to Ewing sarcoma cell lines in vitro, including to chemotherapy-resistant Ewing sarcoma stem cells, and increases radiation sensitivity, and knockdown of DDX3 inhibits cytotoxicity. RK-33 also impairs the growth of a DDX3-positive Ewing sarcoma xenograft. **Conclusions:** Our data implicate DDX3 in Ewing sarcoma tumorigenesis. In light of data implicating other helicases in the pathogenesis of Ewing sarcoma and osteosarcoma, this work supports the idea that this enzymatic family plays a key role in the development of sarcomas in general, and that helicase inhibitors might be an important new class of therapeutics. In fact, we found that a novel DDX3 inhibitor, RK-33, shows strong therapeutic promise, either as a direct cytotoxic agent or as a radiation sensitizing agent.

10027 Poster Discussion Session; Displayed in Poster Session (Board #97), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

The methylome of pediatric acute myeloid leukemia. *First Author: Stanley Pounds, St. Jude Children's Research Hosiptal, Memphis, TN*

Background: DNA methylation can alter gene expression by either creating binding sites for methylation-dependent repressor proteins, or by disrupting the binding of transcription factors to their target sequences. DNA methylation has been studied extensively and associated with survival in adults with AML. However, a detailed genome-wide study of epigenetic regulation of gene expression and its pharmacological and clinical impact in pediatric AML patients has not been performed. **Methods:** In this study, we obtained Illumina 450K methylation array profiles for 175 pediatric patients and Affymetrix U133A gene expression arrays for 166 pediatric patients treated in the multicenter AML02 clinical trial (NCT00136084). **Results:** We found a very significant canonical correlation of methylation with expression (FDR ≤ 0.01) in 1,978 genes with several of the top ranked genes having established roles in the biology and treatment of AML. An analysis adjusting for risk group found that the canonical correlation methylation and expression variables of 24 genes showed statistically significant evidence of a biologically meaningful pattern of associations with in vitro sensitivity to cytarabine, minimal residual disease assessed by flow cytometry after the first course of chemotherapy, and event-free survival ($p \leq 0.001$; FDR ≤ 0.32). Finally, we observed differential methylation according to clinical risk group at 36,667 markers scattered throughout the genome (FDR ≤ 0.01) with low-risk patients showing hypomethylation at 32,920 of those 36,667 (89.8%) markers. **Conclusions:** Given the methylation differences in clinical risk groups incorporation of demethylating agents might be a useful strategy to improve the outcome of high-risk AMLs by modifying the methylome to more closely resemble that of low-risk AMLs, which are most sensitive to cytarabine. Our results illustrate the power of combined profiling of methylation and expression to improve our understanding of the disease and the molecular level and identify potentially useful therapeutic targets.

10028 Poster Discussion Session; Displayed in Poster Session (Board #98), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Accuracy of adverse event reporting on a phase III clinical trial for pediatric acute myeloid leukemia: A report from the Children's Oncology Group. *First Author: Tamara P. Miller, Children's Hosp of Philadelphia, Philadelphia, PA*

Background: Adverse events (AE) on Children's Oncology Group (COG) trials are reported by clinical research associates (CRA) on case report forms using the Common Terminology Criteria (CTC). CTC has increased in complexity from initially 49 AEs to 789 currently. This complexity challenges CRAs to accurately identify AEs. This study sought to evaluate the accuracy of AE reporting on a COG clinical trial and to determine if Pediatric Health Information System (PHIS) billing or microbiology data can improve AE reporting. **Methods:** Two pediatric oncologists performed chart review to identify 12 Grade III-V AEs (Table) for patients enrolled on AAML0531 at 11 hospitals across the United States and establish a gold standard. The sensitivity and PPV for COG AEs and AEs based on PHIS billing or microbiology data were calculated comparing to the gold standard. **Results:** Chart abstraction was performed on 179 patients (661 courses). PHIS billing data were available on all patients and PHIS microbiology data were available on 53 patients (202 courses) at 3 hospitals. The sensitivity of COG AE reports was lower than PHIS billing data, but COG reports had a higher PPV (Table). Sensitivity and PPV for viridians group streptococci (VGS) bacteremia using PHIS microbiology data were 92.3% (95% CI 79.1-98.4) and 97.3% (95% CI 85.8-99.9), respectively. **Conclusions:** The sensitivity of COG AE reports is modest with a relatively good PPV. PHIS billing data are generally more sensitive but have a lower PPV. While nearly 25% of VGS episodes were missed by COG AE report, the sensitivity and PPV of PHIS microbiology data for VGS was greater than 92%. These data suggest that current COG AE reporting is not sensitive and that accuracy may be improved by using external laboratory data.

Sensitivity and PPV of 12 AEs.

	COG AE Report		PHIS Billing Data	
AE	**Sensitivity %**	**PPV %**	**Sensitivity %**	**PPV %**
Hypertension	23.1	66.7	65.4	39.5
Hypotension	56.1	76.7	12.2	55.6
Hypoxia	16.7	96.2	72.0	60.3
ARDS	38.5	50.0	30.8	44.4
Anorexia	32.5	95.7	74.5	98.5
Typhlitis	33.3	88.9	66.7	66.7
DIC	10.4	83.3	72.9	71.4
VGS	76.9	96.8	29.9	70.0
Fungal Infection	62.5	45.5	62.5	31.3
Pain	17.1	88.7	97.8	61.1
Seizure	0	0	100	6.5
Renal Failure	60.0	100	80.0	80.0

10029 Poster Discussion Session; Displayed in Poster Session (Board #99), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Temsirolimus and intensive re-induction chemotherapy for 2nd or greater relapse of acute lymphoblastic leukemia (ALL): A Children's Oncology Group study. *First Author: Susan R. Rheingold, Children's Hosp of Philadelphia, Philadelphia, PA*

Background: PI3K/mTOR signaling, a critical pathway in cell proliferation, metabolism, and apoptosis, is commonly dysregulated in ALL. A phase 1 trial of the mTOR inhibitor temsirolimus in combination with re-induction chemotherapy was performed in children with second or greater relapse of ALL. **Methods:** Temsirolimus was administered with 4-drug chemotherapy (UK R3 ALL re-induction; Parker, Lancet 2010). The starting dose level (DL1) of intravenous temsirolimus was 10mg/m^2 weekly x3 ; subsequent cohorts received temsirolimus 7.5mg/m^2 weekly x3 (DL0); or 7.5mg/m^{2}weekly x2 (DL-1). PI3K pathway inhibition was measured by phosphoflow analysis (PFA) of peripheral blood. **Results:** Sixteen patients, age 1-21, [15 pre B-ALL (3 MLL infants, 2 Ph+); 1 T-ALL] were enrolled, 15 were evaluable. Dose-limiting toxicity (DLT) occurred in 2/5 patients at DL1; 3/6 at DL0 and 3/5 at DL-1. DLTs were hypertriglyceridemia, mucositis, gastric ulcer, hypertension with reversible posterior leukoencephalopathy, elevated GGT and alk phos, and severe infections including 1 death due to sepsis. Seven patients had a complete response, 3/7 had MRD $<$ 0.01% at end therapy. Responses occurred at all dose levels of temsirolimus. Phospho(p)S6 and/or p4EBP1 were inhibited in a subset of patients with compensatory upregulation of pPI3K, pmTOR, and pAkt. High basal PI3K pathway signaling was observed in patients with poorer response to therapy. **Conclusions:** Temsirolimus in combination with UK R3 chemotherapy can induce responses in children with ALL; however, this intensive regimen is associated with unacceptable toxicity. A trial evaluating temsirolimus in combination with etoposide/cyclophosphamide in children with relapsed ALL is ongoing. Clinical trial information: NCT01403415.

Dose Level	ID	Response	DLT
10mg/m^2 x 3	1 MLL	PD	
7.5mg/m^2 x 3	2	N/A	
	3 MLL	PD	HTN, Mucositis, GGT
	4	CRp	
	5	PD	HyperTG
	6	CR	
7.5mg/m^2 x 2	7	PD	
	8	died	Sepsis, Mucositis, RPLE
	9	PD	Ulcer
	10	CRp	
	11 T-ALL	PD	GGT
	12 Ph+	CR	
	13 MLL	PD	
	14 Ph+	CRp	GGT, Anorexia, Alk phos
	15	CR	Hyper TG
	16	CR	HyperTG

10030 Poster Session (Board #100), Sun, 8:00 AM-11:30 AM

Association of higher lung dose received during total body irradiation for allogeneic hematopoetic stem cell transplantation in children with acute lymphoblastic leukemia with inferior progression-free and overall survival: A report from the Children's Oncology Group. *First Author: Natia Esiashvili, Emory Univ, Atlanta, GA*

Background: Lung shielding is not standardized during total body irradiation (TBI) preparative regimens for hematopoietic stem cell transplantation (HSCT), leading to differences in pulmonary radiation dose received by patients. We examined the relationship between lung radiation dose and transplant-related mortality (TRM), relapse-free (RFS) and overall survival (OS) in children and adolescents undergoing TBI-based HSCT for acute lymphoblastic leukemia (ALL) on Children's Oncology Group trial ASCT0431. **Methods:** The lung radiation dose received during TBI (1200 or1320 cGy given bid in 6 or 8 fractions) was analyzed in relation to the following variables: total TBI dose, TBI dose per fraction, TBI dose rate, TBI fields, patient position during TBI, pulmonary toxicity, acute graft versus host disease (GVHD), veno-occlusive disease (VOD), TRM, donor type, minimal residual disease (MRD) levels, RFS and OS. **Results:** From a total of 143 enrolled, 109 patients had lung doses available for analysis. Patients treated with lateral fields were significantly more likely to receive lung doses $\geq$ 800cGy ($p < 0.001$). Patients receiving lung dose $\geq$ 800cGy had higher rates of relapse or TRM ($p = 0.034$), a trend for higher rates of death ($p = 0.078$). There was no significant association between lung dose and rates of reported pulmonary toxicity ($p = 1.000$). In univariate analysis, lung dose $\geq$ 800cGy, grade IV vs. grade I-III GVHD, VOD, pulmonary toxicity, MRD, higher disease risk group and unmatched donor types were associated with significantly inferior RFS and OS. Multivariate analysis identified lung dose $\geq$ 800cGy to be significantly associated with inferior RFS (HR 1.9; $p = 0.031$) and OS (HR 2.1; $p = 0.023$) while controlling for risk group and donor type. **Conclusions: A**nalysis of ASCT0431 data showed that lung irradiation dose $\geq$ 800 cGy as part of TBI was associated with inferior RFS and OS. While understanding the mechanisms underlying these results requires more research, reducing the lung dose to 800cGy for TBI regimens administering $>$ 1200cGy is recommended. Clinical trial information: NCT00382109.

10031 Poster Session (Board #101), Sun, 8:00 AM-11:30 AM

Intramuscular (IM) or intravenous (IV): Impact of *Erwinia* asparaginase route of administration on asparaginase activity. *First Author: Olanrewaju O Okusanya, U.S. Food and Drug Administration, Silver Spring, MD*

Background: *Erwinia* asparaginase (*Erwinia)* 25000 IU/m^2 IM was approved in 2011 as a component of treatment for patients with acute lymphoblastic leukemia (ALL) with hypersensitivity to E. coli-derived asparaginase. In 2014, FDA approved the IV route of administration for *Erwinia*based on the PK and safety findings described herein. **Methods:** Data from a single arm PK study in children (1 – 17 yrs) with ALL given *Erwinia* 25000 IU/m^2 IV every Monday/Wednesday/Friday (M/W/F) were evaluated. The proportion of patients with 2-day and 3-day nadir serum asparaginase activity (NSAA) levels $\geq$ 0.1 IU/mL during the first 2 wks of IV *Erwinia* was compared to that of IM *Erwinia*. Population PK (PPK)-based simulations were used to determine IV *Erwinia* doses that would result in the same proportion of patients with 2-day and 3-day NSAA levels as that achieved with 25000 IU/m^2 IM. The safety of IV and IM *Erwinia* administration was also compared. **Results:** IV dosing resulted in a mean (%CV) t½ of 7.5 h (24%) compared to 16 h (21%) for IM (PMID: 8355045). A smaller proportion of patients achieved 2-day or 3-day NSAA levels $\geq$ 0.1IU/mL while experiencing more adverse events with IV compared to IM administration (Table). PPK-based simulations showed that IV Erwinia doses of 35000 IU/m^2 every M/W/F would be needed to attain NSAA levels of $\geq$ 0.1 IU/mL in 90% of the patients on Wednesday or Friday (2-day NSAA) and doses $>$ 95000 IU/m^{2}every M/W/F would be needed to achieve the same target on Monday (3-day NSAA). **Conclusions:** IV administration of Erwinia 25,000 IU/m^2 every M/W/F, while clinically acceptable, led to a lower rate of target attainment (NSAA $\geq$ 0.1 IU/mL) and a higher rate of serious adverse events and discontinuations. Improving target attainment with higher IV doses would require clinical investigation.

Efficacy and safety of Erwinia.

Endpoint	IM Study	IV Study
Proportion (n/N) and 95% CI		
Efficacy		
2-day NSAA $\geq$ 0.1 IU/mL	100% (35/35) [90, 100]	83% (20/24) [63, 95]
3-day NSAA$\geq$ 0.1 IU/mL	100% (13/13) [77, 100]	43% (9/21) [22, 66]
Safety		
Serious Adverse Events	32.8% (19/58)	50% (15/30)
All Grade Hypersensitivity	9% (5/58)	37% (11/30)
Grade 3/4 Hypersensitivity	5% (3/58)	3% (1/30)
Discontinuation rates	24% (14/58)	40% (12/30)

10032 Poster Session (Board #102), Sun, 8:00 AM-11:30 AM

Long-term outcome of six months maintenance chemotherapy for ALL in children: TCCSG L92-13E study. *First Author: Motohiro Kato, University of Tokyo, Tokyo, Japan*

Background: Standard duration of maintenance therapy for childhood acute lymphoblastic leukemia (ALL) is generally considered as one year or longer. In our previous clinical trial, the TCCSG L92-13 (1992 – 1995, n = 347), maintenance therapy was shortened to 6 months and it resulted in decreased EFS of 59.5% at 5.5 years (Toyoda Y, et al. J Clin Oncol 2000), indicating that excess shortening of maintenance therapy could lead to high relapse rate. Conversely, it should be noted that about 60% of ALL achieved continuous complete remission with this short maintenance therapy. Thus, to confirm long-term outcome of ALL with short maintenance therapy, and to identify subgroups which do or do not require the standard duration of maintenance therapy, we conducted L92-13E study, an extended follow up of patients enrolled on the L92-13 study. **Methods:** In the L92-13 trial, children (15 years or younger) with ALL were enrolled, and were assigned to three risk groups, standard-risk (SR), high-risk (HR) and extremely high-risk (HEX). In this extended follow-up study, 45 patients who relapsed/died before 1 year from diagnosis were excluded in order to assess the long-term effect of the shortened therapy. **Results:** As of December 2014, a median of follow up period (n = 302) was 16.1 years. EFS at 15 years for all patients was 65.4 +- 2.8%. Incidences of relapse and non-relapse mortality were 3.2 +- 2.7% and 1.1 +- 0.7%, respectively. Of interest, patients in HEX group (n = 78) showed good EFS (75.4%), compared to SR (60.4%, n = 117) and HR (63.9%, n = 107). Male gender and high-hyperdiploid (HHD) was strongly associated with poor outcome, EFS was 57.1 +- 4.1% for boys, while 73.9 +- 3.7% for girls (p = 0.003). EFS of HHD was significantly poor (55.6 +- 11.7%), although it was recognized as good prognostic factor. On the contrary, EFS of TCF3-PBX1 positive patients was 80.0% +- 17.9%. **Conclusions:** The L92-13E study showed that a certain portion of ALL, including male, HHD required the standard duration of maintenance, whereas HEX group, female could be cured even with very short maintenance therapy. This result provides precise information of leukemia biology and highlights the role of maintenance therapy.

10033 Poster Session (Board #103), Sun, 8:00 AM-11:30 AM

Identification of patients with post-induction CNS 2 status and outcomes in acute lymphoblastic leukemia. *First Author: Arun Gurunathan, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: In the past decade there has been increased scrutiny of the prognostic implications of low level blasts (CNS 2) in the cerebrospinal fluid (CSF) of pediatric patients with acute lymphoblastic leukemia (ALL). The significance of CSF blasts is complicated by the increased cell recovery by newer cytocentrifuge machines (Huppman, et al. *Am J Clin Pathol.* 2012). **Methods:** A retrospective cohort study was conducted at the Children's Hospital of Philadelphia (CHOP) to compare the proportion of CNS 2 CSF results using Shandon (2005–2008) and Wescor (2010-2014) cytocentrifuge machines. Logistic regression was used to compare CNS 2 results from the two time periods. Outcomes of patients with at least one post-Induction CNS 2 CSF result were tracked, focusing on proportion of patients who ultimately relapsed using Fisher's exact test. Infant ALL was analyzed separately. **Results:** Of the 306 de novo ALL patients (excluding 10 infants) identified, 273 had pre-B ALL and 33 had T-ALL. Of the 4477 lumbar punctures analyzed in this cohort, there was a 6.7-fold increase in proportion of CNS 2 results on the new (Wescor) machine (2% vs. 0.3%, p < 0.0001). This remained significant after adjusting for gender, immunophenotype, and end of induction risk stratification. In both time periods, the majority of CNS 2 results were CNS 2a. Of the 42 patients who were CNS 2 at least once post-Induction in either period, 9 relapsed (8 pre-B ALL; 1 T-ALL). Having a post-Induction CNS 2 CSF did confer an increased risk of relapse (21.4% vs. 8.8%, p = 0.025), primarily due to increased non-CNS relapse. Two of 3 patients with CNS 2 CSF on the Shandon relapsed; 7 of 39 patients who had a CNS 2 CSF on the Wescor relapsed. Despite the small sample size in Infant ALL, there was also an increase in CNS 2 results on the Wescor (4.5-fold increase, p = 0.042). **Conclusions:** The enhanced efficiency of cell recovery afforded by the Wescor cytocentrifuge machine resulted in increased proportion of CNS 2 results. Having a CNS 2 CSF on the Shandon was more predictive of relapse than on the Wescor. The finding that post-induction CNS 2 status is associated with an increased risk of relapse (non-CNS > CNS) warrants further investigation and may influence management decisions.

10034 Poster Session (Board #104), Sun, 8:00 AM-11:30 AM

Kidney Injury Molecule-1 and its association with delayed clearance and drug exposure in pediatric oncology patients treated with high dose methotrexate. *First Author: Andrew J. Bukowinski, Cincinnati Childen's Medical Center, Cincinnati, OH*

Background: High-dose methotrexate (HD-MTX) is a critical component of therapy for pediatric malignancies. The ability to identify patients at risk for delayed MTX clearance and acute kidney injury (AKI) is limited. Kidney Injury molecule-1 (KIM-1) is a urinary biomarker which is an early indicator of tubular injury. The current study evaluates associations between urinary KIM-1, delayed MTX clearance, and MTX exposure. **Methods:** 47 patients (31 M, 16 F; median age 9.5 yrs, range 3-31) received 1-12 g/m^{2}HD-MTX over 4 or 24 hours for a total of 96 courses of MTX. Diagnoses included: leukemia/lymphoma (42 pts), osteosarcoma (5 pts). Data was collected on up to 4 courses of HD-MTX. Serum creatinine (SCr) and MTX were measured per standard clinical practice. Urine samples were obtained prior to the infusion and at 12, 24, and 36-48 hours after start. KIM-1 was measured by enzyme linked immunosorbent assay and normalized to urine creatinine. Delayed methotrexate clearance (DC) was defined by plasma MTX levels exceeding "high risk" concentrations per Crom & Evans (1992) as incorporated into standard oncology treatment regimens, failure to clear MTX within 72 hours, or a 50% rise in SCr. Toxicity data was collected by chart review. Univariate analyses were conducted using Wilcoxon Rank sum testing. MTX area under the curve (AUC) was calculated with MW/Pharm software using Bayesian estimation. Linear regression was used to analyze KIM-1 and AUC for correlations. **Results:** Patients with DC had higher AUC levels ($p < 0.05$). Kim-1 at 12 hours correlated with AUC ($p < 0.04$) in leukemia patients receiving 1st course of HD-MTX. KIM-1 is associated with DC at 12 and 24 hours for 1st and 2nd courses of HD-MTX ($p < 0.05$). Prior to infusion KIM-1 is associated with previous DC ($p < 0.05$). **Conclusions:** Increased KIM-1 is associated with both MTX AUC and DC and is indicative of renal tubular injury. This association is most pronounced in course 1 and may be due to attrition of patients with severe toxicity, dose reduction, and enhanced supportive care. KIM-1 provides an early indication of kidney injury from HD-MTX and with additional evaluation may be a target for enhanced supportive care strategies.

10035 Poster Session (Board #105), Sun, 8:00 AM-11:30 AM

Association of intravenous (IV) and intramuscular (IM) pegaspargase (PEG) administration with rate of adverse events (AE) in standard risk (SR) Acute Lymphoblastic Leukemia (ALL) Children's Oncology Group (COG) trials. *First Author: Kelly W. Maloney, Children's Hosp Colorado, Aurora, CO*

Background: COG AALL0331 administered PEG IM in induction (IND) and Delayed intensification (DI) whereas AALL0932 administers the same dose IV. We compared grade 3/4 toxicities resulting from the single doses of PEG given in the IND and DI phases on the standard arms of AALL0331 and AALL0932 that gave only 2 doses of PEG (excluded arms with additional PEG). **Methods:** AALL0331 and AALL0932 shared a common 3 drug IND: dexamethasone (DEX) 6 mg/m^2/day X 28 days, vincristine (VCR) 1.5 mg/m^2/dose on days 1, 8, 15, 22, IT methotrexate (age adjusted dosing) on days 8, 29, and PEG 2500 units/m^2/dose IM on day 4, 5, or 6 (AALL0331) or IV on day 4 (AALL0932). DI (Days 1-28) for both protocols consisted of: DEX 10 mg/m^2/day (days1-7, 15-22), VCR 1.5 mg/m^2/dose and Doxorubicin 25 mg/m^2/dose IV (days 1, 8, 15), PEG 2500 units/m^{2}on day 4 (AALL03131 IM; AALL0932 IV). Toxicity was graded using CTCAE v4.0, however, AALL0331 collected data using CTCAE v3.0, which was subsequently mapped to v4.0. **Results:** During IND, the rates of anaphylaxis/allergic reaction were similar between IM and IV PEG (0.2% vs. 0.3%, p = 0.842). The rate of anaphylaxis/allergic reaction in DI was 0.5% (IM) vs 1.8% (IV) (p = 0.007). The rates of pancreatitis, elevated lipase and amylase, and hyperglycemia were similar between IM and IV PEG in both IND and DI. **Conclusions:** The rates of AEs with PEG administration (IV or IM) are low but more grade 3/4 anaphylaxis/allergic reactions were reported with IV PEG compared to IM PEG during DI. This may be due to more stringent reporting on 0932 or the challenges of determining infusion reactions vs. allergic reactions when PEG is administered IV. Clinical trial information: NCT00103285.

Toxicities (%)		Grades	AALL0331	AALL0932	p-value
Allergic reaction/ Anaphylaxis	IND	3-4	0.2	0.3	0.84
	DI		0.5	0.8	0.0007
Pancreatitis	IND	3-4	0.5	0.8	0.07
	DI		0.4	0.3	0.79
Lipase increased	IND	4	0.6	0.4	0.22
	DI		0.4	0.3	0.39
Serum amylase increased	IND	4	0.3	0.2	0.53
	DI		0.1	0.1	1.00
Hyperglycemia	IND	4	1.1	1.3	0.46
	DI		0.4	0.1	0.02
Glucose intolerance	IND	4	0.02	0	1.0
	DI		0	0	----

10036 Poster Session (Board #106), Sun, 8:00 AM-11:30 AM

Phase I trial of ontuxizumab (MORAb-004) in children with relapsed or refractory solid tumors: A Children's Oncology Group Study. *First Author: Robin Elizabeth Norris, Rainbow Babies and Children's Hosp, Moreland Hills, OH*

Background: Ontuxizumab is a humanized IgG mAb that targets the cell-surface glycoprotein endosialin (TEM-1/CD248). Endosialin is found in tumor stroma and vasculature across various tumors, with high expression in sarcoma and neuroblastoma but generally limited expression in normal tissue. Ontuxizumab binding to endosialin may interfere with platelet-derived growth factor (PDGF) signaling and prevention of protein interactions involved in tumor-stroma organization and new vessel formation. **Methods:** Ontuxizumab was administered intravenously on days (d) 1, 8, 15, and 22 of a 28 d cycle. Three dose levels (4, 8, and 12mg/kg) were evaluated using a rolling 6 design. Further dose escalation to 16mg/kg would proceed only if the ontuxizumab systemic clearance (CL) was $\geq$ 30% higher in children compared to adults and the maximum tolerated dose (MTD) was not reached. Primary endpoints were to describe toxicities, define MTD or recommended phase 2 dose (RP2D) and to characterize the pharmacokinetics (PK) of ontuxizumab in children. Following determination of MTD/RP2D an additional cohort of 6 pts $<$ 12y was enrolled. PK was evaluated using non-compartmental and population PK modeling. **Results:** Twenty-seven eligible pts (17 male, median age 15y, range 3 – 21y) were enrolled. Twenty-two pts [neuroblastoma (5), Ewing sarcoma (4), rhabdomyosarcoma (4), other (9) tumors] were fully evaluable for toxicity. Five pts did not complete cycle 1 due to tumor progression. Grade $\geq$ 3 regimen-related non-hematologic toxicities included hypophosphatemia (1) and hyponatremia (1). One pt had grade 3 lymphopenia and 1 pt had grade 3 anemia in cycle 1. Grade $\leq$ 2 fever or infusion related reactions occurred in 9 pts. Dose-limiting bacteremia was observed during cycle 1 in 1 pt at dose level 3 (12mg/kg). Clearance was dose-dependent and within 30% of adult value (0.193 mL/h/kg) at 12mg/kg. Therefore there was no further dose escalation. **Conclusions:** The recommended dose of ontuxizumab in children is 12mg/kg administered weekly. This dose appears to be well tolerated in children with relapsed or refractory solid tumors. PK does not appear to be significantly different in children compared to adults. Clinical trial information: NCT01748721.

10037 Poster Session (Board #107), Sun, 8:00 AM-11:30 AM

Exploring Tenascin-C as a novel therapeutic target in pediatric brainstem glioma. *First Author: Amanda Muhs Saratsis, Ann & Robert H. Lurie Children's Hospital of Chicago (Northwestern University Feinberg School of Medicine), Chicago, IL*

Background: Diffuse intrinsic pontine glioma (DIPG) is the most deadly solid tumor of childhood. Histone 3 mutation occurs in up to 80% of DIPGs, causing global epigenetic aberration. Tenascin-C (TNC) is an extracellular matrix protein expressed during brain development by oligodendroglial progenitor cells (OPCs), the purported DIPG cell of origin. TNC is highly expressed in adult glioma, contributing to local invasion and poor survival. We report increased TNC in tumor tissue and cerebrospinal fluid (CSF) from children with high-grade glioma, including DIPG, and characterize TNC expression in relation to histone 3 mutation and DNA methylation. **Methods:** Tissue collected intraoperatively or post-mortem from children with brainstem (DIPG, n = 14), supratentorial (n = 7), and cerebellar astrocytoma (n = 2), and CSF from DIPG (n = 9) and supratentorial astrocytoma (n = 17), were subjected to MS/MS proteomic analysis. Tissue gene expression, DNA methylation, and H3F3A or HIST1H3B sequencing was performed. TNC expression was validated and correlated with tumor grade and H3K27M status via Western blot and immunohistochemistry. Data integration was performed via Partek Genomics Suite and Ingenuity Pathway Analysis. **Results:** TNC protein expression was significantly increased in 75% of glioma tissue specimens compared to normal tissue, including all DIPG specimens tested (fold change $>$ 2, $p < 0.05$). Secreted TNC was detected in 7/9 DIPG CSF specimens (77.8%). Tumor-specific TNC expression was confirmed with Western blot and tissue immunohistochemistry. Greater relative TNC expression correlated with tumor grade and was associated with Notch pathway activation, H3K27M mutation, and TNC promoter hypomethylation. **Conclusions:** We report increased TNC expression in tissue and CSF of pediatric high-grade astrocytomas, including DIPGs, associated with promoter hypomethylation and H3K27M mutation. Given the effect of TNC on OPC proliferation, migration and differentiation, TNC could serve as a clinical biomarker of disease and rational therapeutic target for a substantial subgroup of DIPG patients. Further studies exploring the mechanism of TNC overexpression and effects of targeting TNC expression in DIPG are currently underway.

10038 Poster Session (Board #108), Sun, 8:00 AM-11:30 AM

Diagnostic and prognostic role of circulating *miR-206* in rhabdomyosarcoma patients. *First Author: Mitsuru Miyachi, Department of Pediatrics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan*

Background: *miR-206* is a muscle-specific microRNA and is much more strongly expressed in rhabdomyosarcoma (RMS) tumors than in non-RMS tumors. Here, we analyzed the diagnostic and prognostic significance of circulating *miR-206* values in serum specimens of RMS patients. **Methods:** Total RNA was extracted from serum samples (200 μL) from 60 patients (28 RMS, 32 non-RMS) and quantified by real-time quantitative RT-PCR. Receiver-operating characteristics (ROC) curves were established to evaluate the diagnostic value. Survival curves for RMS patients were calculated by the Kaplan-Meier method and were compared using the log-rank test. The median follow-up time was 30 months. Serum *miR-206* expression level and prognostic factors were evaluated with a univariate analysis. The factors included age, primary tumor size, regional lymph node involvement, distant metastasis, fusion gene status, histologic subtype and primary tumor site. A multivariate analysis was conducted using the Cox proportional hazards regression method. The variables correlated with progression-free survival (PFS) in the univariate analysis were included in the model. **Results:** Serum *miR-206* expression levels were higher in RMS patients than in non-RMS patients ($p < 0.001$) with an area under the ROC curve of 0.8705 (95% confidence interval [CI], 0.7791-0.962), sensitivity of 0.714 and specificity of 0.938. The cut-off value was 164.1 copies/μl serum. PFS was negatively influenced by a high serum *miR-206* expression level (2.5-year PFS; 10.7 % (n = 14) vs 77.9 % (n = 14), p = 0.0019) and the presence of both distant metastasis and locoregional lymph node involvement (2.5-year PFS; 30.9 % (n = 18) vs 80.0 % (n = 10), p = 0.017) in univariate analysis. In the multivariate analysis, a high serum *miR-206* expression level had an independent prognostic significance (hazard ratio: 3.50 [95% CI: 1.12-11.0], p = 0.031). **Conclusions:** *miR-206* can be a novel biomarker for both diagnosis and treatment stratification of RMS. The limitations of our study include a retrospective design, small sample size and non-uniform treatment. The Japan Rhabdomyosarcoma Study Group will prospectively validate its prognostic significance in a large cohort of uniformly-treated patients.

10039 Poster Session (Board #109), Sun, 8:00 AM-11:30 AM

Anti-tumor efficacy in SIOPEL 6: A multi-centre open label randomised phase III trial of the efficacy of sodium thiosulphate (STS) in reducing ototoxicity in patients receiving cisplatin (Cis) monotherapy for standard risk hepatoblastoma (SR-HB). *First Author: Penelope Rachel Brock, Great Ormond Street Hospital, London, United Kingdom*

Background: SR-HB is defined as tumor extension limited to PRETEXT I, II or III, no portal, hepatic veins, or intra-abdominal extra-hepatic disease, AFP $>$ 100ng/ml and no metastases. Cis can cause permanent bilateral high-frequency hearing loss. STS may reduce this risk, but could also reduce Cis anti-tumor efficacy. **Methods:** Newly diagnosed patients with SR-HB were treated with 2-weekly cycles of Cis, 4 before primary tumor resection and 2 after. Patients were randomized to Cis alone or Cis and STS. Cis 80mg/m^2 was administered i.v. over 6 hrs. STS was administered i.v. exactly 6 hrs after stop of Cis over 15 minutes at 20g/m^2. Response was assessed after 2 and 4 cycles pre-operative with serum AFP and liver imaging. In case of progression after 2 cycles, STS was stopped and doxorubicin 60mg/m^2 continuous infusion over 48 hrs added. The primary endpoint is centrally reviewed absolute hearing threshold, at the age of $\geq$ 3.5 years, by pure tone audiometry. With a sample size of 102, the trial has 80% power to detect a reduction in hearing loss defined as Brock grade $\geq$ 1 from 60% of patients with Cis to 35% with Cis+STS. Short term anti-tumor efficacy endpoint is disease status at end of treatment which was evaluated after every 20 patients and submitted to the IDMC. Throughout the trial, the IDMC recommended continuation after interim review of efficacy results. **Results:** From 2007 to end 2014, 45 sites from 12 countries randomized 53 patients to Cis and 60 to Cis+STS, median age at diagnosis was 12.8 months. Treatment was well tolerated and acute toxicity similar between arms. Efficacy results after 4 pre-op chemo cycles for the first 94 patients (47 Cis, 47 Cis+STS) were PR/SD/PD for Cis: 86%/8%/6% and for Cis+STS: 90%/5%/5%. Complete remission after resection and post-op chemo was 92% and 98%. In January 2015, 2 pts had died (Cis arm), and 2 (Cis) and 1 (Cis+STS) had progressed. **Conclusions:** End of treatment anti-tumor efficacy in SR-HB treated on the above protocol shows no adverse outcome related to STS. Final evaluation of hearing loss at $\geq$ 3.5 yrs of age, the primary endpoint, is expected in 2017. Clinical trial information: NCT00652132.

10040 Poster Session (Board #110), Sun, 8:00 AM-11:30 AM

Proton versus conventional radiotherapy for pediatric salivary gland tumors: Acute toxicity and dosimetric characteristics. *First Author: Stephen Richard Grant, Baylor College of Medicine, Houston, TX*

Background: Adjuvant radiotherapy (RT) is often a component of treatment for high-risk salivary gland tumors. Minimizing irradiation of surrounding normal tissues is particularly important for pediatric patients. We compared acute toxicity profiles, clinical outcomes, and dosimetric data for children with parotid or submandibular tumors treated with adjuvant photon/electron-based RT (X/E RT) or proton RT (PRT). **Methods:** We retrospectively identified 24 pediatric patients who had received adjuvant RT at a single institution for salivary gland tumors (20 parotid, 4 submandibular). Demographic, disease control and survival data were extracted from the medical records and dosimetric data from the treatment planning systems. Toxicity was scored according to the Common Terminology Criteria for Adverse Effects 4.0. **Results:** Eleven patients received X/E RT and 13 PRT. The median prescribed dose was 60 Gy for each group. PRT was associated with significantly lower mean doses to the thyroid (1.5 vs. 22.5 Gy, $P< 0.05$), oral cavity (4.6 vs. 20.7 Gy, $P< 0.05$), and larynx (11.3 vs. 44.3 Gy, $P< 0.05$); and the contralateral parotid (0.0 vs. 4.6, $P< 0.05$), hemi-mandible (0.0 vs. 11.9 Gy, $P< 0.05$), and submandibular gland (0.0 vs. 13.5 Gy, $P< 0.05$). In the X/E RT group, 27% had acute grade 3 dermatitis, 18% grade 3 mucositis, and 9% grade 3 dysphagia, and the median weight loss was 5.3%. No patient in the PRT group experienced acute grade 3 toxicity, and a median weight gain of 1.2% was noted. At a median follow-up time of 35 months, no disease recurrence or deaths were observed in either group. **Conclusions:** Compared with X/E RT, PRT significantly reduced the radiation dose to many surrounding normal tissues, which translated to reductions in clinical acute toxicity. Continued follow-up is needed to identify any differences in long-term toxicity and disease control.

10041 Poster Session (Board #111), Sun, 8:00 AM-11:30 AM

Molecular mechanisms for telomere maintenance in neuroblastoma. *First Author: Armita Bahrami, St. Jude Children's Research Hospital, Memphis, TN*

Background: Despite a well-developed risk classification schema utilizing both clinical and biologic factors, the clinical outcome of neuroblastoma (NB) is remarkably heterogeneous. Replicative immortality in cancers is mediated by 2 known telomere maintenance mechanisms (TMMs): telomerase reactivation and alternative lengthening of telomere (ALT). We hypothesized that TMMs are essential for cancer development in high-risk NBs (HR-NBs) but not low-risk or stage 4S NBs that frequently undergo spontaneous regression. We investigated the prevalence of known molecular events involved in TMMs in NB risk categories. **Methods:** The analysis included 47 NBs from 27 patients with high-risk disease and poor outcomes and 19 patients with low- or intermediate-risk disease and good outcomes (LR-NBs). Presence of the ALT phenotype was determined by telomeric fluorescence in situ hybridization (FISH), and its association with *ATRX* alterations was evaluated by immunohistochemistry. Direct sequencing of the *TERT* promoter (*TERT*-p) to screen for hotspot mutations and *TERT* copy number FISH to assess gene amplification were conducted. For methylation analysis, 500 ng of bisulfite-converted DNA was processed and hybridized on the Illumina HumanMethylation450 BeadChip. RNA in situ hybridization (ISH) for TERT was performed on 4 HR-NBs to observe TERT expression. **Results**: Methylation analysis showed that *TERT*-p CpGs at positions ch5:1295737 and 1295799 were the most differentially methylated regions between HR-NBs and LR-NBs ($P< 0.0005$). Of the 27 HR-NBs, 11 (41%) were hypermethylated in one or both CpG regions; 7 (26%) exhibited an ALT phenotype, of which 5 were associated with heterogeneous or loss of ATRX expression; 3 had *TERT* amplification; 2 carried a *TERT*-p mutation; and 5 (19%) showed no alterations. In contrast, the assays were negative in all 19 LR-NBs. RNA ISH for TERT showed high-resolution signals in *TERT*-p methylated but no signals in ALT-phenotype HR-NBs. **Conclusions**: Molecular mechanisms for telomere maintenance in HR-NB are diverse and commonly associated with hypermethylation of the *TERT*-p region. Future studies to assess the prognostic relevance of these biomarkers on clinical outcomes in patients with NB are warranted.

10042 Poster Session (Board #112), Sun, 8:00 AM-11:30 AM

Outcome of recurrent osteosarcoma patients enrolled in seven phase II trials through CCG, POG, and COG: Learning from the past to move forward. *First Author: Joanne P. Lagmay, University of Florida Shands Hospital for Children, Gainesville, FL*

Background: The use of radiographic response as the primary endpoint in phase II osteosarcoma (OS) trials may limit optimal detection of treatment response due to the calcified tumor matrix. We assessed outcome data for children with recurrent/refractory OS enrolled on single agent Children's Oncology Group phase II trial to establish this cohort's baseline expected survival outcome. **Methods:** We performed a retrospective analysis of outcome for children with recurrent/refractory OS enrolled on one of seven phase II trials with an OS stratum conducted by COG and predecessor groups from 1997-2007. Trials included A09713 (topotecan), ADVL0122 (imatinib), ADVL0421 (oxaliplatin), ADVL0524 (ixabepilone), CCG-0962 (docetaxel), P9761 (irinotecan) and P9963 (rebeccamycin analogue). All trials used RECIST or WHO with primary endpoint as response rate. Event Free Survival (EFS) was correlated with the following potential prognostic factors: age, trial, number of prior chemotherapy regimens, gender and race. To determine the historical disease control rate for patients with fully resected disease, we used the EFS in a Phase II study (AOST0221) of osteosarcoma patients given inhaled GMCSF with first pulmonary recurrence, which had a biological endpoint. **Results:** In each included trial the OS stratum failed to meet the primary endpoint. Radiographic responses were observed in only 3 trials. The highest response rate was 11% seen in A09713. EFS for 96 subjects with OS and measurable disease was 12% at 4 months (95% CI: 6-19%). There was no impact of age, gender or race on EFSnor was there a significant difference in EFS across trials or by number of prior treatment regimens**.** The 12-month EFS for the 42 subjects enrolled in AOST0221 was 20% (95% CI: 10-34%). **Conclusions:** The aggregate outcome for children with recurrent/refractory OS in these previously conducted single arm phase II trials was disappointing. Given the poor EFS for children with recurrent/refractory OS it is unlikely that active agents were missed using traditional RECIST response. Nevertheless, we have now defined baseline EFS outcomes that can be incorporated into future phase II trial design for recurrent osteosarcoma.

10043 Poster Session (Board #113), Sun, 8:00 AM-11:30 AM

Vesicular monoamine transporter protein expression in neuroblastoma: A report from the Children's Oncology Group. *First Author: Steven G. DuBois, University of California, San Francisco, San Francisco, CA*

Background: Vesicular monoamine transporters 1 and 2 (VMAT1 and VMAT2) are thought to mediate MIBG uptake in adult neuroendocrine tumors. VMAT expression has not been comprehensively investigated in neuroblastoma. **Methods:** We evaluated VMAT1 and VMAT2 expression by immunohistochemistry (IHC) in neuroblastoma tumors from 76 patients with high-risk disease treated on COG protocol A3973. All patients had baseline MIBG diagnostic scans centrally reviewed. IHC results were scored as the product of intensity grading (0-3+) and percent of tumor cells expressing the protein of interest. Association of VMAT1 and VMAT2 scores with clinical and biological features was tested using Wilcoxon rank sum tests. **Results:** Patient characteristics were typical of high-risk neuroblastoma, though the cohort was intentionally enriched for patients with MIBG non-avid tumors ($n = 20$). VMAT1 and VMAT2 were expressed in 62% and 75% of neuroblastoma tumors, respectively. VMAT1 and VMAT2 scores were both significantly lower in *MYCN* amplified tumors, non-adrenal primary tumors, and in tumors with high mitotic karyorrhectic index. MIBG avid tumors had significantly higher VMAT2 scores compared to MIBG non-avid tumors (median 216 vs. 45; $p = 0.04$). VMAT1 expression did not correlate with MIBG avidity. **Conclusions:** VMAT1 and VMAT2 are expressed in the majority of neuroblastomas. Expression correlates with clinical and biological features. Expression of VMAT2 but not VMAT1 correlates with avidity for MIBG.

10044 Poster Session (Board #114), Sun, 8:00 AM-11:30 AM

Meta-analysis of effects of demographic and treatment variables on outcome for localized paratesticular rhabdomyosarcoma (PT RMS) in North America and Europe. *First Author: David Walterhouse, Ann and Robert H Lurie Children's Hosp of Chicago, Chicago, IL*

Background: Treatment recommendations for localized PT RMS differ based on clinical trials conducted by cooperative groups in North America and Europe. We conducted a meta-analysis to identify effects of demographic features and treatment choices on outcome for patients with localized PT RMS. **Methods:** We analyzed demographic and treatment variables from 12 studies conducted by the Children's Oncology Group (COG; n = 416), Cooperative Weichteilsarkom Studiengruppe (CWS; n = 106), European paediatric Soft Tissue Sarcoma Group (EpSSG; n = 99), Italian Cooperative Group (ICG; n = 64), and SIOP Malignant Mesenchymal Tumor Group (MMT; n = 159) that enrolled 844 eligible patients with localized PT RMS from 1988-2013. Categorical and continuous variables were checked for association. Event-free survival (EFS) and survival (S) were compared among groups using univariate and multivariate analyses. **Results:** Mean patient age at enrollment differed among the cooperative groups (7 yrs [MMT] – 11 yrs [EpSSG]; $p < 0.05$). Patients ≥ 10 yrs were more likely to have tumors > 5 cm (60%; $p < 0.05$), enlarged nodes (N1) (17%; $p < 0.05$), and pathologically involved nodes (33%; $p < 0.05$) than younger patients. 89% of N1 nodes and 19% of N0 nodes were pathologically involved in patients ≥ 10 yrs. With a median follow-up of 7 yrs, 87.5% of patients were event-free and 94.9% were alive. Variables that impacted EFS ($p < 0.05$) were cooperative group, era of enrollment, age, IRS group, T-stage, tumor size, and surgical assessment of nodes in patients ≥ 10 yrs with tumors > 5 cm. Using a stepwise variable selection procedure on a proportional hazards regression model starting with all demographic and treatment variables, the EFS model selected era, age, size, and surgical assessment of regional lymph nodes ($p < 0.05$) and the S model selected era, age, size, and histology ($p < 0.05$). **Conclusions:** Localized PT RMS has a favorable prognosis using approaches of North American and European cooperative groups. Surgical assessment of regional nodes is important in boys ≥ 10 yrs as this impacts EFS (but not S), and in younger boys with N1 disease. Clinical lymph node staging is otherwise sufficient to guide therapy.

10045 Poster Session (Board #115), Sun, 8:00 AM-11:30 AM

Treatment outcomes of pediatric and young adult sporadic desmoid tumors. *First Author: Sara Helmig, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH*

Background: Desmoid tumor (DT) is a non-malignant soft-tissue neoplasm of children and adults that is often treated with surgery, radiation and/or chemotherapy. DTs may recur even after complete resection, and the benefit of medical therapy is unpredictable. Data driven DT therapy guidelines are lacking for children and young adults. **Methods:** A retrospective review of DT patients treated at a single institution between 2003 and 2014. **Results:** Twenty-three patients, aged 3 months to 25 years of age at diagnosis, were identified from a complex patient population that included 7 patients with congenital deformity or syndromes. Anatomic locations included extremity (15), head/neck tumors (2), and trunk/abdomen (6). Both head/neck and 5 of 6 trunk patients demonstrated no evidence of disease (NED) at last follow-up, whereas only 1 extremity patient was NED ($p = 0.0001$). Of the 23 patients, all but 2 patients had at least one surgical resection. Six patients required a single surgery only: R0 (n = 4), R1 (n = 1), and R2 (n = 1). Eight patients received vinblastine and methotrexate (VBL/MTX), 5 received sorafenib, and tamoxifen (TAM) with sulindac, hydroxyurea, and liposomal doxorubicin were each administered to 1 patient. One VBL/MTX patient experienced a partial response while 3 others experienced prolonged stabilization (> 36 months). Two of four patients treated with sorafenib experienced stabilization (> 24 months). The single patient treated with TAM/sulindac experienced prolonged stabilization. Five patients received radiation therapy, with one developing a secondary sarcoma and two others stabilizing without further sequela. There were no deaths related to DT. **Conclusions:** Our findings demonstrate that a subset of tumors can be adequately treated with a single surgery. Head/neck and trunk tumors were more likely to be rendered NED than extremity tumors. Another subset of unresectable/recurrent tumors treated with mild medical therapy stabilized without significant morbidity, although RECIST response was rare in this complex cohort. Given the unpredictable benefit of therapies for unresectable/recurrent disease, genome directed approaches and observation-only strategies merit further exploration in this age group.

10046 Poster Session (Board #116), Sun, 8:00 AM-11:30 AM

The prognostic significance of MIBG uptake in left supraclavicular lymph nodes in high risk neuroblastoma patients. *First Author: Shifra Ash, Pediatric Hematology Oncology, Schneider Children's Medical Center of Israel, Petah-Tikva, Israel*

Background: Metastatic MIBG localization in the soft tissues of the left supraclavicular (LSC) region is occasionally seen in children with high risk (HR) neuroblastoma. The purpose of the study was to evaluate the prognostic significance of this uptake. **Methods:** We performed a retrospective analysis of MIBG studies and clinical data of 77 HR neuroblastoma patients treated at Schneider Children's Medical Center of Israel between 1998 – 2015. The median age was 2.8 years (0.1-7.6) and the median follow up was 39 months (1-202). HR was defined as patients diagnosed as stage 3 with MYCN amplification and stage 4. Treatment consisted of induction chemotherapy, surgery, autologous bone marrow transplantation, local radiation and retinoic acid with or without immunotherapy. MIBG studies included whole body surveys, SPECT or SPECT/CT with the supraclavicular regions in the field of view. **Results:** LSC uptake was identified in 13/77 children (17%). All children with LSC MIBG uptake had abdominal primary tumors. Patients with LSC uptake had a 5y relapse free survival (RFS) of only 16%±14 as opposed to 42%± 7 for patients with no uptake ($p = 0.021$). Five year overall survival (OS) was 0% in children with LSC uptake and 57%±7 in those without ($p = 0.001$). Within the group of 46/77 patients without MYCN amplification, 5y OS was 0% in 8 children with LSC uptake and 51%± 9 in 38 without ($p = 0.014$). On multivariate analysis for survival, only LSC MIBG uptake was found to be a poor independent prognostic factor, with an increased risk of 3.69 fold (95% CI 1.6-8.3, $p = 0.002$). **Conclusions:** Avid metastases identified by MIBG in the LSC region can identify HR patients with worse prognosis. This phenomenon resembles metastatic spread to Virchow nodes from gastric cancer and can be used as a prognostic factor. Cross sectional imaging with MIBG (or other modalities) should always include the left supraclavicular region. The presence of left supraclavicular disease should be considered for therapy planning.

10047 Poster Session (Board #117), Sun, 8:00 AM-11:30 AM

Comparison of ^{18}F-FDG-PET-CT and bone scintigraphy for evaluation of osseous metastases in newly diagnosed and recurrent osteosarcoma. *First Author: Caitlin Hurley, St. Jude Children's Research Hospital, Memphis, TN*

Background: Bone scintigraphy (BS) is routinely used to detect osseous metastases in osteosarcoma. The use of ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG-PET-CT) to assess tumor extent in pediatric sarcomas has increased recently. We compared the sensitivity, specificity, and diagnostic accuracy of PET-CT and BS for detection of osseous metastases in osteosarcoma. **Methods:** We retrospectively reviewed 39 patients with osteosarcoma who underwent paired PET-CT and BS at diagnosis and/or first recurrence between 2003 and 2012. PET-CT and BS studies were independently reviewed by 2 pediatric imaging specialists who were blinded to results of the opposing modality and reference standard. Reviewers categorized lesions as benign, malignant or indeterminate. Reference standard for lesion histology was biopsy or clinical follow-up. Diagnostic performance of PET-CT, BS, and combined modalities were determined. **Results:** Forty-two examinations from 39 patients were reviewed and 123 bone lesions were evaluated. Median age was 11 years (range 5-19 years). Four patients had 13 osseous metastases at diagnosis (3 biopsied, 10 clinically), and 3 had 9 osseous metastases at recurrence (2 biopsied, 7 clinically). For all sites combined, sensitivity, specificity and diagnostic accuracy were 92%, 76%, and 84% respectively for PET-CT, 77%, 94%, and 85% for BS, and 98%, 69%, and 84% for PET-CT and BS combined. For metastatic sites alone, sensitivity, specificity and diagnostic accuracy were 77%, 76% and 76% for PET-CT, 41%, 94% and 80% for BS, and 96%, 69% and 76% for combined modalities. Improved sensitivity of PET-CT for metastatic sites compared to BS was borderline significant ($p = 0.077$). PET-CT and BS combined did not improve sensitivity over PET-CT alone ($p = 0.125$), but was significantly higher than BS alone ($p < 0.001$). BS specificity was superior to both PET-CT ($p = 0.02$) and combined imaging ($p < 0.001$). **Conclusions:** ^{18}F-FDG-PET-CT is at least as sensitive as BS in detecting osseous metastases in osteosarcoma; combined use with BS further increases sensitivity. Our findings support the use of both ^{18}F-FDG-PET-CT and BS for staging of osteosarcoma.

10048 Poster Session (Board #118), Sun, 8:00 AM-11:30 AM

ImmunoPET compared with conventional imaging modalities for the detection of Ewing sarcoma metastases in a preclinical model. *First Author: Allison Frances O'Neill, Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Ewing sarcoma is a solid tumor arising from bone and the soft tissues that affects approximately 250 children and adolescents each year. Localized disease confers a favorable 75% 5-year survival, but the prognosis for metastatic disease remains dismal with only a 20% 5-year survival. The ability to accurately diagnose disease extent is therefore crucial. Conventional imaging modalities provide high-resolution anatomic data but lack specificity. The goal of this preclinical study was to compare the detection of metastatic Ewing sarcoma using a ^{89}Zr-labeled anti-CD99 antibody (Ab) with conventional imaging modalities including MRI and [^{18}F]FDG-PET. **Methods:** NOD scid gamma mice were injected via tail vein with luciferase-transduced TC32 Ewing sarcoma cells and monitored for tumor growth by bioluminescence imaging until development of 2-3 mm liver metastases at 4 weeks. Disease burden and lesion distribution were assessed by MRI and [^{18}F]FDG-PET. Mice were then injected with the ^{89}Zr-labeled anti-CD99 Ab and imaged from 16 to 144 h post-injection. **Results:** Liver metastases were detected by immunoPET from 16 h to 144 h post-injection with the maximum tumor-to-background ratio observed at 72 h (SUVmax = 12.5 for tumor and 4 for local normal tissues). Liver metastases of 2-3 mm diameter were identified on MR images guided by immunoPET data, but were not detected using [^{18}F]FDG. Autoradiography data demonstrated a ^{89}Zr-Ab metastases-to-liver uptake ratio of 13:1. **Conclusions:** The ^{89}Zr-labeled anti-CD99 Ab PET probe out-performed [^{18}F]FDG and MRI in the detection of Ewing sarcoma metastases, validating our prior work with a ^{64}Cu-labeled anti-CD99 probe. The longer half-life of ^{89}Zr allowed imaging at later time points (72 h) than ^{64}Cu yielding a tumor-to-background ratio that was two-fold higher. The more sensitive and specific detection and monitoring of metastatic disease may have tremendous implications for the clinical care of patients with Ewing sarcoma. In light of existing safety data for the imaging of adult solid tumors with ^{89}Zr-labeled Abs, this study supports next steps for translation to pediatrics.

10049 Poster Session (Board #119), Sun, 8:00 AM-11:30 AM

Analysis of prognostic factors of clinical outcome in children and adolescents enrolled in phase I trials: a multicentre European collaborative study. *First Author: Fernando Carceller Lechon, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: Phase I trials play a key role in the evaluation of novel agents for pediatric patients with advanced cancer. One of the major challenges remains the selection of patients who are most likely to benefit from investigational treatments and have a life expectancy ≥ 8-12 weeks. Two clinical scores have been validated in adult oncology to optimise patient selection: the Royal Marsden (RM) score (albumin, lactate dehydrogenase (LDH), number of metastatic sites); and the MD Anderson Cancer Centre (MDACC) score (RM score plus performance status (PS) and gastrointestinal tumor type). These scores have not been validated for children/adolescents enrolled in phase I trials. **Methods:** Retrospective study of patients aged < 18 years, with solid tumors, enrolled in phase I trials at Innovative Therapies for Children with Cancer (ITCC) centres between 2000-2014. Descriptive and uni/multivariate analyses of overall survival (OS) were carried out. **Results:** 172 patients were studied; median age 9 years. Tumor types included: primary central nervous system 42%, bone sarcomas 23%, neuroblastoma 10%, others 25%. Best response: complete/partial in 21 patients (12%); stable disease in 42 (24%). Overall, 30 and 90-day mortality on study were, respectively, 8% and 29%. Median OS (months) as per RM score was: 15.2 ± 2.4 for scores 0-1 *Vs* 5.7 ± 1.7 for scores ≥ 2 (p = 0.015); and, as per MDACC score, 15.9 ± 2.6 for scores 0-1 *Vs* 7.7 ± 2.3 for scores ≥ 2 (p = 0.022). In univariate analysis, tumor type, PS, school/work attendance at inclusion, use of opioids, creatinine above upper limit of normal (> ULN), total bilirubin > ULN, LDH > ULN, albumin < 35 g/dl, prior radiotherapy, and prior autologous stem cell rescue (ASCR) significantly correlated with OS. In multivariate analysis, poor PS, LDH > ULN and no prior ASCR correlated with lower OS. **Conclusions:** The RM and MDACC scores select patients with an inferior OS in pediatric phase I studies, but cannot be deemed fully fit for purpose in children. Clinical characteristics which independently predict impaired survival will identify children who are unlikely to benefit from participation in phase I trials and improve the efficiency of these studies.

10050 Poster Session (Board #120), Sun, 8:00 AM-11:30 AM

Efficacy in six courses of nonmethotrexate three-drug chemotherapy and surgery in osteosarcoma: 25-year experience. *First Author: Rejin Kebudi, Istanbul University, Oncology Institute and Cerrahpasa Medical Faculty, Pediatric Hematology-Oncology, Istanbul, Turkey*

Background: Chemotherapy and surgery are the mainstay of osteosarcoma (OS) treatment. Using 2-4 drugs and short or long duration in chemotherapy protocols have been evaluated in various trials. A metaanalysis (Anninga JK, 2011) has reported, 3-drug regimen is better than 2, but not inferior than 4-drug. Our study aims to evaluate the outcome of Osteosarcoma (OS) patients treated with a nonmethotrexate 3-drug regimen and surgery. **Methods:** Children and adolescents with oteosarcoma treated between January,1990- January,2015 at Istanbul University, Oncology Institute were retrospectively evaluated in terms of demographic features and survival outcomes. The patients recieved 6 courses of a 3 drug regimen comprising of ifosfamide 1.8 g/m2/d x 3 days, epirubicin 90 mg/m2/d and sisplatinum 100mg/m2/d administered 3-pre and 3-postoperatively. Methotrexate was not in the protocol because drug levels could not be monitored in the 1990's at our center. Since 2012, mifamurtide was added to the protocol postoperatively for nonmetastatic patients. **Results:** 189 children (105 boys, 84 girls) with a median age of 12 years (3-18yrs) were evaluated. 151 (80%) were non-metastatic and 38 metastatic. Median follow-up was 3,6 years (1mo.-24 yrs). 91.5 % had limb salvage surgery. Relapse/progressive disease was observed in 69 patients at a median 15 months (1mo-63 mo). The 5 and 10-year overall survival and event free survival for the whole group were (OS) 63.1% and 60.5%, and (EFS) 58.8% and 57% respectively. In non-metastatic and in metastatic patients, 5-year OS was 73.8 and 23.9% , 5-year EFS was 69.4% and 20.8%; respectively (p = 0.0001). In 25 nonmetastatic patients recieving chemotherapy and mifamurtide 2-year OS and EFS were 90.9% and 85.5% respectively at a median of 20 months. **Conclusions:** A 3-drug combination of cisplatin,epirubicin,ifosfamide given for 6 courses is an effective, reasonably well tolerated regimen for osteosarcoma; and combined with surgery in experienced hands results in survival rates comparable to other studies in the literature. Longer follow up is needed to assess the contribution of mifamurtide on outcome. Presence of metastasis is associated with poor outcome.

10051 Poster Session (Board #121), Sun, 8:00 AM-11:30 AM

Comparison of clinical features and outcomes in patients with extraskeletal versus skeletal localized Ewing sarcoma: A report from the Children's Oncology Group. *First Author: Thomas Cash, Emory Univ/Children's Healthcare of Atlanta, Atlanta, GA*

Background: The prognostic significance of having extraskeletal Ewing sarcoma (EES) using modern chemotherapy protocols is unknown. The purpose of this study was to compare the clinical characteristics and outcomes for patients with extraskeletal and skeletal Ewing sarcoma. **Methods:** Patients had localized Ewing sarcoma and were treated on two consecutive protocols using 5-drug chemotherapy (INT-0154 and AEWS0031). Patients were analyzed based on having an extraskeletal (n = 213) or skeletal (n = 826) site of tumor origin. Patient characteristics were compared using Wilcoxon rank sum, Fisher exact, and chi-square tests. Event-free survival (EFS) was estimated using the Kaplan-Meier method and compared using the log-rank test. Relapse, death, or second malignancy were considered events. **Results:** Age of diagnosis and sex did not differ according to tissue of origin. Patients with EES were less likely to be white (80.8% vs. 87.7%; p = 0.02), and were less likely to have tumors > 8cm (22.3% vs. 36.3%; p = 0.01) compared to patients with skeletal Ewing sarcoma. There was a trend to suggest superior EFS for patients with EES compared to skeletal tumors (hazard ratio 1.34; p = 0.053). Among patients with extraskeletal tumors, the EFS was inferior for those patients who were not white (p = 0.005) and who were > 18 years of age (p = 0.02). The distribution of event types experienced by each group did not differ. **Conclusions:** Clinical characteristics differ between patients with extraskeletal and skeletal localized Ewing sarcoma and outcomes may be superior for patients with EES. The origin of these differences requires further investigation.

10052 Poster Session (Board #122), Sun, 8:00 AM-11:30 AM

A phase I study of sirolimus in combination with metronomic therapy in children with recurrent and refractory solid/CNS tumors. *First Author: Muna Qayed, Emory Univ, Atlanta, GA*

Background: Sirolimus, an oral mTOR inhibitor, has anti-tumor effects mainly by blocking signals which drive cells from G1 to S phase. It has antiangiogenic activity and has shown antitumor activity in pediatric solid tumor xenografts. At higher doses, with prolonged exposure, sirolimus has been shown to inhibit mTORC2 thereby inhibiting feedback loops that could lead to tumor growth. The safety of combining escalating doses of sirolimus with low dose metronomic chemotherapy was tested in a phase I trial. **Methods:** Patients ≤ 30 years of age with recurrent or refractory solid (including CNS) tumors were eligible. Treatment consisted of continuous sirolimus and celecoxib (100 mg twice a day), oral etoposide (50 mg/m^2/day, maximum dose 100mg) alternating every 21 days with oral cyclophosphamide (2.5 mg/kg/day, maximum dose 100mg) in 42 day cycles. The starting dose of sirolimus was 1 mg/m^2 daily and was escalated by 0.5 mg/m^2, following a Bayesian method of Escalation With Overdose Control. Samples for MTOR pathway evaluation in peripheral blood mononuclear cells were obtained during cycle 1. **Results:** 18 patients were enrolled: four on dose level (DL)1(one patient not evaluable), four on DL2, eight on DL3, and two on DL4. Median age was 11.0 years (2.3 – 19.4 years). Diagnoses included Ewing sarcoma, osteosarcoma, MPNST, rhabdoid tumor, retinoblastoma and CNS tumors (GBM, DIPG, high grade glioma, medulloblastoma, ependymoma, astrocytoma, PNET, GCT). One DLT (grade 4 neutropenia) was observed on DL2, two DLTs (grade 3 abdominal pain-,grade 3mucositis) on DL3, and two DLTs (grade 3 dehydration, grade 3 mucositis) on DL4. The recommended phase II dose was determined to be 2 mg/m^2 (DL3). Additional ≥ grade 3 regimen-related toxicities during cycle 1 were leukopenia, lymphopenia, thrombocytopenia, febrile neutropenia and vomiting. Best response was stable disease (SD) in 8 patients and partial response (PR) in one patient with GBM. One patient with high grade glioma was removed from study with SD due to toxicity and developed a PR without further therapy. **Conclusions:** The combination of sirolimus with metronomic chemotherapy is well tolerated in children. A phase II trial of this combination is planned. Clinical trial information: NCT01331135.

10053 Poster Session (Board #123), Sun, 8:00 AM-11:30 AM

A phase I/II clinical trial of veliparib (ABT-888) and radiation followed by maintenance therapy with veliparib and temozolomide in patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG): A Pediatric Brain Tumor Consortium Interim Report of Phase I Study. *First Author: Patricia Ann Baxter, Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX*

Background: We report the results of the dose escalation component of a phase 1/2 trial in children with newly diagnosed DIPG designed to determine the maximum tolerated dose (MTD) and toxicities of veliparib in combination with radiation therapy (XRT) as well as the optimal dose for veliparib and TMZ post-XRT. We also evaluated the pharmacokinetics (PK) of veliparib and its impact on poly(ADP-ribose) (PAR) levels in PBMCs. **Methods:** Veliparib was given daily x 5, BID, during XRT (6-7 wks) followed by maintenance therapy with daily TMZ and twice daily veliparib for 5 days, every 28 days for up to 10 cycles. The veliparib starting dose during XRT was 50 mg/m2/dose BID. Maintenance therapy began at week 10 with veliparib 25 mg/m2/dose BID and 135 mg/m2/day TMZ. Blood for PK studies was obtained pre- and post veliparib days 1 and 4 of XRT. PAR levels, as measured using an ELISA assay, were assessed on days 1 and 3 to 5 of XRT. **Results:** 18 patients were enrolled in the phase 1 portion of the trial. Dose-limiting toxicities (DLT) during the XRT phase were a grade 2 intra-tumoral hemorrhage (n = 1), grade 3 maculo-papular rash (n = 2), and grade 3 nervous system disorder (generalized neurologic deterioration) (n = 1). The RP2D for veliparib was 65 mg/m2/dose BID during radiation therapy. After completion of veliparib and radiation, patients received veliparib at 25 mg/m2/dose BID and TMZ at 135 mg/m2/day for 5 days every 28 days, which was the RP2D from preceding PBTC027, a phase I trial in children with recurrent CNS tumors. Intra-patient escalation of TMZ during maintenance was attempted but was not feasible due to hematologic DLT. **Conclusions:** Veliparib, 65 mg/m2/dose BID, plus radiation therapy, followed by veliparib plus TMZ was reasonably well tolerated in children with newly diagnosed DIPG. A phase 2 trial is ongoing to study the efficacy of this treatment in children with newly diagnosed brainstem gliomas. Clinical trial information: NCT01514201.

10054 Poster Session (Board #124), Sun, 8:00 AM-11:30 AM

Pharmacogenetic markers for efficacy and toxicity of chemotherapy in osteosarcoma patients. *First Author: Hanneke I. Vos, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Despite multiagent chemotherapeutic treatment, osteosarcoma patients relapse frequently and survival has reached a plateau in the past decades. A poor response to chemotherapy is considered as risk factor for an unfavourable outcome. We have previously identified genetic markers predictive of treatment outcome in genes of cisplatin and doxorubicin metabolic pathways. However, the complex metabolism of the drugs used in osteosarcoma treatment involves a broader range of drug metabolic enzymes and transporters. Therefore we have performed large scale screening of 1,936 genetic variants in 231 genes known to be involved in drug metabolism and transport. **Methods:** From two cohorts of osteosarcoma patients (n = 139 and n = 177), germline DNA was genotyped using the DMET Plus array. Associations between genetic variants and ototoxicity (SIOP grade 1-4), histological response (HR) to preoperative cisplatin and doxorubicin based chemotherapy, and 5-year Disease Free Survival (DFS) were assessed by logistic regression models in PLINK and Cox proportional hazards models in GenABEL respectively. **Results:** 689 markers and 136 patients (cohort 1), and 669 markers and 174 patients (cohort 2) passed quality control (call rates > 0.9, minor allele frequency > 0.01). Upon meta-analysis, 16 markers were significantly associated (P< 0.05) with ototoxicity, including *AOX1* encoding a protein involved in homeostasis of reactive oxygen species. A total of 14 variants showed association with HR, and 23 markers with 5-year DFS, with an overlapping marker in the energy metabolism gene *SLC25A27*. In addition, a previously detected association between an *ABCC5* variant and DFS was confirmed. **Conclusions:** To the best of our knowledge, this is the first pharmacogenetic study in osteosarcoma patients studying a large number of drug metabolism and transporter genes. We have detected significant associations of treatment response and ototoxicity with genes previously unknown to be related to cisplatin and doxorubicin metabolism and transport. Upon replication, biological validation and prospective testing, these markers are of potential interest for the development of new treatment strategies and optimizing current therapy.

10055 Poster Session (Board #125), Sun, 8:00 AM-11:30 AM

Developmental pharmacokinetics of topotecan (TPT), a renally excreted drug, in infants and young children with brain tumors. *First Author: Vinay M. Daryani, St. Jude Children's Research Hospital, Memphis, TN*

Background: We investigated TPT pharmacokinetics (PK) in a clinical trial evaluating risk adapted therapy for infants and young children with brain tumors (NCT00602667). During consolidation, TPT is administered over 4 hrs to high risk patients on days 1 – 5; the initial dosage is based on age (patients < 6, 6 – 11.9, and > 12 months receive 2, 2.5, and 3.5 mg/m^2, respectively). **Methods:** PK studies are performed using a limited sampling strategy (time points: pre-infusion, 5 mins, 1, and 3 hours post infusion). TPT lactone concentrations are measured by HPLC-UV using a CLIA-approved assay. We use a PK-guided approach to individualize the TPT dosage to achieve a daily target plasma $AUC_{0-\infty}$ of 120 – 160 ng/mL*h. In this report we analyzed the individual TPT data from 38 patients using a population PK approach. A two-compartment PK model was fit to the TPT concentration-time data using nonlinear mixed effects modeling to estimate population PK parameters and inter- and intra-subject variability. Estimated PK parameters included volume of the central compartment (V_c), total systemic clearance (Cl_t), and intercompartmental rate constants (K_{cp}, K_{pc}). **Results:** In the 38 patients, we collected and analyzed 396 samples. The median (range) age, body surface area (BSA), and actual weight are 22.6 months (6 – 42 months), 0.54 m^2 (0.31 – 0.69 m^2), and 12 kg (5.4 – 16.9 kg), respectively. The population mean (RSE%) estimates of plasma TPT lactone Cl_t and V_c were 25.7 (4.8) L/h/m^2 and 24.2 (5.8) L/m^2, respectively, with interindividual variability (%CV) of 24% for Cl_t and 22% for V_c. The median (range) TPT Cl_t in 9 patients < 12 months old was 20.6 L/h/m^2 (10.8 – 29.9 L/h/m^2) and was significantly lower (Mann-Whitney p < 0.0001) compared to 29 patients ≥ 12 months old with a median (range) TPT Cl_t of 28.3 L/h/m^2 (16.7 – 45.1 L/h/m^2). **Conclusions:** TPT Cl_t exhibits an age-dependency independent of BSA and the increase in TPT Cl_t parallels the physiological maturation in renal function that occurs during infancy. These results validate our use of lower initial TPT dosages in infants and point to incorporation of a maturation function on clearance to further refine our dosing approach for TPT in infants and young children with brain tumors. Clinical trial information: NCT00602667.

10056 Poster Session (Board #126), Sun, 8:00 AM-11:30 AM

Haploidentical stem cell transplantation and subsequent immunotherapy with antiGD2 antibody for patients with relapsed metastatic neuroblastoma. *First Author: Peter Lang, University Children's Hospital, Tübingen, Germany*

Background: Pediatric patients with relapsed metastatic neuroblastomas have a poor prognosis and additional therapeutic strategies are needed. We present results of a phase I/II-trial with subsequent immunotherapy with an anti-GD2mAb (CH14.18/CHO) after HLA mismatched, haploidentical stem cell transplantation (SCT). **Methods:** T- and B-cell depleted stem cells from parental donors were used in combination with Melphalan140mg/m^2, Thiotepa10mg/kg, Fludarabin160mg/m^2 and ATG-F. Infusions with CH14.18/CHOmAb were started on day 60-180 posttransplant: 6 cycles with 20mg/m^2/day x 5 days; in cycles 4-6, 1x10^6 U/m^2 Interleukin 2 (IL2) was given additionally. The disease status was evaluated with whole body MRI, MIBG scan and bone marrow aspirates. **Results:** 34 patients with 1st or 2nd metastatic relapse were enrolled. During antibody infusions, endogenous secretion of IL2 was increased (928U/ml prior vs. 1690U/ml post, $p < 0.001$), which resulted in significantly increased numbers of activated CD69+ Natural Killer (NK) cells (3 vs. 13% $p < 0.01$). In 5/7 investigated patients, effective ADCC and complement mediated (CDC) anti-tumor effects against neuroblastoma cells were detectable in vitro (85% specific lysis, E:T-ratio = 20:1, BATDA-release). 14/34 patients did not reach the end of the protocol (due to side effects, n = 2; TRM, n = 1; progression or relapse, n = 11). 8/34 patients could maintain a CR, 9/34 patients improved their partial remission and achieved CR, 3/34 patients had stable disease. Thus, success of treatment defined as stable disease or improvement was shown in 59%. Progression free survival at 2 and 3 years was 55% and 38% (median follow up: 550 days). Frequent side effects were pain, fever and CRP elevation; rare side effects comprised SIRS/capillary leak syndrome, seizures, and accommodation disturbances. Only 1 patient developed transient acute GvHD grade II. **Conclusions:** CH14.18/CHO infusions after haploidentical stem cell transplantation appear to be feasible without increased risk of inducing GvHD. Results of our study also suggest an anti tumor effect of the new, donor-derived immune system in vitro and in vivo. Clinical trial information: NCT02258815.

10057 Poster Session (Board #127), Sun, 8:00 AM-11:30 AM

Association of pharmacogenetic variants with progressive disease in osteosarcoma patients. *First Author: Hanneke I. Vos, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Despite treatment, some osteosarcoma patients have refractory/progressive disease and a very poor prognosis. We have previously identified genetic markers predictive for disease free survival. We hypothesize that osteosarcoma patients with refractory/progressive disease have a pharmacogenetic profile different from patients with recurrent disease. To investigate this, we have analyzed these subgroups of patients using a large scale screening including 1,936 genetic markers in 231 drug metabolism and transport genes. **Methods:** Germline DNA of Dutch osteosarcoma patients treated with cisplatin and doxorubicin-based chemotherapy (n = 316) was genotyped with the DMET Plus array. Patients with refractory/progressive disease (primary tumor growth/ growth or development of new metastases, up to 3 months post chemotherapy) were compared to control patients (without refractory/progressive disease or recurrence), as were patients with recurrent disease (local or distant relapse). Associations between genetic variants and refractory/progressive disease or recurrent disease were assessed by logistic regression models in PLINK. **Results:** 710 markers and 310 patients passed quality control. Of 280 eligible patients, 36 experienced progression and 76 recurrence. In multivariate association analyses of genetic variants and refractory/progressive disease or recurrent disease, adjusted for presence of primary metastases, sex and age at diagnosis, 25 genetic markers were significantly associated ($P< 0.05$) with refractory/progressive disease. Of these, 18 genetic variants in 13 genes were uniquely associated with refractory/progressive disease and not with recurrent disease in this cohort. **Conclusions:** This is the first pharmacogenetic analysis of osteosarcoma patients to distinguish between refractory/progressive disease and recurrent disease. In this exploratory study we have identified genetic variants specifically associated with refractory/progressive disease in osteosarcoma patients. This analysis represents the first step to identify patients for whom chemotherapeutic treatment is ineffective and should be further explored in future studies.

10058 Poster Session (Board #128), Sun, 8:00 AM-11:30 AM

Safety and tolerability of crizotinib in combination with chemotherapy for relapsed or refractory solid tumors or anaplastic large cell lymphoma: a Children's Oncology Group phase I consortium study. *First Author: Emily Gustava Greengard, University of Minnesota, Eden Prairie, MN*

Background: Crizotinib is a small molecule inhibitor of the c-Met/HGFR, ALK, and ROS1 receptor tyrosine kinase (RTK). The Children's Oncology Group (COG) Phase I study of crizotinib determined the recommended phase 2 dose (RP2D) to be 280 mg/m^2/BID. Objective tumor responses in patients with known activating ALK aberrations were demonstrated. This phase I study aims to determine the safety, tolerability and RP2D of crizotinib in combination with conventional chemotherapy for children with refractory solid tumors and ALCL. **Methods:** Pediatric patients with measurable or evaluable solid tumors or ALCL, refractory to therapy were eligible. Using a 3+3 design, crizotinib was escalated in 3 dose levels from 165 mg/m^2/dose to the RP2D of 280 mg/m^2/dose BID. Patients were enrolled on either Part A, crizotinib with topotecan and cyclophosphamide, or Part B, crizotinib with vincristine and doxorubicin. The oral solution of crizotinib was used for all patients. In part C of the study, patients received crizotinib as formulated capsules in combination with topotecan and cyclophosphamide. Pharmacokinetic evaluation prior to the first dose and at steady state were required. Correlative studies for ALK aberrations were performed on patients with neuroblastoma. C-Met expression was performed on non-ALCL, non-neuroblastoma patients. **Results:** To date, 22 eligible patients have enrolled with 17 patients fully evaluable for toxicity. In part A, crizotinib was escalated to 215 mg/m^2/dose, however, two patients experienced DLT of diarrhea and dehydration at 215 mg/m^2/dose. In part B, crizotinib was escalated to 280 mg/m^2/dose, however, two patients experienced DLT of nausea, dehydration and prolonged QT interval at 280 mg/m^2/dose. Due to concerns that toxicities may be due to palatability of the oral solution, Part C subsequently opened and is currently enrolling patients. **Conclusions:** The safety and tolerability of crizotinib with conventional chemotherapy warrants further investigation. The oral solution of crizotinib may not be palatable. Alternative formulations are being developed. Clinical trial information: NCT01606878.

10059 Poster Session (Board #129), Sun, 8:00 AM-11:30 AM

Phase 1 trial of p28 (NSC745104), a non-HDM2 mediated peptide inhibitor of p53 ubiquitination in children with recurrent or progressive CNS tumors: A final report from the Pediatric Brain Tumor Consortium. *First Author: Rishi Ramesh Lulla, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL*

Background: Wild type and mutated TP53 are common in pediatric CNS tumors. p28 is a cell penetrating peptide that preferentially enters cancer cells and binds to wild type and mutant p53 protein inhibiting COP1 mediated ubiquitination and proteasomal degradation. This results in an increase in levels of p53, which induces cell cycle arrest at G_2/M. A Phase I trial in 15 TP53 positive, adult patients with stage IV tumors reported no AEs and 1CR and 3PR with 4 patients alive greater than 40 weeks. Regression analysis suggested that p28 has activity in patients whose tumors express both wild type and mutated TP53. **Methods:** Intravenous p28 was administered 3 times weekly for 4 consecutive weeks of a 6-week cycle at 4.16 mg/kg/dose (the adult MTD) using a rolling 6 study design. TP53 expression status was characterized by immunohistochemistry and serum pharmacokinetics were established on the second dose. **Results:** Of the 18 patients registered on the study, 12 patients (8 males, median age 11 years (range 3-19)) completed the DLT period and are evaluable for toxicity with malignant glioma (n = 4), choroid plexus carcinoma (n- = 2), medulloblastoma (n = 2), pineoblastoma (n = 2), DIPG (n = 1) and AT/RT (n = 1). p28 was well tolerated; 7 patients received 2 or more courses and the most common adverse event attributed to drug was transient Grade I infusional reaction. One patient with metastatic pineoblastoma with bone marrow involvement had 2 DLTs of Grade 4 neutropenia and thrombocytopenia. Pharmacokinetic analysis of 16 patients revealed an overall $t_{½}$ and $t_{½\alpha}$ similar to adults. An increased AUC was observed in pediatric patients, as a result of a higher C_{max} and longer $t_{½\alpha\beta}$. p53 expression in tumor cell nuclei was high in 7 of 12 available tissue samples; correlation with response to p28 will be presented. **Conclusions:** This phase I study demonstrates that p28 is well tolerated in children with recurrent CNS malignancies at the adult MTD. Future combination studies are being explored. Clinical trial information: NCT01975116.

10060 Poster Session (Board #130), Sun, 8:00 AM-11:30 AM

Transcriptome based individualized therapy of refractory pediatric cancer in adolescents and young adults. *First Author: Bushra Weidenbusch, Technische Universität München, Munich, Germany*

Background: Progress in pediatric oncology had little impact on adolescents and young adults (AYAs). Survival rates stagnated and are even worse than in younger and older age groups. Tumor biology in refractory patients is highly heterogeneous inter- and even intra-individually .New approaches are therefore urgently needed. Gene expression analysis may aid in medical decision making in this setting. ***Methods***: We enrolled patients aged 10-40 years for whom standard of care and current clinical trials provided no further treatment options in a one arm open label prospective study to assess survival. Tumor samples obtained for diagnosis underwent transcriptome analysis with Affymetrix arrays. We focused on genes with > 1.5 fold expression vs. normal tissue, identified as drivers by TARGETgene. Targets ranked between 1-100 were considered for therapy. Drug selection criteria were: delivery, no previous use in the patient, citations related to disease, citations related to other cancers, side effects, drug interactions, oral application, approval by German authorities. ***Results***: From 12/12-01/15, 18 biopsies were obtained after informed consent from 16 eligible patients at a single institution (TUM) with a mean age of 15.8 years. Diagnosis was sarcoma in 14 (6 Ewing sarcomas, 4 soft tissue sarcomas, 4 osteosarcoma), and embryonal tumor in 2. Targeted therapy was administered in 10, while in 5 no druggable targets could be identified. One patient was noncompliant. Mean druggable targets per patient was 7.6, with 462 medications assessed. 18 different drugs were recommended with an average of 3 drugs per patient, including PKIs, TKIs, TOP2Is, nucleoside analogs, arsenic trioxide and ATRA. Therapy was well tolerated with no adverse reactions and no side effect-related discontinuation of treatment. In this pilot study survival was at least not inferior to best medical care. ***Conclusions***: Targeted therapy is a feasible alternative to best medical care in refractory cancer in AYAs. In the majority of patients druggable targets can be identified and therapy typically does not cause side effects. Prospective studies to determine potential overall survival benefit are ongoing within the INFORM consortium.

10061 Poster Session (Board #131), Sun, 8:00 AM-11:30 AM

Phase II study of nimotuzumab and radiotherapy in children and adolescents with newly diagnosed diffuse intrinsic pontine gliomas (DIPG). *First Author: Sidnei Epelman, Santa Marcelina Hospital, Sao Paulo, Brazil*

Background: DIPG are amongst the most challenging tumors to treat in childhood with no drug proven to be effective. Standard of care remains focal radiotherapy alone however, rapid disease progression usually occurred. Median overall survival is less than 1 year, and the 2-year survival is less than 10%. **Methods:** Patients with clinically and radiologically confirmed, centrally reviewed newly diagnosed DIPG were eligible for this multicenter phase II study. The anti-epidermal growth factor receptor antibody, nimotuzumab (150 mg/m2) was administered intravenously once weekly concomitant with focal radiotherapy (54Gy) and every 2 weeks until tumor progression. Response evaluation was based on clinical and radiological assessments. Primary objective was to improve survival with a historic cohort that received radiation therapy alone. **Results:** 21 patients entered into this study (7/14, male/female; median age, 7.6 years; range 2-16 years). All received radiotherapy. Treatment was well tolerated. 40/502 cycles had adverse effects related to the drug and very mild. The majority of adverse effects were associated with progression of disease. Disease free survival at 7.3 months was 85.7% (CI95% - 70.7-100). Overall survival at 9 months was 71.4% and at one year, 57.1% (CI95% - 33.8-74) which demonstrated better results when compared with historic trials. **Conclusions:** This trial demonstrated some activity of nimotuzumab in DIPG. It was well tolerated and improved overall survival. A small subset of patients appeared to benefit from this anti-EGFR antibody and can be considered in future trials with synergistic drugs. An upfront biopsy can bring the prospect of a better understanding of DIPG biology and selection of better treatment. Clinical trial information: NTC01145170.

10062 Poster Session (Board #132), Sun, 8:00 AM-11:30 AM

The genomic landscape of anaplastic Wilms tumors with diffuse versus focal anaplasia. *First Author: Gabriel G Malouf, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Medical Oncology, UPMC Univ Paris 06, Institut Universitaire de Cancérologie GRC5, Paris, France*

Background: Anaplasia is a potent marker for adverse outcome in patients with Wilms tumors (WT). While WT patients with focal anaplasia (FA) have similar survival to those with nonanaplastic intermediate risk WT, patients with diffuse anaplasia (DA) display poor outcomes. Beside *TP53* mutations, the genome-wide genetic basis of WT remains unknown. **Methods:** We performed whole-exome sequencing on genomic DNA derived from 11 WT and matched normal DNA from the same patients, using Agilent human V5 (51Mb) capture and the HiSeq sequencing platform. Overall, 8 and 3 matched pairs with DA and FA were assessed, respectively. Paired-end RNAseq was also performed in the same dataset for fusion transcript detection. Chromosome 17p copy number, where *TP53* is located, was assessed by a MLPA assay. **Results:** Overall, we identified 117 (median 10, range 5-25) non-synonymous somatic single nucleotide variants, of which 47 were predicted to lead to a deleterious protein. No difference was observed in term of total number of mutations between WT with DA and FA, respectively. *TP53* mutations were identified in 4 DAWT. In addition, 2 DAWT and 2 FAWT harbored identical hotspot *DROSHA* mutation (E1147K). Ingenuity Pathway Analysis revealed enrichment for mutations in genes involved in embryonal tumor development (*ARMCX3, BCOR, FLT4, KMT2C, REST* and *TP53*) ($p = 2.7x10^{-4}$). All but one case of DAWT with *TP53* mutations harbored *TP53* deletion; the case without *TP53* deletion had in addition *DROSHA* mutation. The 4 patients with *TP53* mutations died as compared to one out of 7 without mutation ($p = 0.01$). No known or novel fusion transcripts were identified. **Conclusions:** Our results reveal an exceptionally low mutational load in anaplastic WT, consistent with previously reported results in pediatric solid tumors. *DROSHA* and *TP53* are likely to be mutually exclusive mutations in WT. Updated results with an independent validation dataset will be presented at the meeting.

10063 Poster Session (Board #133), Sun, 8:00 AM-11:30 AM

Localized vagina/uterus rhabdomyosarcoma (VU RMS): Results of a pooled analysis from four international cooperative groups. *First Author: Veronique Minard-Colin, Institut Gustave Roussy, Villejuif, France*

Background: VU RMS is rare and recognized as one of the most favorable site of RMS. In an attempt to determine optimal therapy in relation both to cure and to late effects, the experience of four international collaborative groups (Children's Oncology Group [COG], SIOP Malignant Mesenchymal Tumor Group [MMT], Italian Cooperative Soft Tissue Sarcoma Group [ICG], and European pediatric Soft Tissue Sarcoma Group [EpSSG]) was shared at an international workshop. **Methods:** From 1985 to2009, a total of 237 eligible patients were identified from group files (132 from COG, 62 from MMT, 24 from ICG, and 19 from EpSSG). **Results:** Median patient age at diagnosis differed among tumor location (1.9 yrs [vagina = 160 pts]; 4 yrs [uterus corpus = 34 pts]; 13.5 yrs [cervix = 43 pts]). Median follow-up was 8 years. Twenty-seven percent of pts received radiation therapy (RT) as part of primary therapy (21% COG, 27% MMT, 46% ICG, 42% EpSSG), and among those, there were significant differences regarding the use of brachytherapy (BT) between the individual groups (14% in COG, 71% in MMT, 55% in ICG, and 75% in EpSSG).Ten-year event-free (EFS) and overall survival (OS) were 72% and 92%. In univariate analysis, low OS was only correlated with enlarged nodes (N1 = 11 pts). While EFS was slightly decreased in pts without initial RT (EFS, 74% *vs* 82% with RT; p = NS), there was no difference in OS (OS: 93% and 90% without or with initial RT). In total, taking into account total burden of treatment (primary therapy and treatment for relapse), 117 (53%) of the 221 survivors were cured with chemotherapy +/- conservative surgery. **Conclusions:** These analyses show that half of patients with VU RMS can be cured without systematic RT or radical surgery. When RT is indicated, BT should be encouraged to limit late sequelae.

10064 Poster Session (Board #134), Sun, 8:00 AM-11:30 AM

Late outcomes among adult survivors of childhood non-Hodgkin lymphoma (NHL): A report from the St. Jude Lifetime Cohort Study. *First Author: Matthew J. Ehrhardt, St. Jude Children's Research Hospital, Memphis, TN*

Background: Adult survivors of childhood NHL are at risk for chronic conditions likely underestimated by patient reported outcomes. Prevalence and severity based on direct clinical assessment are lacking. **Methods:** Clinical, laboratory, and performance-based evaluations were obtained on 200 adult survivors of pediatric NHL at St. Jude Children's Research Hospital. Chronic conditions were graded per CTCAE criteria. Impaired physical function was defined as performance below the 10^{th} percentile of normative data. Multivariable Poisson regression models were used to investigate associations [relative risk (RR), 95% confidence intervals (CI)] between patient characteristics, therapies, and clinical outcomes. **Results:** Survivors (66% male, 87% white) were a median age of 10 years (range 1-19) at diagnosis and 34 years (20-58) at evaluation. Forty-six (23%) received radiation to the brain, 69(35%) high dose methotrexate, and 161(81%) steroids. Most (93%) had $\geq$ 1 chronic condition, 77% $\geq$ 2 chronic conditions, and 50% a severe/life-threatening (grade 3-4) condition. Most prevalent were overweight/obesity (65%), cognitive impairment (46%), dyslipidemia (41%), and impaired fasting glucose (37%). Most prevalent grade 3-4 conditions were obesity (35%), hypertension (15%), and cognitive impairment (13%). Risk-based screening detected cardiomyopathy in 14(8.5%); 50% grades 3-4. There were 27 second cancers (61% grades 3-4) in 23(12%) survivors. Prevalence of abnormal body composition, measured by waist to height ratio and percent fat on dual-energy x-ray absorptiometry was 72%. Many had impaired aerobic (22%), strength (48%), muscular endurance (36%), flexibility (39%), and mobility (36%) assessments. Adjusting for ages at diagnosis and evaluation, race, and methotrexate, male sex (RR 1.2, CI 1.1-1.5), anthracycline $\geq$ 250mg/m^2 (RR 1.3, CI 1.1-1.6), and radiation (RR 1.3, CI 1.1-1.6) were associated with having $\geq$ 2 chronic conditions. Non-white race (RR 1.6, CI 1.2-2.1) was associated with a grade 3-4 condition. **Conclusions:** Prospective systematic evaluation identified significant chronic conditions and performance limitations in adult survivors of childhood NHL.

10065 Poster Session (Board #135), Sun, 8:00 AM-11:30 AM

Patterns and predictors of psychological distress in adult survivors of childhood cancer: A Childhood Cancer Survivor Study (CCSS). *First Author: Norma Mammone D'Agostino, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Screening for psychological distress is an important part of comprehensive survivorship care. While elevated symptoms of depression and anxiety have been reported, patterns of emotional comorbidity have not been examined. The aims of this study are to identify clusters of distress symptoms and to examine disease, treatment and demographic predictors. **Methods:** Latent profile analysis was conducted using 3 domains (depression, anxiety, somatization) from the Brief Symptom Inventory – 18 in siblings (N = 3085) and 5+ year survivors (N = 16032) from the CCSS. High distress was defined using t-score $>$ 63. Bayesian information criterion and Lo-Mendell-Rubin adjusted certainty were used to select the optimal cluster number. Multinomial logistic regression was used among survivors to identify disease, treatment and demographic predictors of cluster membership stratified by sex. **Results:** Four latent clusters were identified: low distress on all 3 domains (well-adjusted); high distress on all 3 domains (global distress); high somatization relative to anxiety and depression (somatic distress); high anxiety and depression relative to somatization (affective distress). Compared to siblings, fewer survivors were well-adjusted (62% *v.* 74%) and more had global distress (11% *v.* 5%), both p's $<$ 0.0001. Diagnosis-specific patterns of distress were identified (leukemia and bone cancer: global distress, CNS: affective distress, Hodgkin lymphoma and neuroblastoma: somatic distress). More male (66%) than female (58%) survivors were well-adjusted, but more females reported somatic (17% vs 10%) and global (12% vs 9%) distress, all p's $<$ 0.0001. Among females, fair/poor perceived health (OR 30.9, 95% CL 19.4-49.1; compared to excellent health), headache (OR 2.69, 95% CL 2.24-3.24), and antimetabolite chemotherapy (OR 1.31, 95% CL 1.10-1.55) were associated with global distress. Perceived health and pain were associated with global distress in males. **Conclusions:** Results support the conceptual distinction between physical (somatic) versus affective (anxiety and depression) symptoms of distress and highlight sex differences and health-related predictors of distress.

10066 Poster Session (Board #136), Sun, 8:00 AM-11:30 AM

***CELF4* variant and Anthracycline-related Cardiomyopathy (anth-card) – A COG Study (ALTE03N1).** *First Author: Xuexia Wang, University of Wisconsin-Milwaukee, Milwaukee, WI*

Background: Identification of genetic variants that modify anth-card risk can facilitate targeted interventions. **Methods: Discovery:** Case-control approach used to conduct GWAS in non-Hispanic white ($>$ 90% Europeans: Multidimensional Scale) childhood cancer survivors (CCS). Anth-card cases: n = 112; median ejection fraction (EF): 44%; age at ca dx: 7.5y; anth dose: 319 mg/m^2. Ca controls: n = 219; EF: 65%; age ca dx: 7.9y; anth: 180mg/m^2 matched on ca dx, age at ca dx, year ca dx, time from ca dx. 2-step method used to detect anth dose-SNP interaction (*Genet Epidemiol,* 2012; **36**:183). **Replication:** Case-only design used in 54 CCS with anth-card (EF: 41%; all race/ethnicity; age at ca dx: 7.6y; anth: 300 mg/m^2). **Functional analyses**conducted. **Results: Discovery:** No SNP was marginally associated with anth-card at GW level. 2-step GxE: *Step 1:* Top 1000 SNPs with modest main effect retained; 643 independent tests estimated after LD-based SNP pruning. *Step 2:* GxE interactions tested between SNPs retained in Step1 (P= 0.05/643$_{\text{independent tests}}$= 7.77x10^{-5}). SNP rs1786814 on *CELF4* gene passed significance cut-off (*P_ge*= 1.14x10^{-5}). (MAF$_{\text{control:}}$ 0.249; minor allele: A). Multivariable analyses adjusted for anth dose, sex, chest RT: in CCS with AA genotype, anth-card was rare at all anth doses; in CCS with anth $>$ 300mg/m^2, GG genotype conferred 5.4-fold (95%CI, 1.8-16.2, P= 0.003) increased anth-card risk compared to AA/GA. **Replication:** GG genotype in anth $>$ 300mg/m^2: OR = 5.1, 95%CI 1.0-25.2, P = 0.046; ref: AA/GA. **Functional analysis:** CELF is implicated in alternative splicing of cardiac troponin T (cTnT) - a myocardial injury biomarker; $>$ 1 cTnT variants results in temporally split myofilament response to Ca^{2+}, and decreased contractility (seen in dilated cardiomyopathy) (*Circ Res,* 1995;**76**:681-6). DNA from 33 healthy non-anth-exposed hearts genotyped for rs1786814; RNA splice isoforms measured (RT-PCR), and verified (DNA sequencing). Coexistence of embryonic and adult cTnT (n = 23) more likely in GG hearts (GG: 78%; GA: 22%; AA: 0%, P= 0.016). **Conclusions:** We report a modifying effect of an intronic polymorphism of *CELF4* (rs1786814) on dose-dependent anth-card risk, possibly through accumulation of $>$ 1 form of cTnT protein.

10067 Poster Session (Board #137), Sun, 8:00 AM-11:30 AM

Longitudinal evaluation of health status and chronic conditions in aging pediatric astrocytoma survivors: A Childhood Cancer Survivor Study (CCSS) report. *First Author: Karen Elizabeth Effinger, Stanford University, Palo Alto, CA*

Background: Astrocytoma is a common pediatric central nervous system tumor. However, little is known about the health status and chronic conditions and their association with social outcomes in aging survivors. **Methods:** We evaluated 1,073 5-year astrocytoma survivors (median age: 28 years, range 9-56; median time from diagnosis: 21 years, range 7-38) and 4,023 siblings enrolled in the CCSS at up to 3 time points. We estimated the prevalence of poor health status in 6 domains (general health, functional impairment, activity limitation, mental health, cancer-related pain, cancer-related anxiety); severe, disabling, or life-threatening chronic conditions; and social outcomes (marriage, education, employment, income) in those $\geq$ 25 years of age. We compared outcomes between survivors and siblings as a function of attained age using generalized linear models with robust variances adjusted for race, sex, and body mass index. **Results:** Compared with siblings, astrocytoma survivors were more likely to report poor health status across all domains, more chronic conditions, and poor social outcomes. Among survivors, increasing numbers of chronic conditions were associated with lower marriage and employment rates, lower income, and poor health status in all domains. All domains of poor health status were associated with unemployment. **Conclusions:** Pediatric astrocytoma survivors have increased odds of poor health status, chronic health conditions, and poor social outcomes compared with siblings. Chronic conditions impact health status and social outcomes highlighting the need for regular screening and early interventions.

	Survivors (%)	Siblings (%)	Odds Ratio (95% Confidence Interval)
Poor general health	16.0	5.1	3.6 (3.0-4.3)
Functional impairment	32.7	3.7	13.3 (11.1-16.0)
Activity limitation	20.3	5.6	4.6 (3.9-5.5)
Poor mental health	21.0	10.9	2.0 (1.7-2.4)
Cancer-related pain	12.4	NA	-
Cancer-related anxiety	12.8	NA	-
Chronic conditions	47.7	9.9	9.1 (7.7-10.6)
Married	41.3	69.3	0.32 (0.27-0.37)
Graduated college	40.5	55.1	0.61(0.52-0.71)
Employed	64.7	87.1	0.26 (0.22-0.31)
Income > $20,000	79.7	95.0	0.24 (0.19-0.30)

10068 Poster Session (Board #138), Sun, 8:00 AM-11:30 AM

Quality of life assessment in retinoblastoma: A cross-sectional study of 122 survivors. *First Author: Atul Batra, All India Institute of Medical Sciences, New Delhi, India*

Background: Retinoblastoma (Rb) is the most common intraocular tumor in childhood. With current modalities, cure rates are high and hence number of survivors is increasing. However, data on quality of life (QOL) in this population are minimal. **Methods:** We analyzed QOL in 122 retinoblastoma survivors using the PedsQL 4.0 generic core scale in local language, which has been validated in Indian population. The self-reported questionnaire was filled by children of more than 5 years of age who had completed treatment for more than 12 months. The questionnaire consists of 23 questions on physical, social, emotional and school domains on a scale from 0 to 4. This was converted to a scale from 0 to 100, where higher values represented better QOL. The QOL was compared with 50 siblings using student's t-test. Factors predicting the QOL were assessed. **Results:** The median age of Rb survivors was 98 (range, 60-247) months and 68% were males. Seventy-nine percent were International Retinoblastoma Staging System (IRSS) stage1 and 25% had bilateral disease. Fourteen percent had extraocular involvement and 22% received radiotherapy. The overall QOL was significantly poorer in Rb survivors as compared to controls (Table). The emotional health domains of QOL (fear, anger and sleeping) were significantly lower in Rb survivors. Difficulties in maintaining friendships and competing were reported in the social health domain. In school health domain, there was significantly higher absenteeism due to sickness and hospital visits among Rb survivors. However, the physical health domain including household work, exercise and self-care was similar in both the groups. Age, sex, IRSS stage and previous radiotherapy did not affect the QOL. **Conclusions:** QOL is often a neglected aspect in survivors of pediatric solid tumors. We found a significantly poorer QOL in Rb survivors. However, no predicting factors for poor QOL were found in this group. Although a high survival rate has been achieved in early stage Rb, efforts need to be made to improve QOL.

Domain	Rb Survivors (N = 122)	Controls (N = 50)	P value
Physical	79.1 ± 9.1	81.4 ± 10.1	0.14
Social	71.8 ± 13.1	83.9 ± 10.5	< 0.001
Emotional	78.2 ± 9.8	82.5 ± 12.5	0.02
School	79.9 ± 12.3	91.9 ± 4.7	< 0.001
Overall	77.3 ± 8.6	84.9 ± 5.9	< 0.001

10069 Poster Session (Board #139), Sun, 8:00 AM-11:30 AM

Risk stratification to guide long-term follow up of teenage and young adult survivors of childhood cancer. *First Author: Susannah Jane Stanway, Royal Marsden Hospital, Surrey, United Kingdom*

Background: Long term survivors of paediatric cancer have increased over time. Optimal models of long term care must be developed dependent on current and predicted morbidity, which is affected by tumour type and intensity of treatment. Currently, survivors are referred to the long term follow-up (LTFU) clinic 5 years post treatment and are followed indefinately. The aim of this project was to assess use of risk-stratification to guide intensity of LTFU of survivors of childhood cancer. **Methods:** A retrospective review of the Royal Marsden Hospital Childrens' Late Effects (LE) database was performed. Electronic records of survivors aged 13 to 24 seen in clinic between 2000 to 2012 were reviewed. Patients (pts) were divided into Wallace levels depending on tumour type and treatment given. Number and grades of LEs of treatment were documented using NCI CTC version 4. **Results:** 316 survivors were divided into Wallace level 1 (n = 18, 6%), 2 (n = 163, 52%) and 3 (n = 135, 43%). At a median follow up of 10.9 years from end of treatment, there were a total of 21 groups of LEs identified. Total LEs were 7 for level 1 pts, 128 for level 2 and 373 for level 3. There were 0.39 LEs seen per pt in level 1, the majority of which were grade 1 or 2, in contrast to 2.72/pt in level 3. The relative risk of at least one grade 3 LE at level 3 compared to level 2 was 4.16. The number lost to follow up was 37, 70% of which were in level 2. **Conclusions:** All survivors of childhood cancer need a treatment summary and care plan at 5 years post treatment, when the risk of relapse is very small. Stratification using Wallace levels is feasibile and helps define level of care required. Level 1 and 2 pts can be discharged to a primary care colleague informed by a treatment summary and personalised LTFU care plan. Level 3 pts with higher prevalence and grade LEs will need on-going specialist input from a LTFU service.

10070 Poster Session (Board #140), Sun, 8:00 AM-11:30 AM

Long-term outcomes by race/ethnicity in the Childhood Cancer Survivor Study (CCSS) cohort. *First Author: Smita Bhatia, University of Alabama at Birmingham, Birmingham, AL*

Background: Racial/ethnic differences in risk for long-term adverse outcomes in childhood cancer survivors are not well established. **Methods:** Hispanic (H: 750, 5.4%) and African American (AA: 694, 5%) survivors were compared to non-Hispanic whites (NHW: 12,397, 89.6%) for late mortality, subsequent malignant neoplasms (SMN), and CTCAE-graded chronic health conditions. Poisson regression models adjusted for demographic/clinical factors were used to calculate relative rate (RR) and 95% confidence intervals (CI). **Results:** AA and H survivors were younger at diagnosis, and had lower SES. *Mortality:* No racial/ethnic difference was observed (Table). *SMN:* Risk did not differ by race/ethnicity (cumulative incidence 30y from diagnosis: NHW: 9.0%, AA: 6.6%, H: 7.0%, p=0.3). However, risk for non-melanoma skin cancer (NMSC) was very low among irradiated AA and H survivors (Table). *Chronic Health Conditions (grades 3-5):* Compared to NHW, AA were more likely to report cardiac conditions and H endocrine conditions (Table). These differences were attenuated after adjusting for cardiovascular risk factors (CVRF: dyslipidemia, hypertension, smoking). **Conclusions:** By and large, when adjusted for SES and treatment, morbidity/mortality did not differ by race/ethnicity. However, specific morbidities (H: endocrine, AA: cardiac) were more prevalent, and were partially explained by CVRFs. Risk of NMSC was negligible among irradiated AA and H, relative to irradiated NHW. These findings inform targeted intervention opportunities.

	NHW	AA	H
Late Mortality		RR (95% CI)*	
All-cause	Ref	1.0 (0.8 – 1.4) P = 0.9	0.9 (0.7 – 1.2) P = 0.5
SN		1.3 (0.7–2.2) P = 0.4	0.9 (0.5-1.6) P = 0.7
Cardiac		1.6 (0.5–4.6) P = 0.4	1.5 (0.7–3.5) P = 0.3
SMNs		RR (95% CI)*	
		1.3 (0.8-2.0) P = 0.2	1.2 (0.8-1.7) P = 0.4
NMSC (irradiated cohort)		0.0 (0.0-0.2) P < 0.001	0.3 (0.1-0.8) P = 0.01
Chronic Health Conditions (grade 3-5)		RR (95% CI)*	
Any		1.1 (0.9-1.4) P = 0.5	1.2 (1.0-1.5) P = 0.06
Cardiac		**1.6 (1.0-2.4)** P = 0.03	1.2 (0.8-1.7) P = 0.5
CardiacΩ		1.4 (0.9-2.1) P = 0.1	1.1 (0.7-1.7) P = 0.7
Endocrine		1.0 (0.6-1.5) P = 0.8	1.7 (1.2-2.3) **P = 0.001**
EndocrineΩ		0.9 (0.6-1.4) P = 0.7	1.4 (1.0-1.9) P = 0.08

*From Poisson models adjusted for treatment, SES. Ω Further adjusted for CVRF.

10071 Poster Session (Board #141), Sun, 8:00 AM-11:30 AM

Intestinal obstruction in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Arin L Madenci, Brigham and Women's Hospital, Boston, MA*

Background: For adult survivors of childhood cancer, knowledge about the long-term risk of intestinal obstruction from surgery, chemotherapy, and radiotherapy is limited. **Methods:** Intestinal obstruction requiring surgery (IOS) occurring 5 or more years after cancer diagnosis was evaluated in 12,316 five-year survivors from the CCSS cohort (2,002 with and 10,314 without abdominopelvic tumors) and 4,023 sibling participants. Cumulative incidence of IOS was calculated with second malignant neoplasm, late recurrence, and death as competing risks. Piecewise-exponential models assessed the associations of clinical and demographic factors with rate of IOS. **Results:** IOS was reported by 165 survivors (median age at IOS=19 years, range=5-50 years; median time from diagnosis to IOS=13 years) and 14 siblings. Cumulative incidence of IOS at 35 years was 5.8% (95% confidence interval [CI]=4.4-7.3%) among survivors with primary abdominopelvic tumors, 1.0% (95% CI=0.7-1.4%) among those without abdominopelvic tumors, and 0.1% (95% CI=0.1-0.5%) among siblings. Survivors of abdominopelvic lymphoma had the highest 35 year cumulative incidence of IOS, 7.2% (95% CI=2.8-12.5%). Among all survivors, abdominopelvic tumor (adjusted rate ratio [ARR]=3.6, 95% CI=1.9-6.8, $P<0.001$) and abdominal/pelvic radiotherapy within 5 years of diagnosis (ARR=2.4, 95% CI=1.6-3.7, $P<0.001$) increased the rate of IOS, adjusting for year of diagnosis; sex; race/ethnicity; age at diagnosis; age during follow-up (as natural cubic spline); primary cancer type; and chemotherapy, radiotherapy, and surgery occurring within 5 years of diagnosis. Developing IOS increased the subsequent mortality among survivors (ARR=1.8, 95% CI=1.1-2.9, $P=0.016$), adjusting for the same clinical and demographic factors. **Conclusions:** In the decades following diagnosis and treatment, survivors of childhood cancer are at increased risk of developing late-onset IOS, with subsequent increased risk of mortality. These findings underscore the need to promote long-term awareness of these risks among patients and providers, especially for survivors with abdominal or pelvic tumors who have undergone treatment with surgery or radiotherapy.

10072 Poster Session (Board #142), Sun, 8:00 AM-11:30 AM

Neurocognitive, emotional, and quality of life outcomes in long-term survivors of rhabdomyosarcoma: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Melissa Schapiro, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Previous studies of rhabdomyosarcoma (RMS) survivors have focused on outcomes related to chronic health conditions. We evaluated neurocognitive, emotional, and quality of life (QOL) outcomes of > 5-year survivors. **Methods:** 482 survivors diagnosed 1970-1986 (mean age [SD] 7.2 [5.4] years at diagnosis; 24.3 [4.8] years of follow-up) and 393 siblings from the CCSS rated their neurocognition, emotions, and QOL using the Neurocognitive Questionnaire (NCQ), Brief Symptom Inventory-18 (BSI-18), and Medical Outcomes Short Form-36 (SF-36). Based on normative data, impairment was defined as the bottom 10^{th} percentile of performance on the NCQ, the top 10^{th} percentile of symptom prevalence on the BSI-18, and the bottom 15^{th} percentile on each SF-36 subscale. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression. **Results:** Survivors reported more impairment than siblings on NCQ task efficiency ($p < 0.001$), higher symptom prevalence on BSI-18 depression (13.3% vs. 8.1%, $p = 0.020$) and anxiety (7.9% vs. 4.4%, $p = 0.038$), and poorer QOL on all SF-36 subscales: physical (12.5% vs. 3.1%, $p < 0.001$), social (15.5% vs. 9.4%, $p = 0.009$), and emotional (19.2% vs. 13.5%, $p = 0.030$) functioning, pain (12.4% vs. 14.8%, $p = 0.015$), general health (26% vs. 11.5%, $p < 0.001$), vitality (27.6% vs. 20.6%, $p = 0.022$), and role limitations due to physical (17.4% vs. 9.9%, $p = 0.002$) and emotional (21.3% vs. 13%, $p = 0.002$) problems. Among survivors, women were more likely than men to report impaired vitality (OR 2.2, 1.3-3.5) and social functioning (OR 2.3, 1.3-4.3). Adjusting for age at diagnosis and sex, cranial radiation therapy was associated with poorer task efficiency ($p = 0.004$) and greater likelihood of depression (OR 2.0, 1.1-3.8). Survivors with recent use of antidepressants/anxiolytics reported significantly worse task efficiency and poorer QOL on all SF-36 subscales than survivors not using these medications. **Conclusions:** Adult RMS survivors demonstrate substantial long-term impairment of neurocognitive function, emotional status, and QOL, warranting clinical assessment and appropriate interventions.

10073 Poster Session (Board #143), Sun, 8:00 AM-11:30 AM

Adverse fat depots, marrow adiposity, and skeletal deficits in long-term survivors of pediatric hematopoietic stem cell transplantation. *First Author: Sogol Mostoufi-Moab, The Childrens Hospital of Philadelphia, Philadelphia, PA*

Background: Allogeneic hematopoietic stem-cell transplantation (alloHSCT) survivors treated with total body irradiation (TBI) exhibit bone deficits and excess adiposity, potentially related to altered mesenchymal stem cell differentiation into osteoblasts or adipocytes. **Methods:** We examined associations among fat distribution, bone microarchitecture, and insulin resistance in alloHSCT survivors after TBI. This was a cross-sectional observational study of 25 alloHSCT survivors (aged 12-25 years) a median of 9.7 (4.3-19.3) years after alloHSCT compared to 25 age-, race-, and sex-matched healthy controls. Vertebral MR spectroscopic imaging and tibia micro-MRI were used to quantify marrow adipose tissue (MAT) and trabecular microarchitecture. Additional measures included DXA whole-body fat mass (WB-FM), leg lean mass (Leg-LM), trunk visceral adipose tissue (VAT), and CT calf muscle density. Insulin resistance in alloHSCT survivors was estimated by HOMA-IR. **Results:** AlloHSCT survivors had lower Leg-LM ($p< 0.001$), and greater VAT ($p< 0.01$), MAT ($p< 0.001$) and fat infiltration of muscle ($p= 0.04$) independent of WB-FM, vs. matched-controls; BMI did not differ. Survivors had lower bone volume fraction and abnormal microarchitecture including greater erosion and more rod-like structure vs. controls (all $p= 0.04$); 14 had vertebral deformities and two had compression fractures. Greater WB-FM, VAT, MAT and muscle fat infiltration were associated with abnormal trabecular microarchitecture ($p< 0.04$ for all). AlloHSCT HOMA-IR was elevated, associated with younger age at transplantation ($p< 0.01$), and positively correlated with WB-FM and VAT (both $p< 0.01$). **Conclusions:** Long-term survivors demonstrate sarcopenic obesity, insulin resistance, and vertebral deformities. The markedly increased marrow adiposity, abnormal bone microarchitecture, and abnormal fat distribution highlight the risks of long-term treatment-related morbidity and mortality in alloHSCT recipients after TBI. Future studies are needed to identify strategies to prevent and treat metabolic and skeletal complications in this growing population of childhood alloHSCT survivors.

10074 Poster Session (Board #144), Sun, 8:00 AM-11:30 AM

Temporal changes in treatment exposures in the Childhood Cancer Survivor Study (CCSS). *First Author: Ann Mertens, Emory University, Atlanta, GA*

Background: Well-designed epidemiologic investigations of pediatric cancer survivors inform clinical practice guidelines and future clinical trials. Expansion of the CCSS cohort to include survivors diagnosed across three decades (1970-99) affords the opportunity to evaluate associations between key temporal changes in survivor and treatment characteristics and risk for subsequent adverse health outcomes. **Methods:** We analyzed cancer and treatment characteristics of 24,000 CCSS participants. Treatment exposures were abstracted from medical records. Trends across 5 year intervals were evaluated using logistic regression models with weights to account for sampling probabilities. **Results:** Within the expanded CCSS, the use of chemotherapy significantly increased overall (Table, T1-T6) for all diagnoses except leukemia which was always 100%. Exposure to radiation (RT) decreased overall and for all diagnoses except soft tissue sarcoma. Overall, chest RT exposure was reduced and notably, exposures of ≥ 30 Gy declined from 85% to 6% (T1 to T6) for Hodgkin lymphoma. Alkylating agent use increased by 15% overall, and among leukemia, lymphoma and sarcoma patients proportions were on the order of 40% higher at T6 than at T1. Use of anthracyclines (ANT) increased significantly, predominantly for doses lower than 250 mg/m^2. **Conclusions:** The expansion of the CCSS cohort provides a unique resource to evaluate the impact of historical changes in primary cancer therapy, including reduction of therapeutic intensity for low- and standard-risk populations, as well as intensification of specific therapies for high-risk populations on health and psychosocial outcomes.

	% With Characteristic					
	T1 1970-74	T2 1975-79	T3 1980-84	T4 1985-89	T5 1990-94	T6 1995-99
Any RT*	79	75	64	50	40	34
RT to brain*	30	36	32	24	18	16
RT to neck*	24	19	16	9	7	7
RT to abdomen*	28	22	19	12	8	9
RT to chest ≥ 30 Gy*	21	13	8	4	1	1
Any Chemotherapy*	75	81	81	85	86	87
Any alkylating agents*	45	49	55	57	58	60
ANT 1-250 mg/m^2*	3	12	18	34	45	52
ANT >250 mg/m^2*	11	24	24	23	17	14
Any epipodophyllotoxins*	1	4	9	25	34	36
Platinum*	<1	2	7	12	14	17

*Trend p-value <0.0001.

10075 Poster Session (Board #145), Sun, 8:00 AM-11:30 AM

Longitudinal smoking patterns in survivors of childhood cancer: A Childhood Cancer Survivor Study (CCSS) update. *First Author: Todd M. Gibson, St. Jude Children's Research Hospital, Memphis, TN*

Background: Survivors of pediatric cancer have elevated risks of mortality and morbidity. Many morbidities associated with cancer treatment (e.g. second cancers, cardiac and pulmonary disease) are associated with cigarette smoking, suggesting survivors who smoke may be at higher risk for these adverse health conditions. **Methods:** We examined self-reported smoking status in 10,430 CCSS participants (age ≥ 18 years) across 2 questionnaires, at a median time of 7.9 years (range 1.4-11.9) apart. Smoking prevalence was compared among survivors, siblings, and the U.S. general population (standardized by age, sex, race/ethnicity and calendar time). Among a subgroup of survivors who also completed an additional follow-up questionnaire (N = 3908) a median of 12.5 years (range 4.3-16.3) after the first questionnaire, multivariable regression models evaluated characteristics associated with longitudinal smoking patterns. **Results:** At baseline, 19% of survivors were current smokers, compared with 24% of siblings and 29% in the standardized U.S. general population. At first follow-up, 17% of survivors were current smokers, compared to 21% of siblings and 24% of the U.S. population. Characteristics associated with consistent "never smoking" over all three questionnaires included higher household income (RR 1.17, 95% CI 1.08-1.25 for ≥ $60,000 versus < $20,000 per year), higher education (RR 1.36, 95% CI 1.26-1.47 for > high school versus ≤ high school), and receipt of cranial radiation therapy (RR 1.10, 95% CI 1.05-1.16). Among "ever smokers", higher income (RR 1.22, 95% CI 1.09-1.38) and education (RR 1.26, 95% CI 1.13-1.40) were associated with quitting, whereas cranial radiation was associated with not having quit (RR 0.85, 95% CI 0.76-0.96). Development of an adverse health condition was not associated with smoking patterns. **Conclusions:** Although smoking prevalence may be declining, the substantial number of consistent, current smokers reinforces the need for continued development of effective smoking interventions for survivors.

10076 Poster Session (Board #146), Sun, 8:00 AM-11:30 AM

The effect of sociodemographic factors and therapy on survival in pediatric liver cancers: A SEER population study. *First Author: Minzhi Xing, Division of Interventional Radiology, Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, PA*

Background: To investigate long-term survival in pediatric primary liver cancers, including hepatoblastoma & hepatocellular carcinoma (HCC) based on sociodemographic factors & therapy in a large-scale population study. **Methods:** The Surveillance, Epidemiology and End Results (SEER) database was queried for pediatric cancer patients with the liver as the primary site (C22.0), diagnosed 1973-2011. Overall survival (OS) was stratified by tumor & patient characteristics. Analysis of OS via therapy was further stratified based on socio-demographic factors. Kaplan-Meier & Cox proportional hazard models were used to assess independent predictors for OS. **Results:** Of 1145 newly diagnosed pediatric cancer patients with liver as primary site, 1012 had primary liver cancers, of whom 725 had hepatoblastoma and 287 had HCC, median age 2yrs, 60.47% male. Overall median OS was 210.7±6.4 mo. Median OS significantly correlated with younger age at diagnosis ($<$ 2 vs. $\geq$ 2yrs, 240.7 vs. 159.7 mo, $p <$ .001), ethnicity (white, black, other; 193.1, 81.6, 166.5 mo; $p = .0136$), geographic location (Alaska, East, Northern Plains, Southwest, Pacific Coast; 106.2, 91.6, 173.1, 112.0, 144.3; $p = .0144$), median family income ($\geq$ \$75k vs. $<$ \$75k/year, 194.1 vs. 184.5 months, $p = .013$), and regional education levels (% bachelor degree or above, $\geq$ 25% vs. $<$ 25%, 198.5 vs. 191.5 months, $p < .0247$). Surgery was performed in 684 patients (67.6%), 40 patients received radiation (3.95%), 15 patients received both surgery and radiation (1.48%), and 274 patients received best supportive care (27.0%). OS was significantly lower in patients who received best supportive care (22.6 mo) compared to surgery (275.4 mo, $p <$ .001), radiation (77.3 mo, $p <$ .001), or both surgery & radiation (171.3 mo, $p <$ .001). Favorable sociodemographic factors significantly correlated with higher therapy rates. **Conclusions:** In pediatric primary liver cancers, socio-demographic factors including younger age at diagnosis, white ethnicity, higher family income & higher regional education levels correlated with prolonged survival. Significantly higher survival with treatment was observed; favorable socio-demographic factors predicted higher treatment rates.

10077 Poster Session (Board #147), Sun, 8:00 AM-11:30 AM

Palonosetron vs ondansetron: Prevention of chemotherapy-induced nausea and vomiting in pediatric patients in a multicycle study. *First Author: Edita Kabickova, Department of Paediatric Haematology and Oncology, Charles University 2nd Medical School, Prague, Czech Republic*

Background: Palonosetron (PALO) has been shown to be non-inferior to ondansetron (OND) at preventing chemotherapy-induced nausea and vomiting (CINV) in adult patients (pts) receiving moderately/highly emetogenic chemotherapy (MEC/HEC). **Methods:** This phase III study evaluated the efficacy/safety of two PALO doses (10, 20 μg/kg) vs OND (3 $\times$ 150 μg/kg) in pediatric pts receiving up to 4 MEC/HEC cycles. For the primary objective statistical analysis was used to show non-inferiority for PALO (δ = -15%) vs OND from complete response rates (CR, no emesis/rescue medication) in the acute phase (0–24h after first MEC/HEC dose) of cycle 1. Secondary objectives included CR rate in the delayed (>24–120h) and overall (0–120h) phases and safety. **Results:** In 493 pts aged 64 days–16.9 years the CR rate was highest in the PALO 20 μg/kg group in all phases of cycles 1, 3 and 4 with statistical non-inferiority shown for this dose vs OND in the acute phase of cycle 1 (see table). In cycles 1–4 treatment-emergent adverse events (TEAEs) were fewer in the PALO 20 μg/kg group (69.3%, 64.4%, 55.9%, 48.4%) vs the PALO 10 μg/kg (80.2%, 76.2%, 72.1%, 75.0%) and OND (81.7%, 82.6%, 68.2%, 72.2%) groups. Drug-related TEAEs (cycles 1–2 only) were comparable although highest in the OND group (4.7%). TEAEs in cycles 3–4 plus all study withdrawals and fatal TEAEs were not considered drug-related. Laboratory and ECG evaluations, inclusive of the QT interval raised no concerns. **Conclusions:** In pediatric pts receiving up to 4 MEC/HEC cycles palonosetron 20 μg/kg was non-inferior to OND in the acute phase of cycle 1, numerically superior to OND across all cycles and presented no significant safety risks. Clinical trial information: NCT01442376.

CR rate Phase, %	PALO 10 μg/kg N	PALO 20 μg/kg N	OND 3 $\times$ 150 μg/kg N
Cycle 1	**166**	**165**	**162**
Acute	54.2	59.4	58.6
97.5% CI* of ΔCR†	-16.4–7.6	-11.7–12.4	
P-value‡	0.0242	0.0022	
Delayed	28.9	38.8	28.4
Overall	23.5	32.7	24.1
Cycle 2	**82**	**90**	**86**
Acute	66.7	65.6	59.3
Delayed	35.8	38.9	32.6
Overall	33.3	35.6	29.1
Cycle 3	**43**	**59**	**44**
Acute	44.2	81.4	63.6
Delayed	30.2	42.4	27.3
Overall	27.9	40.7	27.3
Cycle 4	**19**	**31**	**19**
Acute	47.4	64.5	52.6
Delayed	31.6	32.3	26.3
Overall	21.1	29.0	21.1

*Mantel-Haenszel; †$\Delta CR = CR_{Palonosetron} - CR_{Ondansetron}$; ‡Non-inferiority confirmed if $p < 0.0125$.

10078 Poster Session (Board #148), Sun, 8:00 AM-11:30 AM

Risk assessment in children presenting with fever and chemotherapy-induced neutropenia. *First Author: Kristen Schratz, Department of Pediatrics, Columbia University Medical Center, New York, NY*

Background: Febrile neutropenia (FN) is a common complication of cancer treatment and predisposes children to develop severe infections. The purpose of this study was to identify clinical and laboratory factors predictive of a serious infectious complication in pediatric cancer patients with FN. **Methods:** A retrospective cohort study was performed in 188 children admitted for management of 381 episodes of febrile neutropenia. The primary outcome was development of a severe infectious complication (SIC), which included an infection diagnosed by clinical exam, a proven bacterial infection of the blood, urine or other sterile site or a radiologically diagnosed infection. Twenty-five variables assessable at the time of presentation to the oncology clinic or emergency department were analyzed for significance, and included patient-specific, treatment-related and episode-specific variables, as well as complete blood count results. **Results:** The cohort's mean age was 8.4 years. The underlying diagnosis was a solid tumor in 57.1%, and a hematologic malignancy in 42.9% of patients. The rate of SIC was 30.6% with the most prevalent complication being bacteremia in 49% of those. Of the episodes of bacteremia gram-negative bacilli were isolated in 58.6%. Factors identified in univariate analysis to be significant predictors were maximum temperature, leukocyte count, hemoglobin level, platelet count, baseline disease activity and hypotension. Multivariate regression analysis identified relapsed or advanced disease status, presence of hypotension and degree of leukopenia as significant predictors for a SIC. **Conclusions:** This study identifies several predictors of SIC in pediatric patients with FN, which will enable the development of a prediction model to distinguish patients at low risk of developing SIC. Risk stratification will allow for the design of a prospective safe outpatient management for the low-risk group.

TPS10079 Poster Session (Board #149a), Sun, 8:00 AM-11:30 AM

A multicentric study of interval compressed multiagent chemotherapy and metronomic chemotherapy for patients with Ewing sarcoma family of tumors: The Latin American Pediatric Oncology Group trial. *First Author: Lauro José Gregianin, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil*

Background: Large cooperative group studies have shown the efficacy of risk-adapted treatment for Ewing sarcoma (ES). However, validation and local adaptation by national cooperative groups is needed. A multicenter protocol to determine the efficacy and safety of adapted regimen was developed by the Latin American cooperative group (GALOP). The primary endpoint is investigate the feasibility and progression free survival (PFS) of combined modality therapy that incorporates interval-compressed VDC/IE as shown by the AEWS0031 study, and metronomic chemotherapy (CT). Secondary endpoints include safety, overall survival and duration of response. **Methods:** Induction (Indct) CT consisted of alternating cycles of VDC (vincristine 1.5 mg/m2 d1, doxorubicin 37.5 mg/m2 d1 and d2, cyclophosphamide 1.2 g/m2 d1) and IE (ifosfamide 3 g/m2 d1, d2 and d3, and etoposide 165 mg/m2 d1, d2 and d3), followed by local control. Pts with localized disease received 6 cycles at Indct and 8 at consolidation (Cons), and pts with metastasis received 9 at Indct and 5 at Cons. The time interval between cycles at Indct and Cons are 14 and 21 days, respectively. After Cons, pts with metastasis received metronomic CT, which consisted in oral cyclophosphamide (25 mg/m2/day, continuously) and vimblastin (3 mg/m2, weekly), for 1 year, while pts with localized disease are randomized (1:1) to receive or not metronomic CT according to the following risk factor: , age above versus (vs) below 14-years-old, pelvic vs non-pelvic primary tumor, tumor size more vs less than 8 cm, and male vs female. Toxicity is assessed following cycles of CT according to the CTC criteria. Enrollment began in April 2010, and, as of January 2011, 234 pts (107 with metastasis) have been recruited across 37 centers from Argentina, Brazil, Chile, and Uruguay. Statistical design: Target enrollment is 500 subjects; 200 pts with metastasis, and 300 pts with localized disease, of which 150 is randomized to the metronomic CT arm and 150 receive no further CT, in order to identify a difference in 5-years PFS of 15% (power 0.80, 2-tail type 1 error of 0.05).

TPS10080 Poster Session (Board #149b), Sun, 8:00 AM-11:30 AM

Long-term infusion of anti-GD2 antibody ch14.18/CHO in combination with interleukin-2 (IL2) activity and efficacy in high-risk relapsed/refractory neuroblastoma patients. *First Author: Holger N. Lode, University Med Ctr of the Ernst-Moritz-Amdt Universitat Greifswald, Greifswald, Germany*

Background: Long-term infusion (LTI) of anti-GD_2 antibody ch14.18/CHO may improve outcome in patients (pts) with high risk relapsed/refractory neuroblastoma (NB). **Methods:** 97 pts received 6x10^6 IU/m^2 sc IL2 (d1-5; 8-12), LTI of 100 mg/m^2 ch14.18/CHO (d8-17) and 160 mg/m^2 oral 13-cis-RA (d19-32) in an ongoing SIOPEN Phase II study (APN311-202) (NCT01701479) (44 pts) and a closed single center program (53 pts) (APN311-303). Response assessments followed INRG criteria. Fcγ-receptor polymorphisms FCGR2A (H131R), -3A (V158F) and -3B (NA1/NA2) were determined. **Results:** A decreasing degree of morphine usage and low pain scores were observed. Clinical overall responses were 30% (APN311-303) and 31% (APN311-202). The survival update of the APN311-303 cohort revealed a 1-y & 4-y OS of 94.2±3.2% & 60.9±9.0% (median FU 2.9y [0.7-5.2y]) and a 1-y & 4-y PFS of 54.4±6.9% & 32.3% ±6.9% (median FU 2.8y [0.7 - 4.9y]). Median TTP was 571d (95% CI: 232.7d). The comparator is the reported historical gold standard with 1-y & 4-y PFS of 19±2% & 8±3% and OS of 56±3% & 14±4% and a median TTP of 63 d (95% CI: 56.8d). NB pts with high affinity FCGR alleles and an increase in ADCC (cut off 15%) are associated with longer PFS and OS rates ($p < 0.03$; $p < 0.005$), which supports NK-cell mediated ADCC as the mechanism of action. Parameters of immune modulation (CDC, and WBT) and pharmacokinetics (PK) of ch14.18/CHO were comparable between APN311-202 and -303 cohorts. PK of ch14.18/CHO was analyzed in cycle 1: C_{max}= 12.2±0.4μg/ml, $t_{½}$= 8.4±1.1 d, AUC = 145.3± 5.8 μg*d/ml, Vd = 9.3±0.5L/m^2. A pro-inflammatory cytokine response (IL-2, IL-6, IL-8, IFNγ) translated into the expansion of effector NK- (3x) and T-cells (2x). We observed HACA in 17/97 pts (17.5%) of which only 9/97 (9.3%) were neutralizing with respect to the inhibition of CDC and WBT activity. In HACA negative patients, levels of ch14.18/CHO and functional parameters (CDC, WBT) analyzed before subsequent treatment cycles indicate persistent anti-NB activity for the entire treatment period. **Conclusion:** LTI of ch14.18/CHO is active and effective in high-risk relapsed/refractory NB. Clinical trial information: NCT01701479.

TPS10081 Poster Session (Board #150a), Sun, 8:00 AM-11:30 AM

A phase II study of pazopanib in children, adolescents, and young adults with refractory solid tumors. *First Author: Alice Lee, Columbia University, New York, NY*

Background: Pazopanib (VOTRIENT; GlaxoSmithKline) is an angiogenesis inhibitor targeting VEGFR-1, -2, and -3; PDGFR-α and -β; and c-Kit, and is indicated for the treatment of adults with advanced RCC and advanced soft tissue sarcoma. Data from adults with sarcoma support the study of soft tissue and bone sarcomas, as well as embryonal tumors, in pediatric subjects. The current Phase II study undertaken by the Children's Oncology Group (COG-ADVL1322/ VEG116731) was preceded by a Phase I trial of pazopanib tablets and powder for oral suspension (PfOS) in children (N = 51). The maximum tolerated dose (MTD) for tablets was 450 mg/m^2/dose and 160 mg/m^2/dose for the PfOS, with two dose-limiting toxicities (DLTs) seen at 225 mg/m^2 of the PfOS. Hematologic and non-hematologic toxicities were generally mild. One subject each with hepatoblastoma or desmoplastic small round cell tumor had a partial response; 8 had stable disease ($\geq$ 6 cycles); 7 of these had sarcoma (Glade Bender; J. Clin. Oncol. 2013; 31:3034). Given these findings, this Phase II trial will further evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics in children. **Methods:** This is a multi-center study of pazopanib in US and Canadian subjects age 1 to 18 years with solid tumors relapsed or refractory to prior therapy. Tumor types include rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma, Ewing sarcoma, osteosarcoma, neuroblastoma, and hepatoblastoma. Subjects will be stratified by tumor type, and the response rate to pazopanib will be assessed for each of the six disease strata using a two-stage design. Pazopanib will be administered orally once daily as a tablet at 450 mg/m^2 or as PfOS at 225 mg/m^2. The phase I PfOS MTD of 160 mg/m^2 may result in suboptimal exposure. Given that the toxicity at 225mg/m^2 was isolated and reversible, the first 6 patients receiving PfOS will be dosed at 225 mg/m^2 and assessed for first-cycle DLTs and PK. The study will also evaluate pazopanib pharmacokinetics and toxicity in this pediatric population and will assess the relationship between efficacy and levels of cytokines and angiogenic factors, and VEGF and KDR polymorphisms. Four of 77 subjects have been enrolled. (NCT01956669) Study funded by GSK. Clinical trial information: NCT01956669.

TPS10082 Poster Session (Board #150b), Sun, 8:00 AM-11:30 AM

A randomised phase IIb trial of BEvACizumab added to Temozolomide ± IrinOtecan for children with refractory/relapsed Neuroblastoma - BEACON-Neuroblastoma, a European Innovative Therapies for Children with Cancer (ITCC) - International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial. *First Author: Lucas Moreno, CNIO, Spanish National Cancer Research Centre, Madrid, Spain*

Background: Current therapy for relapsed/refractory high-risk neuroblastoma is not evidence based and long-term disease control is poor. Advances in frontline therapy have been achieved through randomised clinical trials. BEACON-Neuroblastoma trial is designed to identify a backbone chemotherapy regimen to be combined with targeted agents and determine if inhibiting angiogenesis with bevacizumab(B) adds to the activity of chemotherapy. It is the first randomized European study for refractory/relapsed neuroblastoma **Methods:** BEACON-Neuroblastoma is a factorial phase 2, multicentre, international, randomized clinical trial (EudraCT 2012-000072-42, sponsored by the University of Birmingham). Patients 1-21 years with relapsed/refractory high-risk neuroblastoma are randomised to 1 of 4 arms: T (temozolomide), IT (irinotecan-temozolomide), BT (B-T) or BIT (B-IT). The trial tests whether B added to chemotherapy (T or IT) demonstrates activity and whether the addition of I to T increases activity. Primary endpoint is best response at any time during trial treatment. During 2015, whether the addition of topotecan to T increases activity will be addressed by changing to 3 x 2 design with 6 arms and requiring 160 patients. The trial incorporates functional imaging (FI) to elucidate the role of anti-angiogenic therapy in neuroblastoma; a biomarker study measuring neuroblastoma mRNAs and molecular characterisation. This work is supported by Cancer Research UK [grant number CRUK/11/056] and Imagine for Margo. 21 sites in 7 countries are open (11 further sites are to open). From Jul-2013 to Jan-2015, 30 patients have been included. BEACON-Neuroblastoma is the recommended approach for relapsed/refractory neuroblastoma in SIOPEN/ITCC. The trial will answer 2 randomised questions in a small population and has developed a European network of centres performing biomarker and FI studies. It will be the foundation of a European multi-arm multi-stage trial to evaluate new drugs in the future Clinical trial information: NCT02308527.

TPS10083 Poster Session (Board #151a), Sun, 8:00 AM-11:30 AM

Early detection of transformation of plexiform neurofibromas to malignant peripheral nerve sheath tumors in neurofibromatosis type 1. *First Author: Sucharita Bhaumik, Children's Natl Med Ctr, Washington, DC*

Background: Neurofibromatosis 1 (NF1), an autosomal dominant genetic disorder, is characterized by development of benign plexiform neurofibromas (PN) and malignant peripheral nerve sheath tumors (MPNST) that often develops from malignant transformation in a preexisting PN. Complete surgical resection is only curative treatment, making early detection of malignant transformation an important goal. A preliminary study by Meany et al [Pediatr Blood Cancer. 2013, 60(1): 59-64] using ^{18}Fluoro-deoxy-glucose positron emission tomography (FDG-PET) to identify concerning lesions, described high FDG uptake in both malignant and benign PN.^{18}F-3′-fluoro-3′-deoxy-L-thymidine (FLT) PET measures cell cycling and proliferation. We hypothesize that FLT-PET may be more sensitive and specific in the identification of malignancy. This pilot study in NF1 patients with lesions concerning for MPNST will evaluate 1) feasibility of FLT-PET 2) ability of FLT-PET to distinguish benign from malignant and 3) perform comprehensive genomic analyses from tumor and blood samples. **Methods:** Trial design: Fifteen patients with NF1 and lesions concerning for malignant transformation are eligible. Patients undergo clinical evaluation of NF1 manifestations, whole body MRI with volumetric analysis of tumor burden, FDG and FLT-PET, guided biopsies of the concerning lesion and of adjacent presumably benign PN for detailed pathologic analysis. Germline blood samples, tissue samples from concerning lesion and surrounding presumably benign PN (Trios) will undergo genomic analysis. The reader of the PET studies will be blinded to the pathologic diagnosis. Exploratory statistical methods will be used to evaluate the differences in uptake between the two groups (FDG and FLT), followed by logistic regression to identify uptake values most associated with benign versus malignant classification. Clinical, imaging, histopathologic, and genomic features will be correlated in an exploratory fashion, to describe features associated with malignant transformation. This single institution trial (NCT02211768) is open for enrollment at the NCI, and has enrolled the first patient. Clinical trial information: NCT02211768.

10500 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

GeDDiS: A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas (EudraCT 2009-014907-29). *First Author: Beatrice M. Seddon, University College Hospital, New Malden, United Kingdom*

Background: Standard first-line treatment of locally advanced/metastatic soft tissue sarcoma (STS) is Dox. GemDoc has activity in STS and is used in relapsed STS after failure of at least one line of chemotherapy. Our aim was to compare GemDoc with Dox as first-line treatment of locally advanced/metastatic STS. **Methods:** Patients (pts) from 24 UK sites and 1 Swiss site were randomised to receive 6 cycles of Dox 75 mg/m^2 intravenously (IV) day 1 every 3 weeks, or Gem 675 mg/m^2 IV days 1 and 8 and Doc 75 mg/m^2 IV day 8 every 3 weeks (wks). Pts had locally advanced/metastatic STS, Trojani grade 2 or 3, disease progression prior to enrolment, no prior chemotherapy for sarcoma, no prior Dox, WHO performance status 0-2, age $\geq$ 13 years. Pts were stratified by age ($\leq$ 18 or $>$ 18 years) and histological subtype (uterine leiomyosarcoma [uLMS], synovial, pleomorphic, and other). Primary endpoint was progression free survival (PFS) rate (PFR) at 24 wks. Results: From Dec 2010 - Jan 2014, 257 pts were randomised (n = 129 Dox; n = 128 GemDoc). Median follow up was 19 months. 61% of pts were female; median age was 55 years. Baseline characteristics were balanced. Histology was 27% uLMS, 4% synovial, 12% pleomorphic, 56% other. PFR at 24 wks was 46.1% v 46.0%, median PFS was 23 v 24wks, for Dox v GemDoc, but the hazard ratio (HR) was 1.28 (95% CI 0.98-1.67, P = 0.07) in favour of Dox. Median OS was 71 v 63 wks (HR = 1.07; 95% CI 0.77-1.49) for Dox v GemDoc. Although the PFS Kaplan-Meier curves did not violate the proportional hazards assumption (p = 0.53), they initially overlapped, and then separated after 24 wks in favour of Dox. Best response (CR/PR/SD) was 65.9% (Dox) v 58.6% (GemDoc). Mean dose intensity was 94.6% (Dox) v 83.3% (GemDoc). 46% (Dox) v 61% (GemDoc) of pts had at least one dose delay; 1 pt (2%) on Dox v 13 pts (16%) on GemDoc stopped treatment early due to toxicity. Conclusions: Although the PFR at 24 wks was the same for Dox and GemDoc, the HR indicated superiority of Dox. Dox was less toxic and easier to deliver than GemDoc, and should remain standard first-line treatment for locally advanced/metastatic STS. Clinical trial information: ISRCTN07742377.

10501 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor α (PDGFRα) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS). *First Author: William D. Tap, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Options for patients (pts) with unresectable/metastatic STS are limited. While Dox is standard of care, Dox combinations have yet to improve overall survival (OS) over Dox alone. Olaratumab (IMC-3G3), a fully human monoclonal antibody, selectively binds PDGFRα (a signaling pathway implicated in STS), blocks ligand binding, and enhances Dox activity in preclinical sarcoma models. **Methods:** We conducted a phase Ib, open-label, randomized phase II study of Dox $\pm$ olaratumab in unresectable/metastatic STS (NCT01185964). Pts received Dox (75 mg/m^2 Day 1) with (Arm A) or without (Arm B) olaratumab (15 mg/kg Days 1 and 8, every 21 days), a dose and schedule confirmed safe in phase Ib, for up to 8 cycles. In Arm A, olaratumab monotherapy continued after Dox until disease progression; in Arm B, pts could cross over to olaratumab at progression. The primary endpoint was progression-free survival (PFS; target hazard ratio [HR] = 0.67, 80% power, α = 0.2) with OS as a secondary endpoint. **Results:** Of 133 pts randomized, 129 (97%) were treated (64, Arm A; 65, Arm B). Demographics were balanced. Final PFS analysis (103 events) revealed medians of 6.6 months (Arm A) and 4.1 months (Arm B) (stratified HR; 95% confidence interval [CI]: 0.672 [0.442-1.021]; p = 0.0615). Interim OS analysis (83 deaths) revealed medians of 25.0 months (Arm A) and 14.7 months (Arm B) (HR = 0.44; p = 0.0005). Objective response rates were 18.8% (Arm A) and 12.3% (Arm B) (p=0.3407). The following Grade $\geq$ 3 adverse events (AEs) occurred in $\geq$ 5% of the population: Arm A $>$ Arm B, neutropenia (51.5% vs 33.8%), anemia (12.5% vs 7.7%), fatigue (9.4% vs 3.1%), thrombocytopenia (9.4% vs 7.7%); Arm A $<$ Arm B, febrile neutropenia (12.5% vs 13.8%), infections (6.3% vs 10.8%). **Conclusions:** This study of olaratumab in combination with Dox met its primary PFS endpoint and achieved an improvement of 10.3 months in median OS that was highly statistically significant (HR = 0.44; p = 0.0005). Olaratumab is the first agent added to Dox to improve OS in advanced/metastatic STS in a randomized trial. Clinical trial information: NCT01185964.

LBA10502 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Randomized, open-label, multicenter, phase III study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI). *First Author: Patrick Schöffski, University Hospital Leuven, Leuven, Belgium*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 30, 2015, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2015, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

10503 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A randomized phase III study of trabectedin (T) or dacarbazine (D) for the treatment of patients (pts) with advanced liposarcoma (LPS) or leiomyosarcoma (LMS). *First Author: George D. Demetri, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA*

Background: This phase III multicenter trial compared T with D in pts with advanced LPS or LMS previously treated with an anthracycline and at least one additional systemic therapy. **Methods:** Pts were randomized to T or D in a 2:1 ratio. Dosing of T and D were q 3 wks IV infusion: T (1.5 mg/m^2 over 24 hr) vs D (1 g/m^2 over 20-120 min). The primary end point was overall survival (OS), and secondary end points were progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), duration of response (DOR), symptom severity and safety. Cross-over to T after disease progression (PD) on D was not allowed until revision after this planned interim analysis (IA) of OS (50% events). The study is ongoing for final OS. Final results of secondary endpoints are presented. **Results:** The IA included 518 pts (T = 345, D = 173), 73% with LMS and 27% with LPS. Treatment with T resulted in a 45% reduction in the risk of PD or death compared with D (hazard ratio [HR] = 0.550; P $<$ 0.0001; Median [M] 4.2 vs 1.5 months [mo], respectively), with benefit observed across all subgroups, and validated by independent radiologists audit. Other end points demonstrated improved efficacy of T: TTP (HR = 0.522, p $<$ 0.0001; M = 4.2 vs 1.5 mo), clinical benefit rate (CR+PR+SD $\geq$ 18wks) (34.2% vs 18.5%; Odds Ratio[OR] = 2.291; p = 0.0002), ORR (9.9% vs 6.9%; OR = 1.467; p = 0.3269), DOR (HR=0.471, p = 0.1415; M = 6.5 vs 4.2 mo). The IA of OS (64% censored) demonstrated a 13% reduction in risk of death in T arm compared with D (HR = 0.872, p = 0.3741; M = 12.4 vs 12.9 mo). 34% of T and 17% of D pts received $\geq$ 6 cycles. The safety profiles were consistent with the well-characterized toxicities of both agents, with the most common grade 3-4 toxicities in T vs. D arm being ANC (40% vs 25%), platelets (19% vs 20%), increased ALT (29% vs 1%), and drug-related death (2.1% vs 0%). Patient-reported outcomes were similar across the arms, with low symptom scores during treatment. **Conclusions:** This phase III trial demonstrates improved disease control with T vs. D in advanced LPS and LMS, and confirms the acceptable benefit-risk profile of T from the prior randomized Phase 2 study (STS-201). T is a meaningful treatment option for pts with advanced LPS and LMS. Clinical trial information: NCT01343277.

10504 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Activity of regorafenib (RE) in leiomyosarcomas (LMS) and other types of soft-tissue sarcomas (OTS): Results of a double-blind, randomized placebo (PL) controlled phase II trial. *First Author: Olivier Mir, Institut Gustave Roussy, Villejuif, France*

Background: RE is a multikinase inhibitor that has demonstrated activity in gastrointestinal stromal tumors. We investigated its activity and safety in anthracycline pretreated metastatic soft tissue sarcomas (STS). **Methods:** REGOSARC (NCT01900743) consisted of four independent cohorts of patients (pts) with LMS, OTS, synovial, and adipocytic sarcomas who were randomized (1:1) to receive either RE (160 mg/d, 21/28 d) or PL, with optional cross-over. Key-eligibility criteria were age $\geq$ 18, measurable progressing STS not amenable to curative-intent surgery, $\leq$ 3 previous lines of treatment for metastatic STS. The primary endpoint was progression-free survival (PFS) with blinded central radiological review. Statistical assumptions for LMS and OTS cohorts were PFS = 1.6 months (mo) with PL, PFS = 4.6 mo with RE, 1-sided $\alpha = 0.1$ and $\beta = 0.05$. **Results:** From July 2013 to July 2014, 57 LMS and 53 OTS pts were enrolled (55 with PL, 55 with RE). The two most common OTS types were Undifferentiated Pleomorphic Sarcomas (n = 21, 40%) and Solitary Fibrous Tumors (n = 7, 13%). Eighty-four (77%) tumors were grade 3. In both cohorts, the most common primary sites were retroperitoneum and uterus (n = 23, 21%, each). There were 48 men (44%). The median age was 60 (20-81) years. The median number of prior lines was 2 (1-3): 106 (97%), 59 (54%), 39 (35%) and 4 (4%) pts were previously treated with doxorubicin, ifosfamide, trabectedin and pazopanib, respectively. Both arms in each cohort were well balanced. The most common Gr 3 AEs were hypertension (10 vs 2 pts; RE vs PL), skin toxicity (9 vs 1), asthenia (9 vs 3) and diarrhea (6 vs 2). There was no Gr5 AE and 1 Gr4 AE (anemia in RE arm). The median PFS of LMS pts was 4.0 mo with RE versus 1.9 mo with PL (HR = 0.49; 95CI 0.27-0.89; p = 0.017). The median PFS of OTS pts were 4.6 and 1.0 mo, with RE and PL respectively (HR = 0.38, 95CI 0.20-0.74; p = 0.002). The 6-mo OS rate of LMS pts was higher in the RE arm (87.0% vs 75.9%; HR = 0.25; 95CI 0.08-0.81; p = 0.013), this difference was not significant in the OTS cohort (79.0 vs 62.0%; HR = 0.64, 95CI 0.23-1.74; p = 0.4). **Conclusions:** RE demonstrates promising activity and an acceptable toxicity profile that warrant further clinical evaluation in LMS and OTS pts. Clinical trial information: 2012-005743.

10505 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Three vs. 1 year of adjuvant imatinib (IM) for operable high-risk GIST: The second planned analysis of the randomized SSGXVIII/AIO trial. *First Author: Heikki Joensuu, Comprehensive Cancer Center, Helsinki University Hospital, and University of Helsinki, Helsinki, Finland*

Background: Three years of adjuvant IM is recommended after surgery for patients (pts) with high-risk GIST with an IM-sensitive mutation. This recommendation is based on the findings from the SSGXVIII/AIO trial that compared 1 year (Arm A) to 3 years (Arm B) duration of administration of adjuvant IM. After a median follow-up of 4.5 yrs, 3 yrs of IM resulted in superior recurrence-free survival (RFS) and overall survival (OS), but the OS benefit was based only on 37 events. **Methods:** Pts with high-risk GIST according to the modified NIH risk stratification who had GIST resected macroscopically completely were eligible. The pts were randomly assigned 1:1 to Arm A or B, and were scheduled to receive IM 400 mg/day either for 12 or 36 months after surgery. Tumor histology was reviewed centrally after randomization. The study protocol was amended in October 2006 to exclude pts who had completely resected metastatic disease from the study. We now present the second planned analysis of the trial based on a median follow-up time of 7.5 years. **Results:** 400 patients were entered to this multicenter, open study between February 4, 2004, and September 29, 2008. The 397 pts who provided informed consent formed the Intention-To-Treat (ITT) population (A, 199; B, 198 pts). Pts who did not have GIST at central pathology review (n = 15) and those with metastatic GIST at study entry (n = 24) were excluded to form the Efficacy Population (i.e. "the true adjuvant GIST population"; A, 181; B, 177). In this second analysis, 171 recurrences and 68 deaths were detected (ITT). Pts assigned to 3 yrs of IM had longer RFS (HR 0.60, 95% CI 0.44 - 0.81; P $<$ 0.001) and longer OS (HR 0.61, 95% CI 0.38 - 1.00; P = 0.046) than those assigned to 1 yr of IM in the ITT population, and also in the Efficacy Population (HR 0.62; 95% CI 0.45-0.85; P=0.003; and HR 0.54, 95% CI 0.31-0.96; P = 0.032, respectively). 5-year OS was 86.8% and 93.4% in the 1-year and 3-year groups, respectively, despite the high-risk features of GISTs (Efficacy Population). The frequency of cardiac events (A, 10; B, 6) and the numbers of second cancers (A, 18; B, 23) were similar in the groups. **Conclusions:** Three years of adjuvant IM resulted in superior RFS and OS as compared to 1 year of IM. Clinical trial information: NCT00116935.

10506 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Final results of the multicenter randomized phase II PAZOGIST trial evaluating the efficacy of pazopanib (P) plus best supportive care (BSC) *vs* BSC alone in resistant unresectable metastatic and/or locally advanced gastrointestinal stromal tumors (GIST). *First Author: Jean-Yves Blay, Centre Léon Bérard, Department of Medicine, Lyon, France*

Background: GIST is the most common mesenchymal neoplasm of the gastrointestinal tract. Imatinib followed by sunitinib then regorafenib is the usual sequence in advanced setting. P is effective in soft tissue sarcomas; it has never been evaluated in a randomized setting in GIST. **Methods:** Eligible patients (pts) were randomized (1:1; stratification on number of prior drugs (2 *vs* $\geq$3)) to receive P+BSC or BSC. Primary endpoint was Progression-Free Survival (PFS). 80 pts were planned to detect an improvement in the 4-month PFS rate (PFS-4m) from 15% (BSC) to 45% (P+BSC) with 5% two-sided α and 80% power. Secondary objectives included Best Overall Response (BOR), Overall Survival (OS), safety and trough plasma P concentrations (Ct). **Results:** From Apr 11 to Dec 13, 81 pts (P+BSC: 40, BSC: 41) were randomized. Arms were well balanced; median age: 63y (27-85), 70% males and 54% with $\geq$ 3 prior drugs. The intent-to-treat analysis based on investigator-assessed progressive disease (PD) showed an improved PFS with PFS-4m of 45.2% (95% CI 29.1-60.0) for P+BSC *vs* 17.6% (95% CI 7.8-30.8) for BSC (HR: 0.59, 95% CI 0.37-0.96; p = 0.03). 36 pts out of 41 switched to P following investigator-assessed PD (median P duration: 3.5 months (0.1-19), main reasons for discontinuation: PD (52.8%) and toxicity (22.3%)). Centrally-assessed BOR showed stable disease in 84.2% *vs* 70.7% and PD in 15.8% *vs* 26.8% of pts in P+BSC and BSC arms. Among all pts treated with P (n = 76), 72.4% experienced grade $\geq$ 3 related adverse events (AE) (hypertension: 36.8%), including 25% of related serious AE (pulmonary embolism, 9.2%). At the time of analysis, 29 *vs* 31 pts had died in the P+BSC and BSC arms (OS HR: 0.94, 0.56-1.56). 1 toxic death occurred (hepatic cytolysis). Preliminary results showed a higher median Ct at steady state in pts progression-free at 4 months *vs* progressive: 25 (2-63) vs 17 (8-35) μg/ml (n = 43; p = 0.08). **Conclusions:** P combined to BSC improves PFS in advanced GIST resistant to imatinib and sunitinib. In the context of a high switch rate, no difference in OS was found. Further PK analyses are ongoing. Clinical trial information: NCT01323400.

10507 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

A phase Ib/II study of MEK162 (binimetinib [BINI]) in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST). *First Author: Ping Chi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ETV1, a lineage-specific survival factor for GIST and its precursor interstitial cells of Cajal, represents a promising therapeutic target in GIST. In preclinical models, MEK inhibition with BINI, synergizes with imatinib in destabilizing ETV1 protein and suppressing GIST tumorigenesis and progression. Combined MEK and KIT inhibition therefore represents a novel therapeutic approach for patients with GIST. **Methods:** The phase Ib portion of the imatinib (400 mg daily) plus BINI was performed in patients (pts) with imatinib-resistant advanced GIST. A standard 3+3 dosing schema was utilized to determine the recommended phase II dose (RP2D) of this combination. Additional pts were enrolled on an expansion cohort at the RP2D. Responses were assessed by RECIST1.1 and Choi criteria every 8 weeks. Custom targeted next-generation sequencing with the Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) was performed on archived tumor samples for all pts. **Results:** Eighteen pts enrolled to the phase I portion, with 9 pts each in the dose escalation and the expansion cohorts. Median age 60 (range 30-74), 44% women, median prior therapy 3 (range 1-6, 14/18 pts had $\geq$ 3 prior therapies). Imatinib 400 mg daily with BINI 45mg BID was established as the RP2D. Dose limiting toxicity (DLT) was asymptomatic grade 4 Creatinine Phosphokinase (CPK) elevation (1/6 pts at RP2D). The most common non-DLT grade 3/4 toxicity was asymptomatic CPK elevation (12/18 pts). Other common Grade 2 toxicities include peripheral edema (5/18), rash (3/18). No unexpected toxicities observed. Of the 15 pts with evaluable CT scans, 5 pts (33%) had Choi PR; and 9 pts had RECIST SD at 8 weeks. Seven pts remain on trial at data cutoff (range 4-53 weeks). Median progression free survival is not reached. Correlation of outcome with IMPACT is forthcoming. **Conclusions:** BINI and imatinib combination is well-tolerated and has clinical activity in imatinib-refractory GIST. Phase II study is on-going in untreated GIST pts and a larger clinical trial in the imatinib-resistant GIST population is warranted. Clinical trial information: NCT01991379.

10508 **Poster Discussion Session; Displayed in Poster Session (Board #152), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

The somatic mutational landscape in soft tissue sarcoma: Early results from TCGA data. *First Author: Andrew Scott Brohl, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The widespread use of next-generation sequencing has uncovered the genomic landscape in many tumor types. Given the disease rarity and histologic diversity, much less is known about the somatic mutational landscape in soft tissue sarcoma. **Methods:** Publicly available whole exome sequencing data from the Cancer Genome Atlas (TCGA) sarcoma project was downloaded and processed using well-established bioinformatics pipelines. Recurrent mutations were analyzed for statistical significance and potential oncologic relevance. Pan-sarcoma and histology-specific mutational frequencies were calculated. **Results:** Matched tumor-normal whole exome sequencing was available for 242 patients at the time of analysis. The disease histologies include 92 leiomyosarcoma, 51 dedifferentiated liposarcoma, 44 undifferentiated pleomorphic sarcoma, 24 myxofibrosarcoma, 9 malignant peripheral nerve sheath tumor, 8 synovial sarcoma, 1 desmoid tumor, and 13 lacking clinical annotation at the time of analysis. There were a median 475 high-confidence somatic variants detected [range 127-7153]. Statistically significant recurrent mutations include recurrent inactivating mutations in 3 well-established tumor suppressors, *TP53, ATRX,* and *RB1*, found in 27.3%, 8.7% and 6.2% of the total cohort respectively. Differential mutational frequency of these genes was noted between histological subtypes. Additional statistically significant recurrent mutations in genes of less clear oncologic significance are noted, as are additional recurrent mutations in other known cancer genes, but found in frequencies not meeting statistical significance. **Conclusions:** To our knowledge this is the first attempt to analyze the somatic mutational landscape in soft tissue sarcoma from TCGA whole exome sequencing data. We report statistically significant recurrent mutation in three tumor suppressor genes with clear oncogenic implication. Additional recurrent mutations of interest due to either mutational frequency or mutational impact in other cancer types are noted. A comprehensive analysis of genomic data is underway by the TCGA sarcoma analysis group.

10509 **Poster Discussion Session; Displayed in Poster Session (Board #153), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

Next generation sequencing of synovial sarcomas. *First Author: Myrella Vlenterie, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Over 95% of synovial sarcoma (SS) share the t(X;18) translocation. Despite this similarity, they show heterogeneous tumor behavior and differ in therapy response. Treatment options are limited and depending on age, 50-90% of patients with localized disease survive 5 year. Therefore we tried to identify targetable mutations in SS. **Methods:** Mutation sequence analysis including copy number variation was performed on 26 tumors from 22 patients (age 11-78 years), using the comprehensive cancer panel (LifeTechnologies) on the Ion Torrent. We sequenced paired samples from 4 patients: 3 primary tumors with corresponding metastasis and 2 metastases of 1 patient responding divergently to pazopanib. In total, we analyzed 17 primary tumors, 6 metastatic lesions and 3 local relapses. Nonsynonymous variations in coding regions were included. Mutations were filtered for known single nucleotide polymorphisms and earlier found variations in our own research database. The remaining variations were verified by Sanger sequencing and compared to matching normal DNA. All research was performed in agreement with the medical ethical committee. **Results:** 8 somatic mutations were found in 8 samples. These mutations have not yet been reported in SS. Two are established mutations in oncogenes previously described in carcinomas: *KRAS* in colon and lung carcinomas and *CCND1* in endometrial cancer. Other somatic mutations, with unknown oncogenic character, were found in *RNF213*, *SEPT9*, *KDR*, *CSMD3*, *MLH1* and *ERBB4*. Similar mutations were found in the paired samples. Chromosomal aberrations, e.g. partial loss of chr 3 or gain of chr 8, were detected in 50% of SS. A loss of chr 6q was seen in the pazopanib resistant lesion and not in the matching lesion responding to pazopanib. **Conclusions:** To our knowledge this is the largest reported cohort of extensively molecularly analyzed SS. We observed a variety of mutations, the *CCND1* mutation being potentially druggable. A possible correlation between 6q loss and pazopanib resistance is subject of ongoing study. The diversity in mutations found underlines the diversity in SS genotypes beyond the known fusion gene. This potentially explains the heterogeneous behavior and emphasizes the challenge in finding new druggable targets in this disease.

10510 **Poster Discussion Session; Displayed in Poster Session (Board #154), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

Clinical application of prognostic gene expression signature in fusion gene-negative rhabdomyosarcoma: A report from the Children's Oncology Group. *First Author: Pooja Hingorani, Phoenix Childrens Hosp, Phoenix, AZ*

Background: Pediatric rhabdomyosarcoma has two common histological subtypes: embryonal (ERMS) and alveolar (ARMS). *PAX/FOXO1* fusion gene status is a more reliable prognostic marker than alveolar histology while fusion gene-negative (FN) ARMS patients are clinically similar to ERMS patients. A five-gene expression signature (MG5) previously identified two diverse risk groups within the fusion-gene negative RMS (FN-RMS) patients but this has not been independently validated. The goal of the current study was to test whether expression of the MG5 metagene, measured using a technical platform that can be applied to routine pathology material, would correlate with outcome in an unrelated cohort of patients with FN-RMS. **Methods:** A series of cases were taken from the Children's Oncology Group (COG) D9803 study of children with intermediate-risk RMS and gene expression profiling for the MG5 genes was performed using the nCounter assay. The MG5 score was correlated with clinical and pathological characteristics as well as overall and event-free survival. **Results:** MG5 standardized score showed no significant association with any of the available clinical-pathological variables. The MG5 signature score showed a significant correlation with overall (N = 57; HR 7.3 95%CI[1.9-27.0], p = 0.003) and failure-free survival (N = 57; HR 6.1 95%CI[1.9-19.7], p = 0.002). **Conclusions:** This represents the first, validated molecular prognostic signature for children with FN-RMS who otherwise have intermediate-risk disease. The capacity to measure the expression of a small number of genes in routine pathology material and apply a simple mathematical formula to calculate the MG5 metagene score provides a clear path toward better risk stratification in a future, prospective clinical trial.

10511 **Poster Discussion Session; Displayed in Poster Session (Board #155), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

The who and what of imaging in sarcoma and correlation with survival. *First Author: Vadim S Koshkin, University of Michigan, Ann Arbor, MI*

Background: Response and progression are surrogates for survival that inform clinical decisions. Comparison of anatomic and functional imaging modalities in a large prospective clinical trial can suggest the optimal method of selecting patients who benefit from further therapy. **Methods:** 115 patients with metastatic, chemo-refractory Ewing's Sarcoma were treated with R1507, a human monoclonal antibody directed at IGF-1 receptor, as part of SARC011 study (J Clin Onc vol 29). Each pt had anatomic imaging with CT or MR at baseline and 6-week intervals and FDG-PET at baseline and on day 9. Anatomic imaging results were reported by each of the 31 sarcoma centers using WHO criteria. An expert central radiology group performed an independent review and volumetric analysis on 76 pts. Using log-rank analysis we defined the optimal volume cut points for progression and response at 6 wk imaging which correlated with OS, and compared this model to previously established criteria including WHO (both central and local), RECIST and PERCIST. **Results:** Volume increase of 175% for prior lesions at 6 wks was the optimal cutoff for decreased OS ($p < 0.001$) and thus progression. Optimal cutoff for response was a 45% volume decrease. OS of patients with PD at 6 wks was significantly reduced compared to non-progressors based on Volume ($R^2 = 0.17$) as well as other criteria: RECIST ($R^2 = 0.17$), WHO_Central ($R^2 = 0.16$), WHO_Local ($R^2 = 0.14$). Patients with PMD by PERCIST on day 9 had reduced OS vs. non-progressors ($p = 0.001$). Progression type impacted survival, as pts with new lesions and enlarging prior lesions had decreased OS compared to pts with either variable alone. **Conclusions:** In a large clinical trial we identified pts with decreased OS based on multiple anatomic imaging criteria at week 6 and functional imaging by PERCIST as early as day 9. A new model using volumetric analysis with cutoffs different from those extrapolated from RECIST or WHO was introduced, and its utility should be assessed in a prospective clinical trial. Clinical trial information: NCT00642941.

	Non-Progressors				Progressors		
	Response		Stable Disease		Progressive Disease		
	N	Median OS (days)	N	Median OS	N	Median OS	p-value (PD vs. non-PD)
RECIST	16	204	26	152	34	91	<.001
VOLUME	19	204	30	149	27	84	<.001
WHO	14	204	25	154	37	91	<.001
LocalWHO	17	166	21	162	38	97	.002

10512 **Poster Discussion Session; Displayed in Poster Session (Board #156), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

Event-free survival and overall survival in 2,253 patients with osteosarcoma registered to EURAMOS-1. *First Author: Sigbjorn Smeland, Oslo University Hospital, The Norwegian Radium Hospital, Scandinavian Sarcoma Group, Oslo, Norway*

Background: EURAMOS-1 (NCT00134030) is an international study in osteosarcoma including two Phase III randomized controlled trials that investigated postoperative treatment optimization on the basis of histological response to preoperative chemotherapy (CT). One study aim was to report outcomes from diagnosis for all registered patients in this large, intergroup study. **Methods:** Patients (pts) were eligible for registration if: < 30 days from diagnostic biopsy; age ≤ 40yrs; with localized or primary metastatic, high-grade extremity or axial osteosarcoma; resectable disease; fit for treatment and follow-up. Treatment was preop CT with methotrexate, doxorubicin, cisplatin (MAP), surgery and then post-op MAP-based CT according to response and optional randomization. The primary outcome measure was event-free survival (EFS), defined as time from diagnostic biopsy until the earliest of: death, local recurrence, new metastatic disease, progression of metastatic disease or secondary malignancy, or date of last contact; a secondary outcome measure was overall survival (OS). Standard statistical methods were used. **Results:** 2260 pts from 17 countries & > 300 centres were registered from 2005 to 2011; this analysis excludes 7 ineligible pts. The site was 13% proximal femur or humerus, 82% other limb site, 5% axial skeletal; 16% had definitive metastases. 92% had conventional osteosarcoma. Median age was 14yrs (quartiles 11, 17). 1334 (59%) were randomized; 919 (41%) were not, mostly for non-consent. Median follow-up was 5.2 yrs. 1000 EFS events and 634 deaths were reported. From biopsy, 5-yr EFS = 54% (95%CI 52%, 57%), and 5-yr OS = 71% (95%CI 69%, 73%). In 1881 pts with localized disease, 5-yr EFS = 59% (95%CI 57%, 62%) and 5-yr OS = 75% (95%CI 73%, 77%); in 357 pts with metastases 5-yr EFS = 29% (95%CI 24%, 34%) and 5-yr OS = 46% (95%CI 41%, 52%); metastases were unreported for 15 pts. Prognostic models will be presented. **Conclusions:** EFS and OS rates in this multinational study were comparable to centres' reported series. We used broader eligibility criteria than most osteosarcoma studies, by including patients with axial or metastatic disease. However, this extends recruitment and relevance of our findings. Clinical trial information: 67613327.

10513 **Poster Discussion Session; Displayed in Poster Session (Board #157), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

Forty years of randomized trials in advanced/metastatic soft tissue sarcoma (STS): Endpoint selection, surrogacy and quality of reporting. *First Author: Alona Zer, Princess Margaret Cancer Center, Toronto, ON, Canada*

Background: Randomized controlled trials (RCTs) in STS have utilized varying endpoints. Surrogacy of intermediate endpoints such as progression-free survival (PFS), response rate (RR), 3 month progression free survival (3moPFS) and 6 month progression free survival (6moPFS) with overall survival (OS) has not been established. The quality of reporting of efficacy and toxicity also remains uncertain. **Methods:** A systematic review of MEDLINE and EMBASE identified RCTs of systemic therapy in STS. Surrogacy between intermediate endpoints and OS was explored using meta-regression comprising a linear regression weighted by study sample size for the hazard ratio (HR) for OS with the HR for PFS or the odds ratio (OR) for RR, 3moPFS and 6moPFS. Quality of reporting of efficacy and toxicity were defined as described previously (Vera-Badillo et al, Ann Oncol 2013) and trends over time evaluated using simple linear regression. **Results:** Of 3329 articles initially identified; 52 RCTs published between 1974 and 2014 and comprising 9762 patients met the inclusion criteria. There was a moderate correlation between PFS and OS and between RR and OS (Table 1). The correlation between 3moPFS and 6moPFS with OS was however, weak. Only 44% of studies defined the primary endpoint clearly, but this deficiency improved over time (p for trend < 0.001). There has been a significant reduction in the use of RR as the primary endpoint over time, favouring time-based events (p for trend = 0.02). In 14% of RCTs, despite the primary endpoint not being met, the concluding statement suggested benefit from the experimental therapy. Toxicity was comprehensively reported in just 52% of RCTs while 17% reported toxicity poorly. Quality of toxicity reporting has not changed significantly over time (p = 0.70). **Conclusions:** In advanced STS RCTs PFS is a better surrogate for OS than RR. The correlation between 3moPFS/6moPFR and OS is weak and its use should be reconsidered. Although the quality of RCT reporting has improved over time, toxicity reporting and interpretation of results remain suboptimal.

Surrogate endpoint	Correlation coefficient with OS
HR for PFS	0.61
OR for RR	0.51
OR for 3moPFS	0.27
OR for 6moPFR	0.31

10514 **Poster Discussion Session; Displayed in Poster Session (Board #158), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

A phase Ib dose-escalation study of TRC105 (anti-endoglin antibody) in combination with pazopanib in patients with advanced soft tissue sarcoma (STS). *First Author: Steven Attia, Mayo Clinic, Jacksonville, FL*

Background: The VEGFR inhibitor pazopanib is approved for the treatment of advanced STS. Resistance to pazopanib is a challenge in the treatment of STS, and endoglin (CD105) activation may be an important resistance mechanism. Endoglin is an angiogenic receptor expressed on proliferating tumor vessels, which is upregulated following VEGF inhibition and expressed on certain STS subtypes, including angiosarcoma. A phase Ib study of TRC105, an anti-endoglin antibody, in combination with pazopanib was performed in patients (pts) with advanced STS. **Methods:** Heavily-pretreated STS pts with leiomyosarcoma (11); angiosarcoma (2); synovial sarcoma (2); epithelioid sarcoma (1); myxofibrosarcoma (1); epithelioid hemangioendothelioma (1); and unclassifiable high grade sarcoma (2), ECOG PS 0-1, were treated with infusional TRC105 weekly in two cohorts (8mg/kg and 10mg/kg). TRC105 was initiated following a 2 to 4 week lead-in period of pazopanib starting at 800 mg PO daily. **Results:** Twenty pts (median age = 57; M:F 9:11; median prior regimens = 2) were treated. Eighteen of twenty pts tolerated pazopanib alone in cycle 1 and received TRC105 beginning with cycle 2. TRC105 dose escalation proceeded from 8 mg/kg (n = 3) to 10 mg/kg (n = 15) without dose limiting toxicity. Grade 1-2 adverse events (AEs) characteristic of each drug were not increased in frequency or severity during concurrent dosing of the two drugs. The most common TRC105 AEs included grade 1-2 telangiectasia (with associated epistaxis and gingival bleeding), while the most common pazopanib AEs included grade 1-2 fatigue and diarrhea. One patient with cutaneous angiosarcoma is ongoing with a complete response, and 5 of 18 pts (28% of those evaluable for efficacy) exhibited > 10% tumor reduction by RECIST 1.1. Duration of therapy ranged from 2 to 12.3+ months. Efficacy endpoints will be correlated with endoglin expression by immunohistochemistry. **Conclusions:** TRC105 was well tolerated at its recommended phase 2 dose of 10 mg/kg weekly, in combination with daily oral pazopanib, in pts with advanced STS, and the combination exhibited evidence of activity. A multicenter phase 2 trial of TRC105 + pazopanib is ongoing. Clinical trial information: NCT01975519.

10515 **Poster Discussion Session; Displayed in Poster Session (Board #159), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

A phase II study of tivozanib in patients with metastatic and non-resectable soft tissue sarcomas. *First Author: Mark Agulnik, Northwestern University, Feinberg School of Medicine, Chicago, IL*

Background: Despite a multi-modality approach, many patients (pts) with early stage soft tissue sarcomas (STS) will develop recurrent or metastatic disease. Treatment options for these pts are limited, thus necessitating new antitumor agents. VEGFR1, VEGFR2 and VEGFR3 are high affinity receptor tyrosine kinases localized in the endothelium of tumor vasculature and are involved in tumor angiogenesis. VEGFR tyrosine kinase inhibitors (TKI) block phosphorylation of the VEGFR and inhibit activation of angiogenesis and, indirectly, tumor growth. Tivozanib is a potent and selective VEGFR 1,2 & 3 TKI with a long half-life, and thus a potential novel agent in the treatment of metastatic STS. **Methods:** A multicenter phase II study of tivozanib in pts with metastatic and non-resectable STS was conducted through the Midwest Sarcoma Trials Partnership. Adequate performance status, organ function, measurable disease (RECIST 1.1) and 1-4 prior therapies were required. Tivozanib 1.5 mg PO daily was given in 28 day cylces (21 days on, 7 days off) until disease progression (PD) or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), assessed at 16 weeks. Secondary endpoints include overall response rate (ORR), clinical benefit rate (CBR), OS, laboratory correlates and safety and tolerability. A Simon 2-stage design was used. **Results:** A total of 56 pts were enrolled at 3 sites, with 53 evaluable for response. Median age was 58 (range 21-82); 57% were female; 73/27% were ECOG PS 0/1; 34/20/21/25% had 1/2/3/4 prior therapies, including 24 pts who received prior VEGF inhibitor therapy. The most common histologies included LMS (46%), pleomorphic sarcoma (14%), liposarcoma (9%) and MPNST (9%). PFS at 4 months is 34.6% with a median PFS and OS of 3.4 and 9.2 months, median follow-up 5.5 months (0.9-18.3). 2 confirmed PR, 28 SD and 22 PD were observed. ORR and CBR are 4 and 58%, respectively. Common grade 3-4 adverseevents included (%): hypertension (22), decreased EF (9) and fatigue (7). **Conclusions:** Tivozanib was well tolerated in this study of highly pretreated patients with multiple sarcoma histologic subtypes. Median PFS and PFS at 4 months are promising. Tivozanib warrants further study in sarcoma. Clinical trial information: NCT01782313.

10516 **Poster Discussion Session; Displayed in Poster Session (Board #160), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

A phase I/II clinical trial of belinostat (PXD101) in combination with doxorubicin in patients with soft tissue sarcomas (STS). *First Author: Joanna Vitfell-Rasmussen, Department of Oncology, Herlev hospital, Herlev, Denmark*

Background: Belinostat is a novel histone deacetylase (HDAC) inhibitor. This study assessed the MTD and DLTs of the combination of belinostat and doxorubicin in solid tumours (phase I) and efficacy as measured by response rate (RR) in advanced STS (phase II). **Methods:** Belinostat was administered as a 30-minute IV infusion on Day 1-4 and on Day 5 in combination with doxorubicin. It was dose escalated using a belinostat starting dose of 600 mg/m^2 combined with 50 mg/m^2 doxorubicin (cohort 1), in subsequent cohorts doxorubicin was administered at 75 mg/m^2 with 600 mg/m^2 belinostat (cohort 2), 800 mg/m^2 (cohort 3) and 1000 mg/m^2 (cohort 4). A phase II trial was then performed in STS patients (pts) using the doses in cohort 4. A stopping rule determined that the phase II trial was stopped if no more than 2 responses (CR/PR) were seen among the 20 pts within the first 2 treatment cycles. The following pharmacokinetic parameters were determined: elimination half-life ($t_{1/2}$), maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the curve ($AUC_{0\text{-}tf}$ and AUC_{∞}), elimination rate constant (λz) and volume of distribution (Vc and Vss). **Results:** A total of 41 pts were included (25 in phase I, 20 in phase II (including 4 pts with STS from cohort 4). Common drug-related toxicities included: fatigue (95%), nausea (76%) and alopecia (63%). One DLT was observed, Rash - Hand and Foot Syndrome, CTC grade 3, in cohort 3 on Day 22. The MTD was declared the highest tested dose level: belinostat 1000 mg/m^2 combined with 75 mg/m^2 doxorubicin. Dose normalised $AUC_{0\text{-}tlast}$ and Cmax appeared relatively consistent across the different cohorts on both Days 4 and 5 indicating that belinostat exhibited linear pharmacokinetics across the dose range and that doxorubicin had no effect on belinostat exposure. Two responses were observed in phase I at cycle 4 (2 PR, RR of 8% (95% CI, 1 - 26%)) and in the phase II trial there were 2 responses (1 PR (cycle 4) /1 CR (cycle 2), RR of 13% (95% CI, 2 - 38%)) and 9 SD, hence the trial was stopped after 20 pts were enrolled. **Conclusions:** The combination of belinostat and doxorubicin was well tolerated and showed activity in 12/20 pts with advanced STS in the MTD population, which warrants further investigation. Clinical trial information: NCT00878800.

10517 **Poster Discussion Session; Displayed in Poster Session (Board #161), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

Detection of *KIT* mutants in circulating tumor DNA (ctDNA) and their association with ponatinib anti-tumor activity in patients (pts) with advanced gastrointestinal stromal tumors (GIST). *First Author: Michael C. Heinrich, Knight Cancer Institute and Portland VA Medical Center, Oregon Health & Science University, Portland, OR*

Background: Ponatinib is a multi-targeted tyrosine kinase inhibitor with potent preclinical activity against a broad range of clinically relevant *KIT* mutants, including primary-activating (especially exon 11) and secondary-resistance (including exons 17/18) mutants. Ponatinib is being evaluated in a phase 2 trial (NCT01874665), in which TKI-resistant metastatic GIST pts are enrolled in 2 cohorts based on the presence (A) or absence (B) of *KIT* exon 11 mutations in tumor specimens. We used ctDNA to explore the association between *KIT* mutation status and anti-tumor activity of ponatinib. **Methods:** Plasma samples were collected at baseline (BL) and every 8 wks, and a subset analyzed for 7 primary (exons 9, 11, 13) and 20 secondary (exons 13, 14, 17, 18) mutations using BEAMing. The primary trial endpoint was clinical benefit rate (CBR = CR+PR+SD at 16 wks) using modified RECIST 1.1 in cohort A. Associations between changes in ctDNA levels and tumor burden (RECIST lesions) were assessed by calculating an odds ratio (OR) and *p*-value. Data as of Dec 1, 2014, based on 32 evaluable pts of 45 enrolled pts. **Results:** 21 pts in cohort A had a BL sample, with secondary mutations detected in 11. All 11 pts had 1 (n = 6) or multiple (n = 5) detectable mutations in exon 17/18, commonly involving residues D820, N822, or Y823 – 1 pt also had a gatekeeper mutation in exon 14 (T670I); the CBR in these pts was 55% (6/11). 11 pts in cohort B had a BL sample, with a secondary mutation (A829P) only detected in 1.Overall (A+B), 15/23 pts (65%) with BL and post BL samples had at least 1 primary or secondary mutation detected. In these pts, a post BL decrease in mutant *KIT* ctDNA was associated with a reduction in tumor burden at that time point (OR = 13.6; p= 0.035). Additional analyses are ongoing. **Conclusions:** Primary and/or secondary *KIT* mutations were detected in ctDNA from a majority of TKI-resistant GIST pts and their levels were associated with tumor burden over time. Importantly, antitumor activity of ponatinib was observed in pts with exon 17/18 mutants detectable by ctDNA. Further exploration of the utility of ctDNA *KIT* mutation analysis for monitoring responses in GIST is warranted. Clinical trial information: NCT01874665.

10518 **Poster Discussion Session; Displayed in Poster Session (Board #162), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

Plasma sequencing to detect a multitude of secondary KIT resistance mutations in metastatic gastrointestinal stromal tumors (GIST). *First Author: Sebastian Bauer, Universitaetsklinikum Essen-Innere Medizin-Essen, Essen, Germany*

Background: Resistance to kinase inhibitors is associated with a marked genomic heterogeneity of secondary mutations of KIT in metastatic GIST which is poorly represented in single tumor biopsies. We sought to evaluate plasma sequencing (plasma seq) as a novel approach to detect or monitor the spectrum of resistance mutations in GIST. **Methods:** We prospectively collected 30 plasma samples from 22 patients with metastatic GIST (incl. corresponding tumor from same time point: n = 13; median pretreatment: n = 2). Circulating free DNA (cf DNA) and tumor DNA were sequenced on an Illumina MiSeq platform using a custom designed targeted sequencing panel. Mutations with a percentage < 0.5% of total reads were excluded. **Results:** We detected 87 non-synonymous KIT mutations in plasma samples with various percentages of total reads (0.5-20% of cf-DNA). Primary mutations were found in 41% (all matching the tumor analysis), resistance mutations were seen in 86% of pts including patients responding to imatinib. Mutations in exon 17 were the most common resistance mutations. Resistance mutations detected in tumor samples were infrequently matched by plasma DNA. Notably, p53 mutations were detected in 77%, mutations of RAS or RAF in 59% of patients albeit at low levels. A comparator group of 19 plasma samples from pts with NSCLC harboured 6 low level KIT mutations at levels of 0.9% fc-DNA (median). Extended storage time, high storage temperature and mechanical stress negatively impacted the purity of cf-DNA. **Conclusions:** Plasma seq in pts with metastatic GIST detects a multitude of resistance mutations of KIT and other genes. Future validations should incorporate comprehensive sequencing of corresponding tumor tissue. Handling of plasma samples should be standardized in order to maximize the yield of mutant DNA. The clinical value of plasma seq should be tested in randomized trials.

10519 **Poster Discussion Session; Displayed in Poster Session (Board #163), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:30 PM-5:45 PM**

An NGS assay strategy with FFPE and cfDNA to determine primary and secondary mutations across the initial diagnosis and subsequent recurrence/progression of patients with localized, recurrent and metastatic GIST. *First Author: Nagavalli Somasundaram, National Cancer Centre, Singapore, Singapore*

Background: Primary and secondary mutations in GIST affect prognosis and treatment response and impacts treatment decision making. A single driver mutation (primary) is found amongst exons of KIT, PDGFRA and less commonly BRAF, KRAS and NRAS. Sequencing multiple genes may be required to determine the primary mutation and the amount of FFPE diagnostic biopsy material can be limiting. Upon disease progression on Imatinib, 1 or more secondary mutations in exons 13,14,15,17 or 18 in KIT can simultaneously develop, affecting response to subsequent therapy. Determining the secondary mutations at progression is limited by the need to test several possible mutations, small sample amount and sampling error from inter and intra-lesional heterogeneity. **Methods:** We developed a strategy employing next generation sequencing (NGS) tools on FFPE and cfDNA. Tumor FFPE and blood (plasma) samples from GIST patients and subjects without GIST were obtained, the latter as negative controls and serial spike-in analytical titrations. DNA from Fresh Frozen Tumor samples, where available were also obtained. **Results:** Initial FFPE samples and subsequent blood (plasma) samples were obtained from a cohort of 96 patients with localized or metastatic GIST and 24 control (non-GIST) patients. Primary mutations are determined from FFPE material and secondary mutations from plasma material. From 100ng of DNA in a multiplexed targeted NGS panel, we can determine the primary mutations from exons 9 and 11 of KIT and exons 12,14 and 18 of PDGFRA, exon 15 of BRAF and exons 2,3,4 of KRAS and NRAS simultaneously. From plasma, using just 10 ng of cfDNA, we are able to simultaneously determine the presence or absence of secondary mutations across exons 13,14,15,17 and 18 of KIT down to a variant allele frequency of 0.1%. **Conclusions:** We have developed a clinically deployable NGS assay strategy to determine primary and secondary mutations across the initial diagnosis and subsequent recurrence/progression of patients with localized, recurrent and metastatic GIST.

10520 Poster Session (Board #164), Sun, 8:00 AM-11:30 AM

A phase II trial of sorafenib (SO) in advanced chordoma patients (pt). *First Author: Eric Amela, Centre Oscar Lambret, Lille, France*

Background: To report in a hypothesis-generating phase II study the activity and safety of SO in advanced chordomas. **Methods:** Pts received SO 800 mg/d until progression, intolerance or up to 9 months (mo) and intolerance. The primary endpoint was progression-free survival according to RECIST 1.1. Secondary end-points were RR, OS and toxicity. **Results:** From 07/2011 to 01/2014, 27 pts were enrolled (median age 64, range 30-86), including 17 men and 10 women. The primary tumor locations were sacrum (21, 77.7%), rachis (4, 14.8%) and clivus (3, 11.1%). Metastasis was present in 14 pts (58.3%). Twenty-six pts (96.3%) had received prior treatment, including surgery (18, 66.7%), radiotherapy (18, 66.7%) and prior systemic therapies (MTT; 12, 44.4%; median number of lines 1, range 1-3). The duration of SO treatment was 4.9 months (range, 0.5-10.1). The median relative dose-intensity was 1 (range, 0.43-1). Because of toxicity, treatment was temporarily discontinued for 11 pts (40.7%) and dose-reduction was necessary in 10 cases (37.0%) A 6 mo, we have observed 1 delayed RECIST-based partial response confirmed at 9 mo. The median follow-up was 8.7 mo (1.2-31.0 mo). The 12 month-PFS rate was 57.4% (95CI 34.7-74.7) in the whole population, and 63.6% (32.7-83.3) and 47.1% (15.2-74.1) in pts naïve to and those previously treated by MTT, respectively. The 12 month-OS rate was 86.5% (55.8-96.5). Three (11.1%) and 14 (51.8%) pts experienced grade (Gr) 4 and Gr 3 toxicities. The Gr 4 toxicities were thyrotoxicosis (1 case), skin toxicity (1 case) and arterial hypertension (1 case). The most common Gr 3 toxicities were arterial hypertension (5), skin toxicity (5) and diarrhea (5, 18.5%). One keratoacanthoma occurred during follow-up. **Conclusions:** This trial showed a promising activity of SO in advanced chordoma. Further clinical explorations (e.g. randomization trial with discontinuation design) are warranted. Clinical trial information: 2009-017020-59.

10521 Poster Session (Board #165), Sun, 8:00 AM-11:30 AM

Patient-reported outcome instruments meaningful and relevant for tenosynovial giant cell tumor (TGCT): A qualitative study. *First Author: Heather Gelhorn, Evidera, Bethesda, MD*

Background: Tenosynovial giant cell tumor (TGCT), a rare locally aggressive neoplasm of the synovium of joints and tendon sheaths, is associated with inflammation, pain and swelling in part due to CSF1R-bearing macrophages recruited to the tumor by genetic elevation of CSF1 activity. Most common treatment is surgery; pharmacological treatments are in development. Patient Reported Outcome (PRO) instruments are potential critical endpoints to demonstrate treatment benefit in clinical trials. Symptoms and other PROs meaningful to TGCT patients have not been formally researched, and instruments to evaluate such outcomes do not exist. **Methods:** PRO instruments of potential relevance were evaluated by literature review and by clinical and PRO experts. TGCT patients were recruited through clinical sites and the internet for participation in qualitative research interviews to identify predominant symptoms and to test relevance and content validity of selected PRO measures. **Results:** 22 subjects participated: 73% female, mean age 42.5 (range 27-56); 19 (86%) diffuse, 3 (14%) localized TGCT; 50% prior surgery. Tumors were located in knee (n = 15), hip (n = 3), ankle (n = 2), elbow (n = 1), forearm (n = 1). Most common symptoms cited were pain (82%), stiffness (73%), swelling (86%), reduced range of motion (64%) and joint instability (64%), which were consistent with clinical expert input and with instruments chosen by PRO experts. The Brief Pain Inventory (BPI) worst pain numeric rating scale (NRS), PROMIS physical functioning items and WOMAC items identified from the literature, as well as a worst stiffness NRS developed for TGCT, were confirmed as meaningful measures of TGCT patient symptoms and were well understood in qualitative interviews. These measures are currently being piloted in an ongoing Ph1 clinical trial of PLX3397, a small molecule inhibitor of CSF1 receptor kinase, in TGCT (NCT01004861). **Conclusions:** Pain, stiffness and physical functioning are important treatment outcomes in TGCT patients. We have identified potentially reliable and valid PRO measures of these concepts, which are being tested in phase I and will be further evaluated in a phase III TGCT clinical trial with PLX3397. Clinical trial information: NCT01004861.

10522 Poster Session (Board #166), Sun, 8:00 AM-11:30 AM

Pilot trial of vigil immunotherapy in Ewing's sarcoma. *First Author: Maurizio Ghisoli, Mary Crowley Cancer Research Centers, Dallas, TX*

Background: Ewing's sarcoma is the second most common primary bone malignancy in children and adolescents. While front-line intensive multimodality treatment significantly improves survival in first line treatment, the prognosis for metastatic patients with either disease relapse within two years of initial therapy or initially resistant to chemotherapy is very poor with few long-term survivors and 1-year survival generally less than 20%. **Methods:** We implemented a Phase I trial of 12 metastatic Ewing's sarcoma patients who were either multiply recurrent (n = 11) or had failed frontline treatment within 2 years (n = 1). Patients received Vigil (previously called FANG) vaccine dosed between $1x10^6$, $4x10^6$, $1x10^7$ or $2.5x10^7$cells/intradermal injection/month for ≥ 4 months. Vigil is comprised of irradiated autologous tumor transfected with a dual DNA plasmid expressive of GMCSF and bi-shRNA furin components. Knockdown of furin down regulates both downstream TGFβ1 and TGFβ2 expression. Safety and clinical responses were monitored. Patient immune responsiveness to unmodified tumor cells was assessed by sequential IFNγ-ELISPOT assay using whole blood mononuclear samples starting at baseline (pre-treatment) and sequentially after treatment. **Results:** None of the 12 patients (47 vaccinations) developed Grade 2/3/4 drug related toxicity. Median product release GMCSF expression was 1858 pg/10^6 cells; median knockdown of TGFβ1 and TGFβ2 was 100% and 99%, respectively. Eight patients have been sequentially assessed for circulating mononuclear cell IFNγ-ELISPOT response, all of whom were IFNγ-ELISPOT negative at baseline. In all eight, follow up IFNγ-ELISPOT at month 1 or month 4 (one patient) post-Vigil converted to positive (> 10 spots/10^6cells and > 2x baseline). One patient achieved a partial tumor response (38% tumor reduction, RECIST 1.1). The estimated Kaplan-Meier median survival of these 12 patients at Year 1 was 75%. **Conclusions:** In this phase 1 study in patients with Ewing's sarcoma, Vigil immunotherapy was well tolerated, elicited a tumor-specific systemic immune response in all patients, and was associated with favorable 1-year survival. Further clinical testing is warranted. Clinical trial information: NCT01061840.

10523 Poster Session (Board #167), Sun, 8:00 AM-11:30 AM

Perioperative chemotherapy with cisplatin (CP) and doxorubicin (DOX) with and without high-dose methotrexate (HDM) in adult osteosarcoma (AOT): Is methotrexate warranted? *First Author: Lucila Soares Da Silva Rocha, Instituto Do Cancer Do Estado De Sao Paolo, Sao Paulo, SP, Brazil*

Background: treatment of AOT consists of perioperative chemotherapy and surgical resection. Standard chemotherapy in AOT consists of CP and DOX. Although considered standard of care in the pediatric population, the use of HDM remains controversial in adults. In addition, it is associated with greater toxicity rates, leading many specialized centers to drop it. This study aims to review treatment efficacy in localized AOT treated at our institution to ascertain the role of HDM in this disease. **Methods:** this retrospective study included consecutive patients with localized AOT treated at the Instituto do Cancer do Estado de São Paulo (ICESP) from 2008 to 2014 that received at least one perioperative chemotherapy cycle. Chemotherapy regimens consisted of DOX and CP (group 1). A subgroup of patients also received HDM (group 2). Analysis of overall survival (OS), disease free survival (DFS) and treatment toxicities were performed. **Results:** final analysis included 26 patients, 16 treated in group 1 and 10 in group 2. Most patients presented ECOG performance status 0-2 (93.8 and 80%) and lower extremity primary tumours (62.5 and 80.0%), for group 1 and group 2 respectively. Despite lower average age (35.0±12.1 and 18.9±2.1 y), group 2 presented more grade (G) 3/4 thrombocytopenia (0 and 15.8%) and G3/4 mucositis (0 and 21.1%), while group 1 presented more neutropenia G3/4 (46.6 and 26.3%). Both groups presented no G3/4 renal toxicities. Two grade 5 toxicities occurred in group 2 (bleeding and neutropenia), both after the first HDM cycle. Efficacy analysis revealed no difference in DFS (4.38±0.61 and 2.3±0.54y, p = 0.228) and OS between groups (4.70±0.56 and 2.52±0.57y, p = 0.107), with a trend to better outcomes in group 1. The 4-year OS was 65.6 and 32.8% for group 1 and 2 respectively. **Conclusions:** HDM chemotherapy was associated with greater severe and lethal toxicity when added to CP and DOX perioperative chemotherapy in AOT. In addition, it does not seem to impact on efficacy. This data does not support the use of HDM in the treatment of AOT.

10524 Poster Session (Board #168), Sun, 8:00 AM-11:30 AM

Prognostic relevance of miRNA let-7e in localized intestinal GIST: A Spanish Group for Research on Sarcoma (GEIS) Study. *First Author: Javier Martin Broto, Hospital Universitario Virgen del Rocio, Sevilla, Spain*

Background: Risk estimation of recurrence in localized GIST relies on factors as mitosis, size, site or capsule rupture. Recently, genotype has shown to add prognostic value at least in intermediate risk group. Nevertheless, there is a remarkable lack of molecular prognostic variables in localized GIST. We had previously performed miRNA arrays in a subset of localized intestinal GIST comparing relapsed vs no-relapsed patients. We identified let-7e (FC = – 1163.9; $p < 0.0001$) and miR-550 (FC = +204.2; $p < 0.0001$) as the most significantly downregulated and upregulated miRNAs respectively. Here we analyze the prognostic role of these miRNA in a validation set (VS) of intestinal GIST **Methods:** Selection criteria used for VS were intestinal GIST, R0 surgery, no tumor rupture, no adjuvant imatinib and size larger than 2 cm. RNA extraction was performed using the RecoverAll Total RNA Extraction kit (Ambion). The expression of miRNAs was determined by means qRT-PCR using specific Taq-Man probes. let-7e and miR-550 expression levels were categorized as above or below median values. Kaplan–Meier and log-rank test were the statistics used and relapse free survival (RFS) was the clinical endpoint **Results:** A subset of 112 patients was selected as VS, 23 of which were excluded (metastatic, tumor rupture, etc). Thus, 89 patients were selected, 58 of whom recurred after median follow of 117 months. Median of size and mitoses were 10 cm and 10 x50hpf. In univariate analyses, let-7e showed statistically significant difference in median of RFS: 26 (19.5-32.6) vs 50 (24.6-39.7) months for below and above median values respectively ($p = 0.011$). For miR-550 no significant differences were seen 35 vs 29 months ($p = 0.99$). Mitosis $\leq 5/ > 5$ with 162 vs 26 months ($p = 0.002$) and size $\leq 10/ > 10$ with 37 vs 29 months ($p = 0.05$) showed also prognostic relevance. In multivariate analysis, mitosis HR 2.7 (1.4-5.3; $p = 0.004$) and let-7e HR 2.1 (1.2-3.8, $p = 0.009$) were independent prognostic factors for RFS **Conclusions:** miRNA let 7-e has demonstrated to be a relevant prognostic factor for RFS in intestinal GIST patients and deserves to be explored for targeting purposes. A further analysis is planned in a larger series of GIST including also gastric cases

10525 Poster Session (Board #169), Sun, 8:00 AM-11:30 AM

Stem cell rescue from irradiation of multiple tumor sites combined with high-dose chemotherapy, followed by reduced intensity conditioning and allogeneic stem cell transplantation in patients with advanced pediatric sarcomas: Preliminary results of the MetaEICESS 2007 protocol. *First Author: Stefan Burdach, Technische Universität München, Munich, Germany*

Background: Advanced pediatric sarcomas are associated with poor prognosis. These truly rare diseases include Ewing's sarcomas (ES), metastatic to more than one bone or early relapse as well as stage IV rhabdomyosarcomas (RMS). We assessed toxicity, relapse free survival (RFS) and overall survival (OS) of advanced ES and RMS patients treated a single institution with the MetaEICESS 2007 protocol. **Methods:** From 2007 to 2015, 9 patients, 7 with ES ($\geq$ three bones/organs or marrow involved at diagnosis, $n = 4$ or relapse < 24 months after diagnosis, $n = 2$) and 2 with stage IV RMS patients were enrolled. The protocol comprised induction-chemotherapy, whole-body MRI/PET directed radiotherapy to the primary tumor and to all metastases, surgery, tandem high-dose chemotherapy with autologous rescue and allogeneic stem cell transplantation (allo-SCT). Data was censured on februay 1st 2015. Radiotherapy was delivered to the primary tumor ($n = 8$, total dose 50-60 Gy), to the lungs ($n = 4$, 15-18 Gy), and to lymph node and osseous metastases ($n = 3$ and $n = 7$, 45-50 Gy). Target volumes ranged from 453 – 9.407 cm^3 (median of 2.762 cm^3). One patient received proton, all others photon irradiation. **Results:** 5 patients are surviving in CR at a median of 27 months (range 0-62) after allo-SCT. Median RFS after allo-SCT was 17 months (range 0-62). 8 patients had reached complete remission (CR) before allo-SCT, three of whom relapsed thereafter, predominantly outside the radiotherapy treatment fields. 4 patients received donor lymphocyte infusions (DLI), of whom two patients showed clinical responses. One patient had to be retransplanted after initial graft rejection, 3 patients suffered ADV reactivation, 3 patients developed acute- and 1 patient chronic GvHD. **Conclusions:** The MetaEICESS 2007 protocol constitutes a feasible option for patients with advanced pediatric ES and RMS. A larger cohort is mandatory to verify OS or RFS improvement over current protocols.

10526 Poster Session (Board #170), Sun, 8:00 AM-11:30 AM

Prognostic factors analysis of extraskeletal osteosarcoma: Updated results of an EMSOS study. *First Author: Alessandra Longhi, Instituto Ortopedico Rizzoli, Bologna, Italy*

Background: Extra Skeletal Osteosarcoma (ESO) account 1% among soft tissue sarcomas. There is no agreement on the best strategy of treatment. **Methods:** An EMSOS collaborative study was performed and data of patients treated for an ESO at different EMSOS centers were collected. **Results:** 147 cases were evaluable. Median age was 53 years(13-84). There were 95 males, 52 females. 114 had localized disease and 32 were metastatic, 1 unknown. Median tumor size was 10 cm, median interval from symptoms onset to diagnosis was 4 months. Primary tumor site was lower limb in 73 patients , upper limb in 33 patients,12 were in viscera. 109/114 with localized disease had surgical resection of primary tumor , 80 had R0 resection, 23 R1, 6 unknown. Among 114 patients with localized disease 79 received chemotherapy: 61 received a bone osteosarcoma-like chemotherapy regimen and 12 a soft tissue sarcoma like regimen;6 unknown type . 34/114 patient with localized disease received RT. Median follow up for all patients was 30 months (1-384 ms), 87 patients were alive and 60 dead at last FUP; median follow up for 87 survivors patients was 51 ms (1-384ms).. 5yrs overall survival (OS) for all 147 was 55%, 62% for patients with localized disease and 28% for those with metastatic disease. Among 114 patients with localized disease, local relapse occurred in 29/114 (25%) , distant metastases in 41/114 (36%). In patients with localized disease the probability of 5-yr OS according to tumor and treatment variables is reported in the table below. **Conclusions:** 5yr OS and prognostic factors (age,size,margins,surgical remission) are similar to soft tissue sarcoma group. Only a positive trend was seen for chemotherapy at univariate analysis but not at multivariate analysis.

	5-yr OS	p-value
Age	71%	0.07
18-40 (23)	67%	
41-65 (59)	47%	
> 65 (24)	47%	
< 18 (8)		
Size	89%	0.0007
< 5cm (21)	69%	
5-10 cm (37)	42%	
> 10cm (42)		
Surgical CR	65%	0.0006
Yes (100)	37%	
No (13)		
Margins	71%	0.003
R0 (80)	57%	
R1 (23)	17%	
UK (6)		
Chemotherapy	69,5%	0.05
Yes(79)	45%	
No (35)		
Radiotherapy	62%	0.8
Yes (34)	64%	
No (79)		

10527 Poster Session (Board #171), Sun, 8:00 AM-11:30 AM

High dose ifosfamide in metastatic high-grade osteosarcoma, after failure of standard multimodal chemotherapy. *First Author: Emanuela Palmerini, Istituto Ortopedico Rizzoli, Bologna, Italy*

Background: Although there are many reports on post-relapse survival for osteosarcoma,studies on validated clinical outcome measures (progression-free survival at 6 months [6-mo PFS], complete response [CR], partial response [PR], stable disease [SD]) are lacking. We explored high dose ifosfamide (HDIFO) activity in patients (pts) with relapsed osteosarcoma. **Methods:** Pts progressing after standard treatment and with measurable disease were eligible. Treatment consisted of ifosfamide 3 gr/m^2/day, day 1–5, continuous infusion, every 21 days, until progression or unacceptable toxicity. Overall response rate (ORR: CR + PR), SD, 6-mo PFS, and overall survival (OS) were assessed. **Results:** Fifty-one pts were enrolled. Median age was 19 (7-68): 21 pts pediatric, 30 pts adult. Female/Male: 18/33. Forty-eight pts were ECOG 0, 3 pts ECOG 1. Line of treatment: 46 pts were in 1^{st}line; 5 pts in $\geq$ 2nd line. 32/51 had already been treated with lower doses of ifosfamide for the primary tumor. Pattern of metastases: 35 pts lung only, 13 multiple sites, 3 bone only. 23/51 patients underwent metastasectomy after HDIFO, achieving surgical complete remission (CR2). ORR: CR: 0/51, PR: 11/51 (22%); SD 28/51 (55%), progressive disease (PD) 12/51 (23%). Median duration of response was 6 months (range: 0-192 months). PRs were mainly observed in pediatric pts (9/21 [43%]) and in pts with lung only disease (9/35 [26%]). 6-mo PFS rate was 53%. 6-mo PFS was significantly better for pts receiving HDIFO in 1^{st}line (6-mo PFS: 1^{st}line 52% vs $\geq$ 2nd line 0%; $p= 0.04$), while there was no difference according to age, gender or pattern of metastases. 1- and 2-year OS were 60% and 31%, respectively, with increased survival for non-progressing pts (1-year OS: PD 25% vs SD 40% vs PR 45%; $p= 0.001$), and for pts undergoing metastasectomy (1-year OS: CR2 96% vs no CR2 33%, p 0.0001). **Conclusions:** HDIFO demonstrated activity in osteosarcoma, especially in 1^{st} line, pediatric pts and lung only disease. This series also confirms the important role of surgical complete remission in this subset of pts.

10528 Poster Session (Board #172), Sun, 8:00 AM-11:30 AM

Sustained response of complex giant cell tumors with denosumab: Single center 8-year experience. *First Author: Neal Shiv Chawla, Sarcoma Oncology Center, Santa Monica, CA*

Background: GCTB are aggressive osteolytic tumors, which are characterized by local bone destruction and soft tissue invasion. There have been limited non-surgical treatments, including radiation therapy. However, an unacceptable rate of post radiation sarcomas has been well established. Such tumors have osteoclast like giant cells/stromal cells that express surface RANK ligand. Denosumab is an FDA approved drug used in the treatment of unresectable GCTB or GCTB with severe morbidity related surgery. It is a monoclonal antibody that targets the RANK ligand characteristic to GCTB. We report our 8-year experience in the treatment of complex GCTB using denosumab. **Methods:** Review of 43 skeletally mature patients (N = 43) who were treated with subcutaneous (SC) denosumab for the treatment of GCTB, in whom surgery was not feasible without severe morbidity. Denosomab was dosed at 120 mg on days 1, 8, 15, 29, and every 4 weeks thereafter. CT, PET/CT, or MRI was used to determine radiographic disease burden, along with clinical examination assessing symptoms of disease and side effects of treatment. **Results:** Average best response per RECIST 1.0 criteria was stable disease. Patients received denosumab on average 159 weeks (range: 12 - 310 weeks), with few complications. 5% (2/43) of patients developed mandible infections, 7% (3/43) of patients developed osteonecrosis of the jaw (ONJ), and 2% (1/43) of patients developed an atypical traumatic fracture during treatment. Overall, as a treatment of GCTB, denosumab proved safe and efficacious over prolonged use, with very low rates of complications and a sustained disease response. **Conclusions:** This study represents the longest reported single center use of denosumab in the treatment of GCTB. Overall, it shows the safety and efficacy in the use of denosumab in the treatment of GCTB.

10529 Poster Session (Board #173), Sun, 8:00 AM-11:30 AM

Functional and clinical long-term outcome of Ewing sarcoma treatment*. *First Author: Andreas Ranft, Pediatric Hematology and Oncology, University Hospital, Muenster, Germany*

Background: Since 1980 patients with Ewing sarcoma have been treated according to consecutive protocols (CESS) of the German Society of Pediatric Oncology and Hematology (GPOH). Rising survival rates have raised the question of the quality of long-term survivorship. Objective and subjective measurement tools are used to evaluate the actual health status and daily-life activity level as an indicator for restitution of function. **Methods:** Long-term outcome of 603 survivors of the CESS 81, CESS 86, EICESS 92, and EURO-E.W.I.N.G. 99 trials, run by the GPOH, diagnosed between 1980 and 2009, was assessed by the Toronto Extremity Salvage Score (TESS), Short-Form Health Survey (SF-36), and Brief Symptom Inventory (BSI) questionnaire scales, and by the StepWatch Activity Monitor (SAM) accelerometer device. Prospective data were correlated retrospectively with standardized primary trial data. A 1:2 non-random peer control group was selected to compare results with healthy individuals. Median age of former patients was 28.7 years, 56% were males. Median observation time was 12.9 years (range 3.7-31.2). **Results:** Former patients were less active than the control group, contributing to a mean step count difference of 1758 steps per day (10394 vs. 12152; $p < .01$), but have reached the recommended level for an active life-style (> 10000). Negative prognostic factors were pelvic tumors (9265; $p < .01$) and primary metastatic disease (9322; $p < .05$). Correlations between self-reported scales and the step measurement were rather low ($r < .30$). The TESS score (> 90), BSI somatization, anxiety and depression scales (raw values < 0.50), and the SF-36 (Physical/Mental Component Summary scores = 47.9/49.7) showed no major clinical or functional limitations. Around 15% of former patients rated their health status as less good or poor compared to 2% of the controls. **Conclusions:** The present study comprised a follow-up period of up to 30 years after the treatment of Ewing sarcoma. Former patients seemed to return to a normal lifestyle with minor limitations. The outcome is an encouraging signal to patients with this severe disease. *supported by BMBF/DLR 01ER0807

10530 Poster Session (Board #174), Sun, 8:00 AM-11:30 AM

Phase II trial of gemcitabine plus rapamycin as second line in advanced osteosarcoma: A Spanish Group for Sarcoma Research (GEIS) Study. *First Author: Javier Martin Broto, Hospital Universitario Virgen del Rocio, Sevilla, Spain*

Background: There are few reports focusing on systemic treatment in osteosarcoma (OS) patients progressing after most active drugs. Preclinical data showed activity of rapamycin in xenograft murine models of OS and in a phase II trial testing m-TOR inhibitor; 4/5 partial responses were seen in OS patients. Likewise, gemcitabine exhibited some activity in retrospective series in OS. Additionally, our group had conducted a phase I trial with gemcitabine (G) plus rapamycin (R) in sarcomas with biological inhibition of m-TOR at recommended doses. All these together supported the design of a phase II trial in advanced progressing OS with G and R combination. **Methods:** Main endpoint was progression free survival rate (PFSR) at 4 months, defining P1 as 40% and P0 as 20%. A minimax Simon's two-stage design was applied with an estimation sample size of 33 evaluable patients. Most relevant inclusion criteria were as follows: Non-resectable locally advanced or metastatic disease; age 2-80 y; ECOG 0-2 and measurable progressing disease after receiving at least cisplatin, doxorubicin and methotrexate. The scheme consisted of G 800 mg/m2 i.v. d1 and 8 every 21 days administered at 10 mg/m2/min and R 5 mg/day p.o. **Results:** From September 2012 to November 2014, 36 patients were enrolled in 12 hospitals of GEIS network with a median age of 24 y (4-60). Two patients were non-eligible for this analysis (chondrosarcoma and early finish of trial drugs). Male/Female distribution was 21/15 and ECOG distribution was 30%, 58% and 12% for 0, 1 and 2 respectively. Overall, 115 cycles were administered with median follow-up for alive patients of 5 (1-17) months. Hematologic grade 3/4 toxicity was neutropenia 42%, thrombocytopenia 25%, anemia 14%, febrile neutropenia 8% and most relevant non-hematologic toxicity was fatigue 14% and transaminitis 5%. There were 2 (6%) PR, 13 (39%) SD and 18 (54%) PD. Regarding the main endpoint, PFSR at 4 months was 44% (27-61) and at 6 months was 28% (13-44). Median of PFS and OS were 2.3 months and 11.2 months respectively **Conclusions:** The trial met the PFSR expectations with low to mild toxicity and therefore deserves further investigation. Translational associated research is ongoing. Clinical trial information: 2012-001106-26.

10531 Poster Session (Board #175), Sun, 8:00 AM-11:30 AM

Clinical Characteristics and Treatment Outcomes of Clear Cell Chondrosarcomas: MD Anderson Cancer Center Series. *First Author: Anthony Paul Conley, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Clear cell chondrosarcomas (CChs) represent 2% of all chondrosarcomas and are defined by cells with abundant clear vacuolated cytoplasm surrounded by a cartilaginous matrix. Understanding clinical characteristics and treatment patterns may improve outcomes. We reviewed our institutional experience with this rare disease. **Methods:** With IRB-approval, CChs patients (pts) treated at MD Anderson Cancer Center from 1994 to 2013 were identified through Tumor Registry and Sarcoma Pathology Database. Descriptive statistics, survival analysis (RFS, OS), and Cox proportional hazards regression models were performed including Kaplan-Meier plots were provided for OS and RFS. All statistical analyses were performed using SAS 9.3 for Windows. **Results:** 15 pts were identified. Median age at diagnosis was 42 years (range 25 to 74 years). 80% were male. Ethnicity included Caucasians (12 pts; 80%), Asians (2 pts; 13%), and Hispanics (1 pt, 7%). The most common presenting symptom/sign was pain (10 pts; 67%) followed by fracture (3 pts; 20%). The most common site of disease was proximal humerus (7 pts; 47%). All pts had MSTS stage I disease. Primary therapy included radical resection in 12 (80%), curettage/resection in 1 (7%), and curettage in 2 (13%) pts. Of 12 pts, 11 had R0 resection. Median tumor size was 5 cm (range, 2.5 cm to 9.6 cm). Local relapse (LR) occurred in 4 (27%) pts; 1 also had distant relapse (DR). 2 pts had DR alone. DR sites included lungs, liver, and bone. 2 LR were associated with intra-lesional procedures, 1 LR with decompressive laminectomy, the LR+DR had fracture at diagnosis while 2 pts with DR occurred despite radical resection with R0 margins. 1 of 3 DR pts received systemic therapy. Median follow-up time from treatment was 55.1 months (range, 10.4 months to 202.1 months). Median RFS was 102.2 months with 95%CI (33.2 months to 200.2 months). Median OS was 185.8 months. Of 3 deaths only 1 was disease-specific. No significant predictors of RFS or OS were identified. **Conclusions:** CChs is a rare tumor for which complete surgical resection can be curative. Relapse may occur years later so long-term follow up is advised. Understanding predictors of metastasis may require a collaborative effort.

10532 Poster Session (Board #176), Sun, 8:00 AM-11:30 AM

Anti-tumor effects of dovitinib in patient-derived gastrointestinal stromal tumor (GIST) xenograft models. *First Author: Yemarshet Kelemework Gebreyohannes, Laboratory of Experimental Oncology, Department of Oncology, KU Leuven, and Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium*

Background: Advanced GIST is treated with the tyrosine kinase inhibitors imatinib, sunitinib and regorafenib, but the majority of patients develop heterogeneous resistance to these agents. In an attempt to overcome such resistance, we tested the efficacy of dovitinib which acts against VEGFR, FGFR, FLT3, PDGFRB and KIT, using patient-derived GIST xenograft models. **Methods:** NMRI *nu/nu* mice (n = 47) were transplanted bilaterally with the human GIST xenografts UZLX-GIST2 (*KIT* p.A502_Y503dup) or -GIST9 (*KIT* p.P577del+p.W557LfsX5+p.D820G) and were treated in 4 cohorts: control (untreated), imatinib (50 mg/kg/bid p.o.), imatinib (100 mg/kg/bid p.o.) and dovitinib (30 mg/kg/qd p.o.). Efficacy was assessed by tumor volume measurement (3x/week), histopathology, immunohistochemistry [Ki67, phospho-Histone H3 (pHH3), cleaved PARP] and Western blotting analysis of KIT signaling. Histologic response (HR) was graded according to Antonescu et al. *Clin Cancer Res* 2005; 11:4182-90. Microvascular density (MVD) was assessed by counting CD31 positive vessels. Mann Whitney U test was used for statistical analysis. **Results:** After three weeks of treatment, dovitinib caused tumor volume reduction (to 37% of baseline) in UZLX-GIST2 and disease stabilization in -GIST9. It induced grade 2-3 HR in $>$ 50% of tumors in both models. Compared to control, dovitinib reduced mitotic activity by 22.6 fold ($p < 0.0001$) in UZLX-GIST2, whereas no significant difference was observed in the other model. Results were confirmed by pHH3 and Ki67 stainings. Apoptotic activity was decreased in dovitinib treated UZLX-GIST2 tumors compared to control. MVD was reduced in both UZLX-GIST2 (1.6 fold; $p < 0.05$) and -GIST9 (1.3 fold; $p = 0.059$) under dovitinib. Furthermore, it partially inhibited KIT, AKT and 4EBP-1 phosphorylation in UZLX-GIST2. **Conclusions:** Dovitinib showed anti-tumor efficacy in GIST xenograft models, with more pronounced effects in *KIT* exon 9 mutant disease. The decrease in MVD in both models suggested that the anti-tumor effects were at least partially mediated by the anti-angiogenic capacity of dovitinib. These results support ongoing and planned GIST trials (NCT01478373, 02268435, 01440959 and 01831726).

10533 Poster Session (Board #177), Sun, 8:00 AM-11:30 AM

ReGISTry Study of High Risk GIST Patients After Complete Resection:The adjuvant therapy and pathological diagnosis in Japan. *First Author: Toshirou Nishida, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Although three-year imatinib adjuvant therapy is recommended by GIST guidelines, there is a lack of clinical data regarding use of adjuvant therapy, adherence, and indications. A prospective registry study for high-risk GIST progressing in Japan examined reality of adjuvant in clinical practice. **Methods:** Between Dec. 2012 and Dec. 2014, 398 pts with histologically-confirmed high-risk GIST in local site were registered. There were 214 males and 184 females with median age of 64 yrs. In the central, H&E, immunohistochemistry, and genotyping were done. **Results:** Disease was located in the stomach (n = 238), small intestine (n = 122), large intestine (n = 26), or others (n = 12). Median tumor size was 8.0 cm and median mitosis (local pathology) was 10/50HPF. Tumor rupture was seen in 52 pts (13%) and 49 pts had received neoadjuvant therapy. After surgery, adjuvant therapy was administered for 304 pts (76%) and withheld for 82 pts (21%). PS of pts with adjuvant therapy was 0 (258 pts), 1 (37 pts) and $>$ 2 (2 pts). Tumor cell type included spindle (n = 327), epithelioid (n = 14) and mixed (n = 33) histology by pathological test at each hospital. Central pathological review was done for 272 pts: KIT was positive in 263 pts (97%), DOG1 in 262 pts (96%), and CD34 in 228 pts (84%). Mutations were analyzed in 260 pts including 209 KIT exon 11 mutations, 15 KIT exon 9 mutations, 8 other KIT mutations, 10 PDGFRA exon18 mutations, 1 PDGFRA exon 12 mutations, and 6 wild type GISTs. Although KIT immunoreactivity was consistent between central and local (concordance = 92%), CD34 immunoreactivity showed lower concordance (76%) and 10 pts (3.7%) were diagnosed as non-GIST in the central review. There was significant correlation between local and central mitotic counts, but median mitotic count by central review (5/50 HPF) was significantly lower than local values, which resulted in 46 pts (18%) was not diagnosed as high-risk in central. **Conclusions:** Adjuvant imatinib was used for 76% of high risk GIST pts locally diagnosed. There are some disparities in the pathological review of high risk GIST between local and central pathologists, which may indicate requirement of improvement in pathological concordance of GIST. Clinical trial information: UMIN000009531.

10534 Poster Session (Board #178), Sun, 8:00 AM-11:30 AM

Selective indications of surgery in esophageal gastrointestinal stromal tumors: A retrospective study of the French Sarcoma Group (FSG). *First Author: Florence Duffaud, La Timone University Hospital, Marseilles, France*

Background: Esophageal GIST (ESOGIST) are rare tumors, accounting for less than 1% of all GISTs, requiring special consideration regarding evaluation, diagnosis, perioperative treatment and conduct of operation. **Methods:** Through a national multicenter retrospective study in the FSG, 17 patients (pts) with localized ESOGIST were identified between 2000 and 2014 in 9 FSG centers. **Results:** Characteristics of pts were: 11 females, 6 males, median age of 69 years (36-81). Weight loss (n = 6), dysphagia (n = 5) were the most common symptoms. Eight (47%) tumors (T) occurred in the lower third of the esophagus, 5 (29%) in the gastro-oesophageal junction, 2 in the superior third, and 2 in the middle third. All pts underwent oesophagoscopy and/or endoscopic ultrasound (EUS) and CT scan. 15 had a pretherapeutic biopsy guided by EUS. Median T size was 70 mm (3-150). Nine pts received imatinib (IM) therapy as 1st treatment resulting in 6 PR, 3 SD, and permitting T resection in one. Tumors were resected in 8 (47%) pts, 7 upfront, one after IM; with enucleation in 4 [median size 4 cm (3-7)], oesophagectomy in 4 [median size 10 cm (0.5-15)]. Resections were R0 in 2, R1 in 6 pts. 9 pts were not operated (4 with age $>$ 75 and multiple co-morbities, 4 due to advanced T, 1 still on neoadjuvant IM). One patient was never treated. T characteristics were: KIT+ (n = 15), CD34+ (n = 8), mitoses/50 HPF $\leq$ 5 (n = 2), mitoses /50 HPF $>$ 5 (n = 6), and mitoses count unknown for 9. Mutations were documented in 11/17 cases, usually in KIT exon 11 (82%). Five pts received adjuvant IM. With a median follow-up of 19 months (7-99), 12 pts are alive, 5 died (4 due to other cause). Two pts relapsed after enucleation, with metastases in one. Among 12 pts alive, 5 are in CR, 7 with measurable disease (4 in PR, 3 with SD) still on IM for 5, on other TKI for 1, and 1 never treated. **Conclusions:** ESOGIST must be differentiated from leiomyoma and can be reliably identified pre-operatively by EUS-guided biopsy. Surgery for ESOGIST is either enucleation or oesophagectomy depending on tumor size**.** Preoperative IM therapy may improve resectability and is an efficient alternative when surgery is contraindicated

10535 Poster Session (Board #179), Sun, 8:00 AM-11:30 AM

Ponatinib efficacy and safety in patients (pts) with advanced gastrointestinal stromal tumors (GIST) after tyrosine kinase inhibitor (TKI) failure: Results from a phase 2 study. *First Author: Michael C. Heinrich, Knight Cancer Institute and Portland VA Medical Center, Oregon Health & Science University, Portland, OR*

Background: The oral TKI ponatinib has potent pre-clinical activity against mutant KIT and PDGFRA, including clinically relevant mutants resistant to available TKIs. We hypothesized that ponatinib might be effective in GIST after prior TKI treatment failure. **Methods:** This phase 2, single-arm study (NCT01874665) evaluated efficacy and safety of ponatinib 45 mg qd in advanced GIST after TKI failure; N = 45. Cohorts were enrolled based on presence (A) or absence (B) of *KIT* exon 11 mutations. Primary endpoint is clinical benefit rate (CBR = CR + PR + SD) at 16 wk by modified RECIST 1.1 in Cohort A. Secondary endpoints include CBR (Cohort B and overall) and objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Due to arterial occlusive events in other ponatinib trials, enrollment criteria were revised in early 2014 to include only pts in whom all 3 TKIs approved for GIST had failed. **Results:** Enrollment is complete (Cohort A, 30 pts; B, 15 pts). Median age was 59 y. Most pts (76%) received $\geq$4 anticancer regimens; 36% received 2 and 58% received 3 approved TKIs. Median time since diagnosis was 6 y. At 10-mo median follow-up (data as of Dec 1, 2014), 9 pts were ongoing; 15 discontinued for progressive disease per RECIST, 9 for AEs, and 12 for other reasons. Cohort A CBR was 37% (10/27); ORR 7% (2/27). Best responses: PR 2; SD 16. Median PFS/OS: 4.3 mo/15.0 mo. Cohort B CBR was 14% (2/14); ORR 0%. Best response: SD 6. Median PFS/OS: 2.0 mo/13.5 mo. Treatment-emergent AEs (TEAEs) in $\geq$40% of pts: rash 58%; fatigue 51%; constipation 42%; headache 42%; myalgia 40%. Myocardial ischemia, cerebrovascular accident, peripheral artery stenosis, deep vein thrombosis, and pulmonary embolism occurred in 1 pt each; 4 pts had evidence of ventricular dysfunction. Serious TEAEs (other than disease progression) in $\geq$2 pts: abdominal pain 9%; pneumonia 7%; fatigue, nausea, small intestinal obstruction, vomiting, 4% each. Two deaths, from pneumonia and pulmonary embolism, were considered possibly ponatinib-related. **Conclusions:** Ponatinib has clinical activity in advanced GIST pts after TKI failure, particularly pts with *KIT* exon 11 mutations. Clinical trial information: NCT01874665.

10536 Poster Session (Board #180), Sun, 8:00 AM-11:30 AM

Clinicopathological impact of protein phosphatase 2, regulatory subunit A, alpha mutations in gastrointestinal stromal tumors. *First Author: Midori Ishii, Department of Orthopaedic Surgery, Juntendo University School of Medicine, Tokyo, Japan*

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in gastrointestinal tract. Approximately 85-90% of GISTs are harboring oncogenic mutations in *KIT* or *PDGFRA*, and the tyrosine kinase inhibitor (TKI) drastically improved the prognosis of GISTs patients. On the other hand, a subset of GISTs acquire secondary resistance to TKI or show primary resistance to TKIs. Recent studies report that the disorder of the protein phosphatase 2, regulatory subunit A, alpha (*PPP2R1A*) is responsible for the constitutive phosphorylation of its substrates including TKs, and the constitutive phosphorylation of TKs plays an important role in the tumorgenesis and the progression of ovarian and uterine carcinomas. The aim of this study was to elucidate the frequency of *PPP2R1A* mutations and their impact on the clinicopathological factors in GISTs. **Methods:** Ninety-six cases of GISTs (formalin-fixed paraffin-embedded material) with prognostic information were collected. These cases were examined for *PPP2R1A* mutations (exon 5 and 6) by PCR followed by direct sequences, and the impacts of *PPP2R1A* mutations on the clinicopathological features were examined. In addition, *PPP2R1A* mutated GISTs were also examined for the mutation status of *KIT, PDGFRA* and *KRAS*. **Results:** Seventeen cases (17.7%) of GISTs harbored mutations in *PPP2R1A*, and types of mutations were various. Among 17 cases, 15 cases (88.2%) harbored either *KIT* or *PDGFRA* mutations, and one case had point mutations in both *KIT* and *PDGFRA*. Among two cases of *KIT/PDGFRA* mutation-negative GISTs, one cases showed *KRAS* mutation. GIST cases with *PPP2R1A* mutations had a tendency for shorter disease free survival (DFS) and overall survival (OS) rate, respectively ($p < 0.05$; DFS, $p < 0.05$; OS). **Conclusions:** These results suggest that *PPP2R1A* mutations play an important role in the tumor progression of GISTs. The effect of *PPP2R1A* alterations on the phosphorylation status of TKs including KIT and PDGFRA are under evaluation.

10537 Poster Session (Board #181), Sun, 8:00 AM-11:30 AM

Adjuvant imatinib (IM) for patients (pts) with primary gastrointestinal stromal tumor (GIST) at significant risk of recurrence: PERSIST-5 planned 3-year interim analysis. *First Author: Chandrajit P. Raut, Division of Surgical Oncology, Brigham and Women's Hospital, Boston, MA*

Background: Adjuvant IM treatment improves survival in pts with primary GIST with significant risk of recurrence. However, optimal treatment duration has not been determined. The ongoing PERSIST-5 trial is evaluating 5 years of adjuvant IM treatment. **Methods:** Beginning in 2009, this single-arm trial has included pts at significant risk of recurrence, defined as either primary tumor $\geq$ 2 cm at any site and $\geq$ 5 mitoses/50 high-power fields or nongastric primary GIST $\geq$ 5 cm. After complete resection of primary KIT+ GIST, pts received IM 400 mg/day for 5 y or until progression, relapse, or intolerance. The primary endpoint was recurrence-free survival (RFS). We report data from a planned 3-y interim analysis. **Results:** Of 91 eligible pts (median age 60 y; range, 30-90 y), median tumor size was 6.5 cm (range, 2.3-30.0 cm), 55% had gastric GIST, and 99% underwent R0 resection. In 85 evaluable pts, the most common GIST genotypes were *KIT* exon 11 (68%) and *PDGFRA* exon 18 (9%). Median time from resection to first IM dose was 9.6 wk (range, 3.1-12.3 wk).As of the data cutoff (May 9, 2014), median treatment duration was 34.2 mo (range, 0.5-55.8 mo). Overall, 4 pts (4%) recurred. There was 1 death; this pt had an IM-resistant *PDGFRA* D842V mutation. No pts without this resistant mutation who stayed on IM recurred. All 3 surviving pts who recurred discontinued (D/C) IM prior to recurrence (range, 7.3-23.1 mo between D/C and recurrence). The most common reasons for D/C (n = 33) were adverse events (AEs; n = 13) or consent withdrawal (n = 13). Grade 3/4 AEs leading to D/C were elevated liver enzymes, alveolitis, and renal cell carcinoma (n = 1 each). The most common AEs were nausea (67%), diarrhea (53%), and fatigue (44%). Dose reduction, occurring in 31 pts (34%), was most frequently due to AEs (n = 22), most commonly neutropenia, nausea, and hypophosphatemia (n = 3 each). **Conclusions:** Adjuvant IM was associated with high rates of survival and RFS.Most recurrences occurred after IM D/C. Data support 3 y of adjuvant IM for higher-risk pts. Additional follow-up will evaluate whether longer treatment improves outcomes. Clinical trial information: NCT00867113.

10538 Poster Session (Board #182), Sun, 8:00 AM-11:30 AM

Treatment of advanced gastrointestinal stromal tumors (GIST): Are results of second-line sunitinib therapy related to duration of response of first-line imatinib? *First Author: Daniela Katz, Hadassah Medical Center, Jerusalem, Israel*

Background: Imatinib (IM) revolutionized the outcome of patients with advanced GISTs; however, disease progression eventually occurs due to IM resistance or intolerance. Sunitinib (SU) is an oral multi-targeted tyrosine kinase inhibitor, approved for second line treatment of advanced GIST after IM failure. Clinical trials have shown that clinical activity of SU after IM failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases. However, since mutational status is not mandatory in the workup of GIST patients, it is difficult to predict response to second line SU. The aim of this study was to explore whether results of SU therapy after IM failure, might be related to the duration of IM treatment. **Methods:** All patients with advanced GIST that are insured by Clalit Health Services, Israel's largest health-care organization were identified. Only patients, who progressed on second-line SU, after receiving IM as first-line therapy, were included. Last date of patient recruitment was Dec 31, 2014. A linear regression model was used to identify the relation between first-line IM duration of response (the independent variable) and duration of response of second line SU. **Results:** We identified 31 consecutive patients with advanced GIST treated with IM and SU, consequently. There were 18 male and 13 female patients, with median age at the start of SU therapy 63.5 years (range: 34-85). Only 7% of patients (n = 3) received adjuvant IM therapy, prior to their metastatic disease. Median duration of response was 25.8 months (2.3-67.4) for IM and 5.2 months (0.8-32.7) for SU. The linear model predicted duration of second-line SU therapy (Y) in relation to duration of IM first-line therapy (X) best with: $Y = 2.36+0.282X$, ($R^2 = 20.6\%$, $p < 0.01$). **Conclusions:** In our study, results of SU therapy in advanced GIST patients were found to positively relate with the duration of first line IM treatment. This relation may serve as a handy estimate for SU duration in the clinic. However, further studies in wider cohorts of patients are needed to confirm this observation.

10539 Poster Session (Board #183), Sun, 8:00 AM-11:30 AM

Identification of therapy options for rare and resistant gastrointestinal stromal tumors (GIST). *First Author: Rebecca Feldman, Caris Life Sciences, Phoenix, AZ*

Background: GISTs are predominantly defined by KIT/PDGFRA mutations which are targetable with a range of kinase inhibitors, however the majority become TKI-resistant (TKI-R). Double (KIT/PDGFRA) wildtype (D-WT) GISTs represent a rare subset of GIST patients in need of treatment options. We investigated a commercial database of theranostic biomarkers for the identification of novel therapy options for GIST. **Methods:** 217 GIST cases were evaluated for D-WT and TKI-R. A multiplatform approach of biomarker testing was used and included a combination of sequencing (NGS, Sanger), protein expression (IHC) and gene amplification (ISH). **Results:** D-WT (n = 15) and TKI-R (n = 23) (including 7 with resistance mutations in the absence of a primary, activating KIT mutation and 4 PDGFRA D842V) were studied for additional targetable alterations. IHC and ISH tests revealed no overexpression or amplification in cMET, EGFR, or HER2. PTEN was intact (positive expression) in the majority of GISTs (92.9% (13/14) D-WT; 100% (19/19) TKI-R). Mutational screening revealed variants in 6/47 genes (excluding cKIT and PDGFRA), most of which are potentially targetable with therapies currently available, or in clinical trials: PIK3CA, ABL, cMET, JAK3, RB1, and VHL. ABL and JAK3 mutations were exclusively found in the TKI-R subgroup. PD-1 positive tumor infiltrating lymphocytes were found in 33% (1/3 D-WT) and 60% (3/5 TKI-R), while PD-L1 tumor expression was found in 67% (2/3 D-WT) and 40% (2/5 TKI-R). Although chemotherapy has historically elicited poor responses in GIST (non-selected patient trials), we observed a high frequency of low expression of predictive markers for gemcitabine (RRM1) and paclitaxel (TUBB3) (77%, 90%; 57%, 73% for D-WT and TKI-R, respectively) and high frequency of TOPO1 overexpression for irinotecan (57%, 32% in D-WT and TKI-R, respectively) which were recently shown to be cytotoxic in TKI-R GIST cell lines (Boichuk, 2014). **Conclusions:** A multiplatform approach of theranostic biomarkers identified non-cKIT/PDGFRA therapy options for rare and resistant GIST. Opportunities for investigating new targetable agents and potentially re-visiting cytotoxics with biomarker guidance in these subpopulations are warranted.

10540 Poster Session (Board #184), Sun, 8:00 AM-11:30 AM

Does aggressive local treatment have an impact on survival in children with metastatic rhabdomyosarcoma? *First Author: Myriam Weyl Ben Arush, Technion Faculty of Medicine, Haifa, Israel*

Background: Due to the extensive initial distant tumour spread in metastatic rhabdomyosarcoma, the importance of local treatment is sometimes underestimated. A retrospective study was conducted to identify the prognostic value of aggressive local treatment in paediatric metastatic rhabdomyosarcoma. **Methods:** Patients with metastatic rhabdomyosarcoma age 1 to 21 treated in France from 1998 to 2011 according to European protocols MMT-4-89, 4-91, 98 and recent national guidelines were selected. Survival comparison were performed between patients with "aggressive local treatment" (surgery and radiotherapy) and exclusive surgery or radiotherapy, after exclusion of patients with early progression. Endpoints were event-free and overall survival (OS). **Results:** A total of 101 children, median age 9 years, with majority of primaries in unfavourable sites (73 patients, pts), T2 tumours (66 pts), alveolar subtypes (65 pts) and large tumours (> 5cm, 83 pts) received various chemotherapy regimens. On univariate and multivariate analysis, OS was better after "aggressive local treatment" (49 pts; 44.3 ± 8%), than after exclusive surgery (10 pts; 18.8% ± 15.5%) or exclusive radiotherapy (29 pts; 16.1 ± 7.2%, $P < 0.006$). Moreover, OS was better in the case of surgery with complete resection (41.1 ± 10.2%) or microscopic residue (56.4 ± 14.9%) than macroscopic residue (20.0 ± 12.6%; $P < 0.03$). **Conclusions:** In this large retrospective analysis, OS appeared to be better for patients receiving "aggressive local treatment" even after adjustment for the initial patient and tumour characteristics. Isolated debulking surgery is associated with a very poor outcome and should be avoided. Aggressive local treatment in patients with rhabdomyosarcoma, even with metastasis, should be seriously considered.

10541 Poster Session (Board #185), Sun, 8:00 AM-11:30 AM

Combined sunitinib and IMRT for preoperative treatment of locally advanced soft tissue sarcoma: Results of a phase I trial of the German Interdisciplinary Sarcoma Group GISG 03. *First Author: Jens Jakob, University Medical Center Mannheim, Department of Surgery, Mannheim, Germany*

Background: Experimental data indicate that concurrent treatment with anti-angiogenic substances such as sunitinib improves the efficacy of irradiation. The aim of this phase I trial was to establish the safety profile and recommended dose of sunitinib combined with irradiation as preoperative treatment for soft tissue sarcomas. **Methods:** Patients with locally advanced, non-metastatic soft tissue sarcomas received sunitinib (orally, continuous dosing, 3+3 study design, dose level 1: 25 mg, dose level 2: 37.5 mg, NCT01498835) two weeks prior and during preoperative intensity modulated radiation therapy (25 x 1.8 Gy for retroperitoneal tumors, 28 x 1.8 Gy for extremity tumors). Surgery was performed 5 to 8 weeks after neoadjuvant treatment. Primary endpoint was the recommended dose for subsequent trials. Toxicity was scored according to CTCAE 4.0 criteria. Secondary endpoints were postoperative morbidity and treatment response. **Results:** Nine patients with a median age of 52 years were enrolled in dose level 1 (6/9) and 2 (3/9). Median tumor size was 11 cm. Tumors were located in the retroperitoneum (4/9), lower leg (3/9) or trunk (2/9). Most frequent toxicities of any grade were hematological (8/9), skin (6/9) and oral (5/9) toxicity. At dose level 1, 1/6 patients developed dose limiting grade 4 lymphopenia but recovered completely after discontinuation of sunitinib. At dose level 2, 0/3 patients developed dose limiting toxicity. 5/9 patients required dose adjustments due to toxicity. Skin toxicity within the radiation field did not exceed grade 2. All patients underwent tumor resection (8/9 R0 and 1/9 R1). 2/9 patients had postoperative complications requiring re-intervention. Treatment response according to RECIST was as follows: partial response 1/9, stable disease 7/9, progressive disease 1/9. Pathological examination revealed ≥ 95% tumor necrosis in 3/9 resected specimens. **Conclusions:** Combined preoperative treatment of extremity and retroperitoneal soft tissue sarcoma with irradiation and sunitinib is tolerable and warrants further investigation. The recommended dose of sunitinib for further testing is 37.5 mg. Clinical trial information: NCT01498835.

10542 Poster Session (Board #186), Sun, 8:00 AM-11:30 AM

Activity of crizotinib (C) in patients (pts) with clear cell sarcoma (CCSA) in EORTC phase II trial 90101 "CREATE". *First Author: Patrick Schoffski, University Hospitals Leuven, Leuven, Belgium*

Background: This phase II trial assesses the safety and activity of the ALK/MET inhibitor C in 6 different *ALK*- or *MET*-driven tumor types including CCSA, an orphan, treatment-refractory malignancy. The chimeric *EWS-ATF1* and *EWSR1/CREB1* fusion genes are hallmarks of CCSA and activate *MET* through the melanocyte master transcription factor. **Methods:** Pts with local diagnosis of advanced/metastatic CCSA consented for shipment of a non-returnable tumor tissue block and were screened for trial participation after central confirmation of the diagnosis and Vysis EWSR1 break apart FISH (Abbot Molecular). Eligible pts received C 250 mg twice daily p.o. A Simon's optimal two stage design was implemented independently in each disease-specific study cohort. If at least 2 out of the first 12 MET+, eligible and evaluable CCSA pts achieved a confirmed RECIST 1.1 PR or CR, a maximum of 35 pts were to be enrolled and treated to assess the activity of C, with no interruption of recruitment planned between the two stages. The abstract presents CCSA enrollment characteristics and activity according to the Simon's design stopping rule. Updated activity/safety results of the fully recruited cohort will be available at ASCO. **Results:** Between 01/2013 and 12/2014, 16 investigational sites in 8 European countries recruited 43 pts, of whom 32 had a centrally confirmed diagnosis of MET+ CCSA (tissue blocks available from 97.7% of pts). Central histological and molecular work-up took a mean lab turnaround time of 4 days (range, 2-10) after receipt of unstained slides. Among the first 12 eligible and evaluable MET+ cases, no RECIST responses were observed; best response was SD in 7 and PD in 5 pts. The mean duration of treatment was 6-7 cycles (range, 2-14; cycle length 3 weeks). **Conclusions:** EORTC is able to perform molecularly driven screening phase II trials in orphan malignancies with mandatory collection of tumor tissue and real time confirmation of diagnosis and genetic profiling. C did not meet prespecified response rates in MET+ CCSA, but achieved long-lasting disease control in a clinically relevant subset of pts, which prompted ongoing correlative studies using available tissue, genetic and clinical data. Clinical trial information: NCT01524926.

10543 Poster Session (Board #187), Sun, 8:00 AM-11:30 AM

High-risk soft tissue sarcoma of extremity and trunk wall: A retrospective comparison of local control in patients treated with or without radiation therapy at a single reference center. *First Author: Marco Fiore, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Wide resection plus RT has been considered in the past 3 decades standard treatment for high-risk STS of extremity and trunk wall. The potential for avoiding RT has been explored in limited groups of patients (pts), e.g. small STS. We retrospectively explored the role of RT in high-risk STS treated at a reference institution over a more recent time spam. **Methods:** Consecutive pts affected by primary, localized, extremity and trunk wall STS surgically treated between 2000 and 2012 were reviewed. All tumors were ≥ 5 cm, deep, and G2-G3 according to FNCLCC grade. Ewing/pPNET and pediatric STS were excluded. Two groups were identified: Group A, pts who received adjuvant/neoadjuvant RT; Group B, pts who did not. Local recurrence-free survival (LRFS) was analyzed. **Results:** Study population included 404 pts. Median follow up was 53 months for alive pts (IQR, 30-85). Median size was 10 cm. In Group A, 319 pts received RT (106 preoperative, 211 postoperative, 2 pre- and post). In Group B, 85 pts did not receive RT for individualized reasons. No significant differences were found between groups according to tumor size, age, sex, histotypes. Margins in Group A were R0/R1 in 252 (78.9%), and 67 (21%) cases, respectively; in Group B, 63 (74.1%) and 22 (25.9%), respectively (P value = .380). Group A and Group B were different for: G3 tumors (80.6% and 68.2%, respectively; P value = .0184); trunk tumors (7.5% and 20%, respectively; P value = .0013); (neo-)adjuvant chemotherapy (57.7% and 38.8%, respectively; P value = .002). Five-years LRFS was 83.91% in Group A, and 81.11% in Group B (P value = .1302). No differences in LRFS were found neither between R0 pts treated in Group A and B (P = .1417), nor between R1 pts treated in Group A and B (P = .6971). **Conclusions:** Local outcome of high-risk STS in pts individually treated without radiation therapy was not significantly different compared to those treated by surgery plus RT. Further studies are needed to investigate which subgroups of high-risk STS may benefit from surgery alone, possibly distinguishing between extremity and trunk sites, as well as between G2 and G3 tumors.

10544 Poster Session (Board #188), Sun, 8:00 AM-11:30 AM

Association of hematological toxicity (tox) and outcome to doxorubicin (DOX) in advanced soft tissue sarcoma (STS): A retrospective analysis of the EORTC-Soft Tissue and Bone Sarcoma Group database. *First Author: Stefan Sleijfer, Erasmus MC, Rotterdam, Netherlands*

Background: DOX pharmacokinetics vary substantially between patients leading to large differences in systemic drug levels. Given potential dose-effect relations, patients with the greatest tox may also have the best outcome. We assessed whether severity of hematological tox during treatment is associated with outcome in advanced STS patients treated with first-line DOX (monotherapy; 75 mg/m2 q 3 weeks). **Methods:** Worst tox (anaemia, leukopenia, neutropenia and thrombocytopenia) scored during treatment according to CTCAE v4.0 was included in this analysis. Differences in overall survival (OS), progression free survival (PFS) and response rate (RR) between patients with or without high haematological tox (grade 0-2 vs 3-4) were assessed using conventional statistical tests in landmarked subsets, to avoid bias from patients stopping treatment early. Potential confounders were collected including relative dose intensity (RDI), patients' and tumor characteristics. **Results:** In 557 patients eligible for this analysis, 32% were between 50-60 years, 51% female, 72% had a grade II/III tumor. Leiomyosarcoma (28%) and liposarcoma (15%) were the most common subtypes. 47.2% of the patients received at least 6 cycles of treatment; 45% stopped treatment early due to progression, 3% because of tox. RDI was constant over the cycles. During treatment, grades 3/4 anemia, leukopenia, neutropenia and thrombocytopenia were observed in 6.1%, 35.9%, 51.9%, and 1.6%, respectively. After cycle 1, grade 3 tox occurrence was constant over the diverse cycles, grade 4 tended to decrease after cycle 1 (21.0% at cycle 2, 12% at cycle 3). OS and PFS did not differ between patients experiencing high versus low tox at the end of cycles 1, 2 and 3. Also for RR, no association was seen with severity of haematological tox. **Conclusions:** In this large series, there was no association between outcome and haematological tox during DOX. This information may be useful to reassure advanced STS patients that failure to experience haematological tox during treatment does not equate to undertreatment.

10545 Poster Session (Board #189), Sun, 8:00 AM-11:30 AM

Metastatic soft tissue sarcoma, an analysis of systemic therapy and impact on survival. *First Author: Samuel John Harris, The Royal Marsden Hospital, London, United Kingdom*

Background: Patients (pts) with metastatic Soft Tissue Sarcoma (STS) are known to have poor outcomes with median overall survival (OS) reported to be circa 12 months. Recent publications have reported median OS circa18 months. We performed a retrospective analysis of all pts with metastatic STS treated at the Royal Marsden between 1991-2010 to examine OS trends. **Methods:** Adult pts with metastatic STS from 1991-2010 were studied, excluding pts with GIST, those referred for a second opinion or lost to follow-up within 2 months. Pts were grouped into time periods of 5 years: T1-T4. Pts were censored at 4 years from diagnosis. OS rates were calculated using Kaplan-Meier and log-rank tests. An univariate analysis of age, sex, systemic therapy, tumour grade, time to metastatic disease and histology was performed. **Results:** 2747 pts were identified: 54% female, 75% $<$ 65yrs, median age 53 yrs. Leiomyosarcoma was the commonest diagnosis: 28%; pleomorphic sarcoma: 9%; liposarcoma: 8%. Median OS was 17.5 months. The median OS of T1-T4 was 14.8, 17.9, 18.4 and 17.3 mths. The only significant difference was T1 to T3 ($p = 0.026$). Nearly 60% of pts in T1-T3 had $\geq$ 1 line systemic therapy, which fell to 50% in T4. The percentage of elderly pts increased from 18 to 31% in T4. Systemic therapy was associated with a highly statistically significant increase in median OS from 12.5 to 19.3 mths (HR 0.63 $p = 0.0003$). Higher grade, shorter time to metastatic disease (except if synchronous) and age $>$ 65 were associated with significantly poorer outcomes. Endometrial stromal sarcoma and low grade fibromyxoid sarcomas had the best outcomes, median OS $>$ 10 yrs. Pleomorphic sarcoma, angiosarcoma & sarcoma NOS had the worst outcomes, OS $<$ 12 mths. **Conclusions:** The median OS of 17.5 months was longer than previous estimates of circa 12 months, consistent with recent reports, and demonstrates improvement compared to the 1980's and early 1990's. However, no further improvements in OS were seen over the past 15 years, in part due to increasing numbers of elderly patients. Although subject to multiple biases, especially fitness for treatment, the substantial improvement in OS in patients receiving treatment is encouraging and may be evidence for a benefit from systemic therapy in patients with metastatic STS.

10546 Poster Session (Board #190), Sun, 8:00 AM-11:30 AM

Longer term cardiac safety of aldoxorubicin. *First Author: Sant P. Chawla, Sarcoma Oncology Center, Santa Monica, CA*

Background: Aldoxorubicin (6-maleimidocaproic acid hydrazide) is a novel prodrug of doxorubicin that binds to the thiol group of cysteine-34 amino acid in circulating albumin. The circulating albumin-drug conjugate preferentially accumulates within tumors, bypassing uptake by most normal tissues, including the heart, liver, kidneys and GI tract. Doxorubicin is released in the acidic tumor environment, either intra-or extra-cellularly, thus avoiding the cumulative toxicity that can occur with doxorubicin treatment. **Methods:** Aldoxorubicin has been investigated in clinical trials since 2011. We reviewed data on the cardiotoxicity of aldoxorubicin from 3 phase I studies and 1 phase IIb study (142 patients). Both MUGA and echocardiograms were administered at baseline then periodically thereafter (usually every 2 months) until either study withdrawal or death. All patients had normal cardiac function at baseline with LVEF $>$ 45% in some studies and 50% in others. Prior exposure up to 225 mg/m^{2}of doxorubicin was permitted. **Results:** The dose range of aldoxorubicin was 175-350 mg/m^2 administered i.v every 3 weeks (equivalent to 130-260 mg/m^2 doxorubicin per cycle). There were 126 evaluable patients who received 1-21 cycles of treatment. While 14% of patients demonstrated a $\geq$ 10% drop in LVEF, 21% had a $\geq$ increase in LVEF. No patient exhibited a decrease in LVEF that was below 50% of their institution's normal value. Where it was collected, 3.9% of patients exhibited QTc $>$ 500 msec. No patient had a clinically significant increase in troponin concentrations. Patients have received up to 5,439 mg/m^2 of doxorubicin equivalents, or 12 times the peak cumulative dose of standard doxorubicin, without any evidence of cardiotoxcity. **Conclusions:** Despite administering cumulative doses of over 1,500 mg/m^2 to the majority of the 126 evaluable patients in these clinical studies, aldoxorubicin has shown no evidence of cardiotoxicty, distinguishing it from doxorubicin itself.

10547 Poster Session (Board #191), Sun, 8:00 AM-11:30 AM

Surrogate properties of survival endpoints in metastatic soft-tissue sarcoma: A meta-analysis. *First Author: Marion Savina, INSERM U897 (Cancer Axis), ISPED, Bordeaux, France*

Background: Alternative endpoints to overall survival (OS) such as progresion-free survival (PFS), time-to-progression (TTP) or time-to-treatment failure (TTF) are increasingly used to assess treatment efficacy in randomized controlled trials (RCT) to reduce inclusions and trials' duration. Their properties in terms of surrogate markers need to be assessed to ensure that they can adequately replace OS. **Methods:** We conducted a literature review to summarize by cancer type studies evaluating surrogate endpoints for OS. In the absence of data for soft-tissue sarcoma (STS), we assessed surrogate properties for OS of PFS, TTP and TTF in advanced STS. We relied on a meta-analytical framework to estimate individual-level association (association between the candidate surrogate endpoint and OS) and trial-level association (association between the treatment effects on the candidate surrogate and on OS). Statistical methods included weighted linear regression (WLR) and the two-stage method introduced by Burzykowski et al., which relies on the joint modeling of 2 survival endpoints with a copula function and a regression model. **Results:** Individual data of 2020 patients from 10 European RCTs were analyzed. We censored OS at 2 years and PFS, TTP and TTF at 1 year. Regardless of the method, the highest individual-level association was observed for PFS ($R^2 = 0.62$ IC95% [0.27; 0.76]; Kendall's tau = 0.43 IC95% [0.40; 0.46]). Even if WLR suggested that PFS had the highest trial-level association, it was not significant for any of the two methods (WLR: $R^2 = 0.44$ IC95% [0.00; 0.69]; two-stage model: $R^2 = 0.01$ IC95% [-0.46; 0.48]). **Conclusions:** Out of the 3 endpoints, PFS had the best surrogate properties. Associations with OS were however moderate and cannot validate PFS as a surrogate for OS. This could be partly explained by a lack of precision due to our small sample size in terms of patients and trials. STS are rare tumors ($<$ 2% of all cancers) which explains the low number of available trials with usually smaller sample sizes compared to other cancers. We are however collecting additional trials to improve these estimations and complementary analyses are ongoing to validate our regression models on external data.

10548 Poster Session (Board #192), Sun, 8:00 AM-11:30 AM

Cost-effectiveness analysis of preoperative versus postoperative radiotherapy in resectable extremity soft tissue sarcoma. *First Author: Melody Xuan Lu Qu, Cancer Centre of South Eastern Ontario, Kingston, ON, Canada*

Background: Preoperative and postoperative radiotherapy (RT) for extremity soft tissue sarcoma (STS) have similar recurrence and overall survival outcomes. However, side effect profiles, costs and long-term functional outcomes are different. The aim of the study was to determine the optimal sequencing of RT in these patients through decision analysis. **Methods**: A cost-effectiveness analysis was conducted using a Markov model, with quality adjusted life years (QALYs) as the primary outcome. Utility values, rates of acute and chronic complications, transition probabilities and cost data were extracted from the published literature. Overall and progression free outcomes were internally validated. One-way and two-way sensitivity analyses were performed to determine the thresholds at which each strategy would be preferred. Probabilistic sensitivity analysis was performed for complication rates and costs to assess the robustness of this model. The time horizon was 5 years with a cycle length of 3 months. QALYs and costs were discounted at a rate of 3%. **Results**: Preoperative RT is a more cost effective strategy ($9,760/QALY) when compared to postoperative RT ($11,752/QALY). Preoperative RT is the preferred strategy for all acute wound complication rates tested on one-way sensitivity analysis. Postoperative RT is the preferred strategy when chronic complications with this modality is less than 17%, or when the rate seen in preoperative RT is greater than 61%. On probabilistic sensitivity analysis, preoperative RT is the preferred strategy in 75% of cases at a willingness to pay threshold of $50,000. **Conclusions**: Our model suggests that preoperative RT is more cost-effective than postoperative RT in the management of resectable extremity STS, primarily due to the lower incidence of chronic wound complications.

10549 Poster Session (Board #193), Sun, 8:00 AM-11:30 AM

Epidemiology, treatment (tx) patterns and outcomes in Asian soft tissue sarcoma (STS) patients: Results from the Soft Tissue Sarcoma in the Asia Pacific Region (STAR) study. *First Author: Richard Hong Hui Quek, National Cancer Centre, Division of Medical Oncology, Singapore, Singapore*

Background: There is a paucity of STS epidemiology and tx pattern information in the Asia Pacific region, with published data only from small or single country studies. STAR, a large multicountry observational study, was initiated to describe epidemiology, tx patterns and clinical outcomes in STS patients (pts) diagnosed in 2006–2010 at tertiary referral centers in Hong Kong, Indonesia, the Philippines, Singapore and Thailand. **Methods:** Data were collected by retrospective chart review. Kaposi's sarcoma, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, bone sarcoma and extraskeletal osteosarcoma were excluded. Demographics, tumor characteristics and tx patterns were analyzed descriptively. Overall survival (OS) and progression free survival (PFS) were estimated by the Kaplan Meier method. **Results:** STAR included 635 adult pts, 25% of whom presented with metastatic STS. Main histological subtypes: leiomyosarcoma (19%), liposarcoma (19%), undifferentiated pleomorphic sarcoma (UPS; 18%), synovial sarcoma (9%) and angiosarcoma (7%). Of 230 pts who had chemotherapy (CTx), 32% had neoadjuvant or adjuvant CTx only and 68% had palliative CTx. In the palliative setting, most pts had 1 (57%) or 2 (27%) lines of systemic tx. Combination CTx was more common than monotherapy (54% vs 47% of regimens). The most common first line (1L) regimens were doxorubicin/ifosfamide (36%) and paclitaxel (10%). The most common 2L regimens were gemcitabine/docetaxel (29%), gemcitabine (9%) and trabectedin (9%). Median PFS (95% CI) for 1L, 2L and 3L palliative CTx were 3.8 (2.2–5.5) months, 4.0 (2.1–5.8) months and 1.9 (1.3–2.6) months, respectively. Median OS of pts who presented with metastatic STS was 11.7 (8.9–14.5) months. **Conclusions:** STAR is the first large observational study to capture STS epidemiology, tx patterns and outcomes across Asia. UPS prevalence was similar to published data, suggesting acceptable pathologic quality, while angiosarcoma prevalence appeared slightly higher than in Western studies. During this period, most CTx regimens were combinations and palliative CTx beyond 2L was uncommon. Funding: GlaxoSmithKline.

10550 Poster Session (Board #194), Sun, 8:00 AM-11:30 AM

Targeted next generation sequencing in well-differentated/dedifferentiated liposarcoma (WD/DD LPS): Multiple gene amplifications but few mutations. *First Author: Neeta Somaiah, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: WD/DD LPS is a common soft tissue sarcoma with approximately 1500 new cases per year. Surgery is the mainstay of treatment but recurrences are frequent and limited systemic options make treatment challenging. 'Tumor genotyping' is becoming more common in clinical practice as it offers the hope of personalized targeted therapy. We wanted to evaluate the results and the clinical utility of available tumor genotyping panels in WD/DD LPS. **Methods:** MDACC patients (pt) who had their tumor analyzed by either Foundation One (FM) (244 gene panel for solid tumors, tumor only) or the institutional T200 panel (202 gene panel, tumor and normal) were included. There were 124 overlapping genes in these panels. FFPE sections were sequenced on the T200 panel using the Illumina HiSeq2000 platform. On average, the cutoff for calling variants on the T200 is 1%-5% for high coverage data (> 500x) and 10-15% for lower coverage(< 200x). **Results:** Total of 20 pt samples were identified, 7 on T200 (1 WD+6 DD) and 13 on FM (5 WD+8 DD). Significant copy number alterations (CNA) were identified in all samples. Only recurrent, potentially clinically actionable CNA (out of the 166 identified) are tabulated below. In the 7 pt samples on T200, 27 mutations were detected: 8 genes (*CTNNB1, MECOM, ZNF536, EGFR, EML4, CSMD3, PBRM1, PPP1R3A*) were identified as deleterious (on Condel, PolyPhen and SIFT) and a truncating mutation was found in *NF2*. Of these only the *EGFR* and *NF2* are known driver mutations and potentially actionable. These mutations have not been reported previously in DD LPS. On the FM panel, *ZNF536, CSMD3 and PPP1R3A*were not evaluated (NE) and no mutations were reported. **Conclusions:** In this series, 20/20 (100%) of the WD/DD LPS had *MDM2* and *CDK4*amplified. Additional recurrent novel deleterious genetic changes were identified, but further studies are needed to determine their therapeutic and pathogenetic significance.

	Gene		
High Amplification (≥ 4)	T200 +FISH N = 7	FM N = 13	Previously reported in DD LPS (50 samples in cbioportal)
MDM2	7	13	Y (90%)
CDK4	7	13	Y (88%)
DDR1	2	NE	N
AURKB	2	0	N
ERBB2	2	0	N
FLT4	2	0	Y (2%)
FGFR4	2	0	N
MAP2K4	2	0	N
NOTCH1	3	0	N
NOTCH4	2	NE	N
AKT1	2	0	Y (4%)
MCL1	NE	2	Y (10%)
High Deletion	2	0	N
BRCA2			

10551 Poster Session (Board #195), Sun, 8:00 AM-11:30 AM

A retrospective analysis of patients with soft tissue sarcoma treated long-term with trabectedin. *First Author: Elizabeth J. Davis, University of Michigan, Ann Arbor, MI*

Background: Treating STS with systemic therapy beyond six months is challenging due to cumulative toxicity. Trabectedin (T) has demonstrated efficacy and tolerability in STS and became available in 2005 through an expanded access program (EAP). Results of the EAP noted better overall survival and response rates in patients (pts) with leiomyosarcoma (LMS) and liposarcoma (LPS) compared to other histologies. Multiple cycles of T were tolerable with 30% of pts receiving ≥ 6 cycles and 7% of pts receiving ≥ 1 year of therapy, but descriptions of pts receiving T beyond one year are limited. **Methods:** We performed a retrospective analysis of pts with STS at the University of Michigan and M.D. Anderson Cancer Center who received long-term (≥ 10 cycles) T. We further subdivided pts into those treated for more than one year (≥ 18 cycles) and two years (≥ 35 cycles). Variables evaluated included age, gender, histology, site of primary tumor, number of prior treatments, number of dose reductions, and reason for discontinuation of T. **Results:** Four hundred and twenty-two pts treated with T were identified. Sixty-two pts (15%) received ≥ 10 cycles; 95% of these pts were treated on the EAP. Twenty-two pts (5%) were treated for ≥ 1 year and seven pts (2%) for ≥ 2 years. All pts treated for ≥ 1 year had LMS or LPS. Five pts (23%) treated for ≥ 1 year did not require a dose reduction. The primary reason for discontinuation of T was sarcoma progression. **Conclusions:** Trabectedin is a tolerable long-term therapy for a subset of pts with STS. Pts with LMS and LPS may derive the most benefit from long-term treatment, but further study is needed in a larger number of pts. Clinically relevant toxicities leading to T discontinuation beyond 1 year were fatigue and myelosuppression.

	≥ 10 cycles	≥ 18 cycles	≥ 35 cycles
Number of patients	62	22	7
Gender			
Male	24	9	4
Female	38	13	3
Median age in years (range)	50.5 (22-74)	50 (37-74)	45 (37-68)
Histology			
Liposarcoma	22	9	4
Myxoid/round cell	18	6	2
Leiomyosarcoma	33	13	3
Other	7	0	0
Site			
Extremity	22	7	3
Abdominal/pelvic (non-uterine)	20	8	3
Uterus	16	7	1
Chest	3	0	0
Head	1	0	0
Reason for discontinuation			
Progressive disease	47	15	5
Fatigue	4	3	0
Myelosuppression	3	2	1
Hepatotoxicity	2	0	0
Surgery/Radiation	4	1	0

10552 Poster Session (Board #196), Sun, 8:00 AM-11:30 AM

Multimodal treatment of pulmonary artery sarcoma: A single center experience. *First Author: Simona Secondino, Medical Oncology, Fondazione IRCCS PoliClinico San Matteo, Pavia, Italy*

Background: Pulmonary artery sarcoma (PAS) is a rare disease arising from the endothelial cells of the pulmonary artery wall, generally presenting with pulmonary hypertension (PI). The therapeutic approach, mainly based on surgery, either pneumonectomy or pulmonary endarterectomy (PEA), depends on the extension of the disease and the patient's clinical condition. The prognosis is extremely poor as survival rarely exceeds 1 year from diagnosis. **Methods:** From October 2010 to December 2014, 8 patients (pts) referred to our Institution for symptoms of acute or chronic pulmonary thromboembolic disease were diagnosed to have PAS. Five pts had PI, one with severe hemodynamic instability requiring emergency surgical treatment. Median age was 64 years (range 32-77), 5 pts were female. In 6 pts the disease was bilateral, and 3 had lung metastases. **Results:** All pts underwent PEA, none having life threatening complications from surgery. Pathology showed 4 high grade and 4 intermediate grade sarcomas. Following PEA and a short course of cardiopulmonary rehabilitation, 7 pts were able to received conventional chemotherapy (CT) with doxorubicin and ifosfamide, starting a median of 42 days (range 22-69) from surgery. Two pts also received radiotherapy after completion of the CT program. Four pts have died for disease progression at 6, 6, 8, and 26 months from surgery while 4 are alive, three being disease free at 8, 15, and 40 months. **Conclusions:** In pts with PAS a multimodal approach including PEA, CT and radiotherapy is feasible. Other than improving quality of life, it appears to considerably extend life expectancy.

10553 Poster Session (Board #197), Sun, 8:00 AM-11:30 AM

Metastatic dermatofibrosarcoma protuberans (DFSP) and fibrosarcomatous DFSP (FS-DFSP): Sensitivity to imatinib (IM) and gene expression profile. *First Author: Silvia Stacchiotti, Istituto Nazionale Tumori, Milan, Italy*

Background: We report on IM activity in patients (pts) with metastatic DFSP/FS-DFSP and on the gene expression profile (GEP) analysis of pure DFSP versus FS-DFSP, aimed at identifying prognostic markers **Methods:** All pts treated with IM at our institution from 2007 to 2014 for metastatic DFSP/FS-DFSP were selected. To estimate the PFS, pts progressing after IM discontinuation who responded after restarting IM were considered PD at the time of definitive PD on IM. Path and cytogenetics of the primary lesion and metastases were compared. We performed RNA Sequencing of 5 DFSP and 5 FS-DFSP (3 metastatic) on HiScanSQ platform. In 2 pts the analysis was done on samples taken before and after IM. GEP analysis was done with Python function htseq-count, differential expression with Bioconductor package edgeR, hierarchical clustering and Principal Component Analysis (PCA) with Multiple Array Viewer. SNV, Ins/del, fusion transcript analyses are ongoing **Results:** 10 pts were identified, all evaluable for response. All showed a FS component in the metastatic tumor, 7/10 in the primary lesion. COL1A1-PDGFb was detected in all cases. Best RECIST response was: 8 PR, 1 SD, 1 PD. 5 pts received complete surgery after IM (4 while under response, 1 after PD) with evidence of path response in 4 (with aspects depending on surgical timing, affecting tumor cells and pericytes). All pts relapsed. IM was restored in 4 pts with a new response. Median PFS was 11 mos (range 2-14+). By PCA all DFSP displayed a unique GEP, clearly different from FS-DFSP. At the supervised analysis, FS-DFSP were marked by over-expression of potential biomarkers such as MCAM and TGM2 (involved in metastatic process and chemoresistance). Many genes were upregulated in pure DFSP, reflecting the enrichment in neural markers and cell adhesion molecules **Conclusions:** All metastatic cases were FS-DFSP. Most pts responded to IM but PFS was shorter than reported in series including all DFSP. All pts who were operated after IM relapsed, suggesting that IM cannot eradicate metastatic DFSP/FS-DFSP and the role of surgery is limited. Restart IM after surgery, as done in GIST, is to be evaluated. DFSP and FS-DFSP presented a clearly different GEP

10554 Poster Session (Board #198), Sun, 8:00 AM-11:30 AM

Natural history and outcome in a large series of primary dermatofibrosarcoma protuberans (DFSP) treated at a reference institution. *First Author: Andrea Pierluigi Fontana, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: DFSP is a rare sarcoma, characterized by an indolent course, although local recurrences (LR) and occasional distant metastases (DM) are described. We sought to investigate its natural history and prognostic factors in a large series of patients (pts). **Methods**: All consecutive pts affected by primary DFSP, located at any sites, treated at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, from January 1993 to December 2012, were retrospectively reviewed. Overall Survival (OS), surgical margins status, LR and DM were analyzed. **Results**: 270 pts were identified, 246 (91.1%) affected by classic (C)-DFSP and 24 (8.9%) by fibrosarcomatous (FS)-DFSP. All pts are alive at a median follow-up (FU) of 6 yrs (range 1-15), save for two of them, dead for other diseases. All pts underwent macroscopic complete surgery. Microscopic margins were negative in 247 cases (91.5%), positive (PM) in 23 (8.5%). Overall, LR occurred in 4 pts (1.5%), 2/21 C-DFSP with PM, 2/2 FS-DFSP with PM, respectively. 3 of the LR were located to the scalp, 1 in the groin. A wider resection was repeated on 3 pts, who are disease-free (DF) after 2, 4 and 8 yrs, respectively. One pt refused surgery, her disease is under control with imatinib (IM) after 3 yrs. DM occurred in 3 pts (1.1% of the whole series; 12.5% of FS-DFSP), all affected by FS-DFSP (2 lung and 1 pancreatic metastases). 2 pts were treated with a lung wedge resection. One was DF after 78 mos, the other recurred again after 14 mos and was further treated with a combination of IM and a second surgery. He is still on IM and DF after 6 mos. The last metastatic pts is also on IM and progression-free after 4 mos. **Conclusions**: Negative margin resection is always curative for C-DFSP, as the observed metastatic risk is nil. PM may be accepted, when cosmesis is an issue, because LR risk remains low and salvaged by a subsequent wider resection. FS-DFSP has a more aggressive course, LR being highly predictable by PM and DM occurring in as many as 12.5% of pts. This should be used to inform treatment decision for the two DFSP variants.

	pts	PM	LR	LR/PM	DM
C-DFSP	246	21 (8.5%)	2 (0.8%)	2/21 (9.5%)	0 (0%)
FS-DFSP	24	2 (8.3%)	2 (8.3%)	2/2 (100%)	3 (12.5%)
Total	270	23 (8.5%)	4 (1.5%)	4/23 (17.4%)	3 (1.1%)

10555 Poster Session (Board #199), Sun, 8:00 AM-11:30 AM

The lipogenic phenotype reprograms the epigenome in sarcomas. *First Author: Warren Allen Chow, City of Hope, Duarte, CA*

Background: The "lipogenic phenotype of cancer" enhances the metastatic potential of cancers by promoting the *de novo* synthesis of fatty acids (FAs) to maintain their enhanced metabolism. Further, epigenetic reprogramming also promotes the malignant sarcoma phenotype. We hypothesized that development of the "lipogenic phenotype" reprograms the sarcoma epigenome to enhance their malignant potential. **Methods:** Soft-tissue (STS) and bone sarcoma cell lines (SK-UT-1 leiomyosarcoma, HT1080 fibrosarcoma, and Saos-2 osteosarcoma) were transduced with a fatty acid synthase (FASN)-expressing retrovirus. FASN catalyzes the synthesis of long-chain FAs from acetyl-CoA. Acetyl-CoA is generated from pyruvate, the excess end-product of aerobic glycolysis, better recognized as the "Warburg effect." FASN-expressing clones were subjected to proliferation, migration, and immunoblot assays. Transcriptome-wide sequencing and DNA methylation arrays were also performed. Finally, FASN expression was detected in STS clinical specimens by immunohistochemistry (IHC). **Results:** FASN overexpression increased sarcoma proliferation (35-47%), enhanced migration (scratch-wound assay), and increased methylation and acetylation of selected histone 3 lysines (H3K9me3 and H3K27ac). Whole transcriptome sequencing demonstrated multiple up- and downregulated genes, which generally correlated with the methylation status of their respective promoters. Finally, FASN expression was detected 1-3+ by IHC in 14/18 STS tumors by a blinded pathologist. **Conclusions:** FASN overexpression induces histone modifications that repress and induce genes that may enhance the malignant phenotype in sarcoma cell lines. Further, FASN is variably expressed in a majority of STS. Therapeutic targeting of FASN and epigenetic reprogramming may be a novel therapeutic approach to recurrent sarcomas.

10556 Poster Session (Board #200), Sun, 8:00 AM-11:30 AM

Primary high-grade myxofibrosarcoma/pleomorphic malignant fibrous histiocytoma: Percent myxoid component to improve outcome prediction. *First Author: Ann Yeelin Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Myxofibrosarcoma and pleomorphic malignant fibrous histiocytoma (PMFH) are aggressive genetically complex sarcomas. We investigated the association of percent myxoid component (MC) with disease-specific (DSS) and distant recurrence-free survival (DRFS) in primary high-grade myxofibrosarcoma and PMFH and determined the optimal %MC cutpoints for defining subgroups. **Methods:** Review of a prospective database identified 200 patients with primary, high-grade extremity/truncal myxofibrosarcoma or PMFH treated during 1992-2013. Histology was reviewed and %MC determined for each case. Optimal %MC cutpoints were determined from minimum p-value analysis of the entire cohort. DSS and DRFS were analyzed using the Kaplan-Meier method, log-rank test and Cox regression. **Results:** Median follow-up for survivors was 5.8 years. Median tumor size was 9.5 cm (range 2.5-30 cm). The optimal %MC cutpoints for both DSS and DRFS were 5% and 70%. Sarcomas with $\geq$ 5% MC were classified as myxofibrosarcoma (n = 128) and $<$ 5% MC (n = 72) as PMFH. The 5-year DRFS was 64% for $>$ 70% MC myxofibrosarcoma, 49% for 5-70% MC myxofibrosarcoma, and 23% for PMFH. %MC, tumor size, and age were independently associated with DSS, while %MC and size were associated with DRFS (Table). **Conclusions:** Percent MC is an important predictor of DSS and DRFS in primary high-grade myxofibrosarcoma and PMFH. Histology-based classification of %MC improves stratification of patient outcome and will aid in selection of patients for systemic therapy and clinical trials.

Multivariate analysis of clinical and pathological variables associated with DSS and DRFS.

Variable	DSS: Multivariate HR (95% CI)	DSS: *p* value	DRFS: Multivariate HR (95% CI)	DRFS: *p* value
MC 5-70% (vs > 70%)	1.6 (0.9-3.0)	0.11	1.9 (1.1-3.3)	0.03
MC < 5% (vs > 70%)	2.8 (1.7-4.8)	<0.001	3.6 (2.2-6.0)	<0.001
Size (> = 8 cm vs < 8 cm)	2.5 (1.5-4.0)	<0.001	2.3 (1.5-3.6)	<0.001
Age (> = 65 years vs < 65 years)	1.6 (1.0-2.5)	0.03		

10557 Poster Session (Board #201), Sun, 8:00 AM-11:30 AM

Postoperative morbidity and mortality in a large series of primary retroperitoneal sarcoma (RPS) treated at 8 tertiary centers: A study from the Transatlantic RPS Working Group. *First Author: Dirk C Strauss, The Royal Marsden Hospital, London, United Kingdom*

Background: To explore postoperative morbidity and mortality of patients (pts) with primary retroperitoneal sarcoma (RPS) undergoing surgery at 8 high volume centers (the Transatlantic RPS working group). **Methods:** All consecutive pts with primary RPS treated at 2 North American and 6 European centers between 2002 and 2011 were included in a retrospective analysis. Postoperative adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) and mortality at 30, 60 and 90 days were analyzed. Overall survival (OS), local recurrence (LR) and distant metastasis (DM) calculated. Multivariate analysis performed exploring risk factors for postoperative complications considering age, size, number and type of resected organs, preoperative chemotherapy and radiotherapy. **Results:** Total of 1007 pts were included in the database. Median follow-up was 58 months (range 36-90mo). Five and 10yr OS, LR and DM were 67% and 46%, 26% and 35%, 21% and 22% respectively. Postoperative complications of CTCAE grade $\geq$ 3 were observed in 207 pts (21%); grade 3 complications in 128 pts (12.7%), grade 4 in 52 pts (5.2%) and grade 5 for 19 pts (1.9%). The postoperative complication rate varied from 14.4 to 37.0% among centers. The re-operation rate was 10.5%. Most common complications were postoperative bleeding/hematoma (3.0%), bowel anastomotic leak/fistula (2.6%) and bowel obstruction/ileus (2.3%). The 30, 60 and 90-day mortality rate were 1.8 (95% CI 1-2.6), 2.9 (95% CI 1.8-3.9) and 4.1% (95% CI 2.9-5.3) respectively. In multivariable analysis, the occurrence of a postoperative complication was significantly associated with worst OS (HR 1.54, 95% CI 1.08-2.19, p = 0.016) and higher LR rate (HR 1.59, 95% CI 1.09-2.30, p = 0.015) while it was not significantly associated with a worst DM rate (HR 1.33, 95% CI 0.90-1.98, p = 0.153). **Conclusions:** Data about short-term morbidity are consistent with previous studies on RPS and comparable to those other major abdominal cancer surgery. The balance between the expected morbidity and the possible improvement in oncologic outcome should be factored in the management algorithm and tailored to the patient.

10558 Poster Session (Board #202), Sun, 8:00 AM-11:30 AM

Validation of the Royal Marsden Hospital (RMH) prognostic score in 100 patients with advanced sarcoma enrolled in early phase clinical trials at a major cancer center. *First Author: Michael Wagner, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Standard therapy refractory, metastatic and advanced sarcoma patients (pts) have few therapeutic options, and may benefit from enrollment in early stage clinical trials. The Royal Marsden Hospital (RMH) score predicts survival in pts prior to enrollment in Phase I clinical trials. We sought to validate the RMH score as a predictive marker in this population, and to assess if the presence of chromosomal translocations would predict benefit in Phase I clinical trials with targeted agents. **Methods:** Data from medical records of pts referred for enrollment in predominantly VEGF/VEGFR/mTOR inhibitor based Phase I clinical trials at M.D. Anderson Cancer Center were systematically reviewed. Pts were stratified according to RMH score (albumin, LDH, and number of metastatic sites), and the presence or absence of chromosomal translocations. **Results:** Among the 100 sarcoma pts [soft tissue (STS) (n = 79); bone (n = 21)] analyzed, the median age at trial enrollment was 48 (range 14-80). 46 pts (46%) were male. 26 pts (26%) had identifiable chromosomal translocations (17 with EWSR1 rearrangements). Clinical trial enrollment included 31 pts on VEGF agent alone, 16 pts on mTOR inhibitor alone, 13 pts on VEGF+mTOR, 11 pts on VEGF+chemotherapy, 6 pts on VEGF+mTOR+chemotherapy and 23 pts on other targeted agents. Median OS of pts with an RMH score of 0, 1, or 2 or greater was 18.9 mos, 7.5 mos, and 4.0 mos, respectively [HR 2.1 (1.5, 2.9) p $<$ 0.0001]. Median PFS in pts with a translocation was 3.8 mos, and without was 3.5 mos [HR 0.97 (0.60, 1.57), p = 0.89]. Median OS in pts with translocation was 9.5 mos and without was 10.1 mos [HR 1.19 (0.74-1.94), p = 0.48]. Median PFS in STS pts was 4.2 mos (2.8-6.3), and bone sarcoma pts was 2.8 mos (2.0-7.6). Median OS in STS pts was 10.2 mos (95%CI: 8.4-15), and in bone sarcoma pts 7.8 mos (95%CI: 6.5-29). Clinical benefit rate (CR+PR+SD $>$ 6 mos) across all Phase I trials was 35 % (4 PR+ 31 SD $>$ 6 mos). **Conclusions:** RMH score is a significant predictor of overall survival in metastatic sarcoma pts treated on Phase I therapies. The presence of a chromosomal translocation had no effect on outcomes on sarcoma pts enrolled in Phase I trials.

10559 Poster Session (Board #203), Sun, 8:00 AM-11:30 AM

The benefit of adjuvant radiotherapy in high-grade retroperitoneal sarcoma: A SEER analysis. *First Author: James Edward Bates, University of Rochester Medical Center, Rochester, NY*

Background: There is significant controversy surrounding the use of adjuvant radiotherapy (RT) in patients with retroperitoneal sarcoma (RPS). Grade is a prognostic factor in RPS and high-grade disease is associated with decreased local control (LC) and overall survival (OS). Adjuvant RT has been demonstrated to improve LC but not OS. In extremity sarcomas, recent evidence suggests that the benefit of RT is most significant for high-grade sarcomas. We hypothesized that any benefit in OS for RPS would most likely exist in those with high-grade tumors. **Methods**: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients with pathology-confirmed retroperitoneal soft tissue sarcoma from 1973 to 2010. Clinical characteristics and outcomes were investigated via Kaplan-Meier and Cox proportional hazards analyses. OS was defined as time to death or last follow-up. **Results**: A total of 483 patients with RPS were identified; 144 (29.8%) of who received postoperative radiation, the rest received surgery alone. Patients who received adjuvant RT had improved median OS (36 mo) compared to those who did not (27 mo, HR = 0.79, p = 0.023). On multivariate analysis the use of adjuvant RT (HR = 0.80, 95% CI: 0.65 – 0.97, p = 0.025), male gender (HR = 1.33, 95% CI: 1.10 – 1.60, p = 0.003), patient age greater than 65 years (HR = 1.34, 95% CI: 1.11 – 1.62, p = 0.002), and increasing SEER historical stage (HR = 1.45, 95% CI: 1.21 – 1.75, p $<$ 0.001) were all statistically significant prognostic factors for OS. **Conclusions**: In a retrospective analysis of a large national cancer database, post-operative RT improved OS in high-grade RPS patients. As such, adjuvant RT should be strongly considered in all patients with high-grade RPS. The current standard of care is to administer radiation prior to surgery in order to minimize potential radiation morbidities. A multi-national EORTC study is currently accruing patients to validate this approach in a prospective manner.

10560 Poster Session (Board #204), Sun, 8:00 AM-11:30 AM

A phase II study of temsirolimus and liposomal doxorubicin for patients with recurrent and refractory bone and soft tissue sarcomas. *First Author: Christian Frederick Meyer, Johns Hopkins Hosp, Baltimore, MD*

Background: Sarcomas are a heterogeneous group of connective tissue malignancies with limited palliative treatment options in the unresectable, metastatic setting. Standard chemotherapy treatment offers progression free survival (PFS) benefit measured in months while a significant impact from targeted therapy has not yet been realized. We conducted a phase I/II study of liposomal doxorubicin with temsirolimus in soft tissue and bone sarcomas based on preclinical data showing synergy against sarcoma stem cells. . We previously reported the phase I dose finding data. Here, we report the results of patients treated at the recommended phase II dose. **Methods:** 18 patients were treated at liposomal doxorubicin 30 mg/m^2 monthly with temsirolimus 20 mg/m^{2}weekly. A variety of subtypes were enrolled including 5 rhabdomyosarcomas, 3 leiomyosarcomas, and 2 mesenchymal chondrosarcomas. 11 of the 18 patients had prior doxorubicin exposure and a median of 2 prior lines of chemotherapy. **Results:** PFS was 315 days (range 27-799) and event free survival (EFS) was 119 days. Response rate, defined as stable disease (SD) or better for 60 days (2 cycles) was 53% (8 of 15) at the recommended phase II dosing (RP2D) and 56% (10 of 18) including the subjects treated with the higher dose of temsirolimus. Those who responded to therapy (defined as SD or better at first evaluation) tended to have prolonged responses, with median PFS for this group of 358 days (range = 75 – 799) and median EFS of 249 days. Pharmacodynamic analysis of target inhibition in 12 evaluable patients revealed concordance between inhibition of pS6K and response in 8 patients and inhibition of pAKT and response in 9 patients. The treatment was well-tolerated with only 4 patients experiencing a significant change in their ECOG performance status. **Conclusions:** Overall, the synergy of this combination bears further investigation of both metabolic and traditional chemotherapeutic agents in sarcomas. Clinical trial information: NCT00949325.

10561 Poster Session (Board #205), Sun, 8:00 AM-11:30 AM

Imatinib mesylate (IM) activity in patients (pts) with locally advanced tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT). *First Author: Philippe Alexandre Cassier, Centre Léon Bérard, Department of Medicine, Lyon, France*

Background: TGCT is a rare disease affecting the synovium and tendon sheaths of young adults. This usually benign neoplasm is driven by overexpression of CSF1, in some cases as a result of fusion of the CSF1 gene to the COL6A3 promoter in the t(1;2) translocation. The bulk of the tumor is made of CSF1 receptor (CSF1R) expressing cells. We previously reported on the activity of IM in this disease, here we present updated results. **Methods:** This is a multi-institutional retrospective study to assess the activity of IM in locally advanced/metastatic TGCT. **Results:** Forty-nine pts from 10 centers from Europe, Australia and the US were included. There were 31 females, median age was 38 (range 13-76) at diagnosis and 47 (range 21-80) at the time IM was started. The knee (n = 27; 55%), ankle (n = 9; 18%) and hip (n = 5; 10%) were the most common sites of disease. Most pts had locally advanced disease and/or local relapse (n = 47) and 2 pts had metastatic disease (lung and bone). The median number operations before IM was 2 (range 0-9), and only 4 patients never had surgery prior to IM. All but one pts were treated with IM 400 mg/day. Median follow-up was 18 (range 3-78) months and all pts were evaluable for response: 2 pt (4%) had a CR, 8 (16%) had a PR (ORR 20%) and 69 (37%) had SD. The two pts with metastatic disease had no response to imatinib. Ten patients were operated after a median of 6 (range 1-10) months of IM. Forty patients had symptoms at baseline of which 31 had symptom improvement on IM. The median progression-free survival was not reached. In 11 patients who had symptom improvement and stopped IM before PD, symptom control persisted beyond IM interruption (mean 27 months, median not reached). The most common side effects were grade 1 or 2 fatigue and edema, both seen in 19 (38%) pts, followed by nausea and skin toxicity reported in 8 (16%) and 5 (10%) pts respectively. Five patients had grade 3-4 events and overall, 7 patients (14%) discontinued treatment because of poor tolerance. **Conclusions:** These data confirm the value of IM in patients with advanced symptomatic TGCT, in some patients symptom control may persist beyond IM interruption.

10562 Poster Session (Board #206), Sun, 8:00 AM-11:30 AM

Sunitinib malate in advanced alveolar soft part sarcoma (ASPS): A final update after the closure of the named use program. *First Author: Nadia Hindi, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background:We already reported on the activity of sunitinib (SM) in 9 patients (pts) of ASPS. This series is an update. In addition, based on recent evidence demonstrating a role for lactate metabolism in ASPS pathogenesis, we explored the role of MCT1 and MCT4 lactate transporters in SM response **Methods**: From July 2007 to September 2013, 16 pts with progressive, advanced ASPS (M/F: 10/6; median age: 28 yrs; site of primary: extremities 14, other 2; site of metastases: lung 15, brain 4, bone 3; pretreated with chemotherapy: 10) were put on continuous SM 37.5 mg/day, on a named-use program. Response was evaluated at 2 mos from baseline, then every 3 mos by CT and/or MRI, by RECIST. The expression of MCT1 and MCT4 was analyzed by qRT-PCR in 8 of these cases (7 responders, 1 non-responder) **Results**:All pts are evaluable for response. 14 pts stopped SM: 9 for PD observed while receiving SM 37.5, 4 for PD observed while receiving SM at a low dose (25 or 12.5 mg/day; SM had to be definitively reduced due to leukopenia and/or renal failure), 1 for definitive surgery. Best response was 1 CR, 9 PR, 4 SD, 2 PD. Median OS has not yet been reached, with 6 pts dead at the time of the present analysis. At a median FU of 32 mos (range 7-75), the median PFS was 13 mos (range 2-59), 9 pts being disease-free at > 12mos. One pt underwent complete surgery plus RT after 6 mos of SM; she is progression-free at 19 mos. Four pts progressed to the CNS, being stable to all other sites of disease, and underwent radiotherapy (RT) of brain lesions; 2 of them continued on SM with no further evidence of progression after 18 and 22mos (these pts were considered PD at the time of CNS progression). Two pts who had to stop SM for progression occurring after reducing SM due to toxicity responded to the rechallenge of SM after having been treated with a MET inhibitor; they are still on SM and progression-free at 5 and 2mos, respectively. The role of MCT genes in response to SM is currently assessed **Conclusions**:SM is confirmed to be active in ASPS, with long-lasting, dimensional responses. Near 70% of pts maintained responses for > 6mos. Almost 30% of progressions were isolated to CNS. Re-challenge with SM could be an option in previously responding pts who had to stop their therapy due to toxicity

10563 Poster Session (Board #207), Sun, 8:00 AM-11:30 AM

Phase II trial of PF-03084014 in adults with desmoid tumors/aggressive fibromatosis. *First Author: Shivaani Kummar, Phase I Clinical Research Program Stanford University School of Medicine, Stanford, CA*

Background: Desmoids are rare, invasive, slow growing soft tissue tumors that are sporadic or associated with familial genetic syndromes, such as familial adenomatous polyposis. Desmoids are characterized by stabilization and abnormal nuclear localization of β-catenin. Mutations in the *CTNNB1* gene are found in 85-90% of desmoids. Gamma-secretase cleaves intracellular Notch resulting in Notch signaling. PF-030844014 (PF) is an oral reversible γ-secretase inhibitor (GSI) that is well tolerated. Based on encouraging data from a phase I trial, we conducted a phase II study of PF in patients (pts) with symptomatic desmoid tumors progressing following at least one line of therapy. Objectives: determine the response rate (RR); assess symptom measures and perform genotyping for germline/somatic mutations in *APC* and *CTNNB1* genes. **Methods:** PF was administered orally at 150mg BID; for 21 day cycles. Archival samples were sequenced for germline and somatic mutations in *APC* and *CTNNB1*genes. Dynamic contrast-enhanced MRI (DCE-MRI) was obtained at baseline and restaging. Single stage; 90% power to rule out unacceptably low RR of 10% in favor of 35% RR. The validated MD Anderson Symptom Inventory (MDASI) was used to assess symptoms. **Results:** Accrual completed. 13/17 pts (76.4%) remain on study; 4 pts stopped treatment by choice/co-morbid conditions. No pt has progressed to date. Median follow-up time is 10 months (range 2-14), 6 pts remain on study ≥ 1year. Grade 3 toxicities include hypophosphatemia (3 pts, 17.6%) and diarrhea (1 pt, 5.8%). Dose reduction to 100mg BID daily occurred in 2 pts. 16 pts (94%) have stable disease with 1 (5.8%) unconfirmed PR. In 15/17 pts (88.2%), a somatic or germ line mutation was identified. DCE-MRI and symptom scale analysis ongoing. **Conclusions:** PF is active at the selected dose, with a manageable side effect profile. Copy number analysis, transcriptome sequencing and DNA methylation analysis of archival samples as well as 2 paired biopsies obtained on study is ongoing. Clinical trial information: NCT01981551.

% change in tumor measurements by MRI

Pt	pC1	pC6	pC12
1010001	-3%	-15%	
1010002	-5%	-25%	-28%
1010003	-11%	-25%	-34%
1010005	-5%	-3%	-3%
1010006	-14%	-15%	-13%
1010007	0%	-21%	
1010009	3%	-3%	6%
1010010	-7%		
1010011	-12%	-2%	-16%
1010015	3%	3%	
1010017	0%	-12%	

10564 Poster Session (Board #208), Sun, 8:00 AM-11:30 AM

A phase I trial of the human double minute 2 (HDM2) inhibitor MK-8242 in patients (pts) with advanced solid tumors. *First Author: Andrew J. Wagner, Dana-Farber Cancer Institute, Boston, MA*

Background: HDM2 binds and inhibits wild-type (WT) p53 thereby promoting oncogenesis. MK-8242 is a potent, orally bio-available, small-molecule inhibitor of the HDM2:p53 protein-protein interaction under development as a novel cancer therapy. **Methods:** A multi-center, 2-part (dose escalation/Part I and confirmation/Part 2; using modified TPI design) Phase I study of MK-8242, administered p.o. BID on days 1-7 in 21 day cycles, was performed to determine the safety, tolerability, and recommended Phase 2 dose (RP2D) in pts with advanced solid tumors with WT p53. RP2D was based on tolerability, plasma pharmacokinetics (PK), and pharmacodynamics (PD) in tumor/blood, including expression of the p53 target PHLDA3. Other objectives were characterizing PK/PD relationship, correlation of biomarkers with response, and assessment of tumor response (RECIST v1.1). **Results:** 47 pts received MK-8242 across 8 dose levels ranging from 60 mg to 500 mg. Initially, 6 pts developed DLTs (G2 nausea at 120 mg; G3 fatigue at 250 mg; G2 nausea and G4 thrombocytopenia at 350 mg; G3 vomiting and G3 diarrhea at 500 mg). DLT criteria were revised to permit management of GI toxicity, and 4 additional DLTs were observed (G4 neutropenia and G4 thrombocytopenia at 400 mg; G4 thrombocytopenia [2 pts] at 500 mg). Other drug-related G3-4 events included anemia, leukopenia, pancytopenia, nausea, hyperbilirubinemia, hypophosphatemia, and anorexia. The RP2D was established at 400 mg as tolerability (i.e., 2 DLTs in 14 evaluable pts), PK, and PD targets were achieved at this dose level. Plasma PK analysis of 400 mg on Day 7 found $AUC_{0\text{-}12hr}$ of 16.7 μM*hr, C_{max} 3.1 μM, T_{max} 2-6 hr, and $T_{1/2}$ 6.5 hr. Blood concentration of PHLDA3 correlated with drug exposure ($R2 = 0.69$, $p < .0010$). In 41 pts who had post-baseline scans, 31 showed SD, 2 achieved PR (both with liposarcoma [LPS], at 250 mg and 400 mg), 8 had PD. 7 pts with LPS remain on study. In total, 27 pts had LPS and their median time-to-progression was > 300 days. **Conclusions:** At the RP2D of 400 mg BID, MK-8242 activates the p53 pathway with an acceptable tolerability profile. Preliminary evidence of clinical activity with PR and prolonged PFS was seen providing impetus for further study of HDM2 inhibitors in LPS pts. Clinical trial information: NCT01463696.

10565 Poster Session (Board #209), Sun, 8:00 AM-11:30 AM

Clinical pattern and implication of PD-L1 expression in soft-tissue sarcoma. *First Author: Chan Kim, Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*

Background: PD-1/PD-L1 axis plays a paramount role in tumor immune escape by negative regulation of T-cell functions. Recently, immune checkpoint inhibitors targeting this axis displayed promising anti-tumor activity with durable response, and the predictive role of PD-L1 expression is being investigated in various solid tumors. In the present study, we aimed to characterize the PD-L1 expression pattern and its clinical implication in soft-tissue sarcomas (STS). **Methods:** We analyzed PD-L1 expression in 82 STS patients with 5 subtypes including rhabdomyosarcoma (n = 32), synovial sarcoma (n = 19), Ewing sarcoma (n = 18), epithelioid sarcoma (n = 7), and mesenchymal chondromsarcoma (n = 6). PD-L1 expression was evaluated using anti-PD-L1 antibody (clone 130021, R&D System), and PD-L1 positivity was defined as more than 10% of PD-L1 staining in tumor cells. PD-L1 expression was compared with other clinicopathologic variables. **Results:** Median age at diagnosis of patient cohort was 26 (range: 1-78) and male-to-female ratio was 1.6. Initial disease presentation was locoregional disease in 80% of patients and metastatic disease in the remaining 20%. PD-L1 expression was identified in 43% of STS patients. Histologic subtype of STS was significantly associated with PD-L1 expression ($p = 0.004$). Proportion of PD-L1 expressing tumors was highest in epithelioid sarcoma (100%, 7/7), followed by synovial sarcoma (53%, 10/19), rhabdomyosarcoma (38%, 12/32), and Ewing sarcoma (33%, 6/18), while it was not expressed in mesenchymal chondrosarcoma (0%, 0/6). Baseline clinical characteristics other than histologic subtype was not correlated with PD-L1 expression. Patients with PD-L1 expression had worse overall survival compared with those without PD-L1 expression (5-year survival rate: 48% in PD-L1 positive vs. 68% in PD-L1 negative, $p = 0.015$). Moreover, this negative prognostic role of PD-L1 expression in STS was also confirmed by multivariate analysis with Cox regression model (HR: 2.67, $p = 0.017$). **Conclusions:** PD-L1 is not only expressed in STS but also stand as an independent negative prognostic factor for overall survival of STS patients. Thus, PD-L1 needs to be pursued as a potential therapeutic target in patients with STS.

10566 Poster Session (Board #210), Sun, 8:00 AM-11:30 AM

Time to secondary resistance (TTSR) after rechallenge with trabectedin (T) in myxoid round cell liposarcoma (MRCLPS) patients. *First Author: Roberta Sanfilippo, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Italy*

Background: To explore the time to secondary resistance after rechallenge with T in MRCLPS patients who were responding to T at the time of discontinuation. **Methods:** Since September 2002, 62 patients with recurrent myxoid liposarcoma received T at our institution. According to RECIST, 2/62 patients had a complete response (CR), 34/62 a partial response (PR) (CR+PR = 58%), 18/62 (29%) a stable disease (SD) and 8/62 (13%) a progression disease (PD). Median PFS was 14 months. Among the 54/62 patients who obtained a stable disease or a partial response after the first assessment, 28/54 interrupted treatment in absence of progression, while 26/54 patients received T until progression disease. Time to secondary resistance was defined as time from the first cycle of T to progression, whenever it occurs (including under T reintroduction). **Results:** In the 28 pts in whom Trabectedin was interrupted (11 for surgery of the residual disease, 1 for radiotherapy , 3 for toxicity and 13 for shared decision with clinician) , this was done after a median of 14 cycles (range = 6-21) and the median PFS was 24 months. 17 of them resumed treatment at the time of progression (F = 8, M = 9, median age = 51, range = 32-76). After rechallange, no PD was seen at first assessment, and time to secondary resistance was 48 months. In the 26 pts who went on with T until progression, PFS (i.e., time to secondary resistance) was 11 months. **Conclusions:** Rechallenge with T may be successful in selected patients with myxoid liposarcoma primarily responding to the drug and stopping it after a while. In this series, the choice to continue or stop the drug after response was of course at the discretion of the clinician, and selection biases are likely. Prospective studies on optimization of treatment strategy with T in MRCLPS are worthwhile.

10567 Poster Session (Board #211), Sun, 8:00 AM-11:30 AM

Pazopanib for soft tissue sarcoma (STS) in the first- line setting with denosumab. *First Author: Hiroyuki Narahara, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan*

Background: We established the Japan Sarcoma Association and hold the Japan-United States International Workshop on the Sarcoma Research and Therapy in December 2014. **Aim**: We conducted a retrospective analysis on pazopanib for STS in order to examine the relationships of PFS with denosumab, also from the viewpoint of the first-line setting for metastatic diseases. **Methods:** In this study, the patients with metastatic STS treated with pazopanib from November 2012 till January 2015, consecutively, were retrospectively analyzed. Among first 4 months, the starting dose was fixed at 800mg, but later changed to 400mg because of severe adverse events. **Results:** Eighty seven patients (43 leiomyosarcomas, 8 liposarcomas, 36 other subtypes) were identified. Median age was 56 years old (range 17-84), 69 females and 18 males, 50 pts were treated in the first-line setting and 37 pts were in the second or later-line setting, and 26 pts with multiple bone metastases were all treated with denosumab. Remarkable severe toxicities (G 3/4) were observeded as pheumothorax, hyperbilirubinemia, bladder perforation and perianal abscess, but the rates were infrequent (< 2.2%). All hypertension was manageable by antihypertensive medication and cardio-echogram showed no decrease of EF and it was definitly < 10%. But seum BNP increaseded in some pts. No pts showed symptomatic heart failure in the observation period (median: one year). All the pts, included till July 2014, were evaluable by RECIST 1.1, and 37 pts were evaluated as PR/SD and 31 pts showed PD/NE. Median OS reached 16.9 months (95%CI: 9.7-ND) and median PFS was 2.6 months (95%CI: 2.2-3.7). From the viewpoint of PFS with response, PFS in PR and that in SD were similar. PFS showed no differences between 800mg vs 400mg, leiomyosarcoma vs liposarcoma vs others, PS 0/1 vs 2/3 and 1st line vs later line. But PFS in PR/SD was longer (4.9 months, 95%CI: 2.8-7.1) than that in PD/NE (1.7 months, 95%CI: 1.1-2.3, $p < 0.0001$). PFS with denosumab was not inferior to that without denosumab. **Conclusions:** Pazopanib including first-line setting for metastatic STS is effective and comparable with EORTC trials. The combination chemotherapy of pazopanib with denosumab is promising and further investigations are warranted.

10568 Poster Session (Board #212), Sun, 8:00 AM-11:30 AM

A new simple low-cost multiplexed targeted sequencing assay to detect recurrent fusion genes in sarcomas. *First Author: Emilie Angot, Department of Pathology, University Hospital, Rouen, France*

Background: Sarcomas represent a heterogeneous group of tumors comprising more than 50 histological different types. Ten to fifteen percent of sarcomas are characterized by specific translocations which are routinely used as molecular markers for diagnosis, providing crucial information for prognosis and therapeutic decision. Today, translocations are detected by FISH or RT-PCR. However, these methods can only detect a limited number of transcripts simultaneously. Since the development of high throughput sequencing, the number of specific translocations continues to grow and it seems that we have reached the limits of this molecular "one-shot" approach. **Methods:** We have developed a simple low-cost (less than 6 dollars per patient) assay based on multiplex ligation-dependent RT-PCR for simultaneous screening of more than 50 rearrangements present in sarcomas. To validate this assay, we selected 42 formalin fixed and paraffin embedded (FFPE) sarcomas with known molecular alteration. In the case of non-contributive results, we repeated the analyses with snap-frozen tissue. **Results:** We detected fusion transcript for 9 synovial sarcomas (9/9), 9 alveolar rhabdomyosarcomas (9/9), 4 Ewing sarcomas (4/6), 2 Ewing like sarcomas with *BCOR-CCNB3* fusion transcript (2/2), 6 myxoid liposarcomas (6/7), 2 desmoplastic small round cell tumors (2/2), 1 dermatofibrosarcoma protuberans (1/2), 1 clear cell sarcoma (1/1), 2 angiomatoid fibrous histiocytomas (2/2), 1 infantile fibrosarcoma (1/1) and 1 solitary fibrous tumor (1/1). For 7 tumors, sequence quality was only reached using cryopreserved tissue. We did not detect transcript for 2 primary bone Ewing sarcomas and 1 dermatofibrosarcoma protuberans. Unfortunately, for these latter tumors we did not have cryopreserved tissue. One myxoid liposarcoma transcript was not detected using FFPE and cryopreserved tissue. **Conclusions:** We have developed a multiplexed assay which can reveal a very large number of gene fusions in sarcomas with good sensitivity and excellent specificity. These promising results provide an opening for this new rapid simple low-cost multiplexed targeted sequencing assay as an alternative method to FISH and RT-PCR for routine diagnosis.

10569 Poster Session (Board #213), Sun, 8:00 AM-11:30 AM

A phase 1b study with selinexor, a first in class selective inhibitor of nuclear export (SINE) in patients with advanced sarcomas: An efficacy analysis. *First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Sarcomas are a heterogeneous group of malignancies with diverse genetic abnormalities. Selinexor is a first-in-class, oral, inhibitor of XPO1, (nuclear exportin protein 1) with potent anti-tumor activity in multiple sarcoma cell lines and in murine liposarcoma xenografts. Here we report results from a Phase 1b dose expansion trial of selinexor in sarcoma patients (NCT01896505). **Methods**: Patients (pts) with advanced, refractory sarcomas with radiographic progression received oral selinexor at 50 mg/m^2 twice weekly per 28 day cycle. Pharmacokinetics (PK, n = 12) was assessed in the fasted and fed state. Pharmacodynamic studies were performed on fresh tumor biopsies. Response was evaluated every 2 cycles (RECIST 1.1). **Results**: 36 pts (14 M / 22 F, ECOG 0/1: 19/17, median age 57.5 years [range 18–86], median lines of previous treatments: 3 [range 1–9]). Disease subtypes include liposarcoma (LPS; N = 12), leiomyosarcoma (LMS; N = 8) and other sarcomas (N = 16). Grade 3 drug related adverse events (AEs) occurring in ≥ 2pts included: fatigue (17%), leucopenia (17%), anemia (11%), hyponatremia (8%) and vomiting (6%). One pt had reversible, grade 3 sensory and autonomic neuropathy and two pts had grade 4 thrombocytopenia (6%). Of the 33 evaluable patients, stable disease was seen in 21/33 (64%) of pts along with decrease of tumor burden (ranging from 5 – 23%) in 7 patients. There were 12 pts (36%) that progressed. In pts with progressive LPS and LMS, the median progression free survival (mPFS) on selinexor was 4.2 months (mo) and 3.7 mo, respectively. PK was similar to previously published results and there was better absorption in the fed state compared to fasting and fat content did not affect bioavailability. Matched pre- and post-tumor biopsies (N = 6) showed target inhibition of XPO1 by nuclear localization of p53, apoptosis by increased cleaved caspase, marked reduction in cellularity and Ki-67 and increase in stroma. **Conclusions**: Oral selinexor administered twice weekly was well tolerated with manageable toxicities. Selinexor demonstrated durable stable disease in various soft tissue and bone sarcomas. Based on promising results a larger study is planned. Clinical trial information: NCT01896505.

10570 Poster Session (Board #214), Sun, 8:00 AM-11:30 AM

Pattern of relapse in limb/girdle low-grade liposarcoma/atypical lipomatous tumor (ALT) during guidelines-suggested follow up (FU). *First Author: Raimondo Piana, Department of Orthopaedic Oncology and Reconstructive Surgery, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, CTO Hospital, Torino, Italy*

Background: In soft tissue sarcomas (STS) after complete (marginal/wide/radical margins) surgery, surveillance should be tailored to individual patient's (pts) risk that depends on histotype, grading and site of origin. Unfortunately there is a substantial lack of evidence to personalize FU and most guidelines (GL) suggest both clinical (history and physical examination) and imaging procedures (X-rays, CT, US, MRI) taking into account two broad categories (low- and high-grade STS) but ignoring histotype heterogeneity. We reviewed our prospectively collected STS database to assess ALT pattern and risk of relapse in order to improve our future FU policy. **Methods:** In 2001 our regional-based health system adopted a STS GL (www.reteoncologica.it) suggesting the following FU: pts examination every 4-6 months in the first 3 years, every 6 months until the 5th year, then yearly. Pts underwent local and chest imaging (either CT or X-rays). Average cost and exposure to X-rays were computed for the entire FU. We searched for pts affected by ALT with complete clinical records (centrally reviewed histology, surgical record, and at least 3-year FU). ALT-specific overall survival (OS), relapse-free survival (RFS) and local-RFS (LRFS) were estimated according to Kaplan-Meier method. **Results:** Between 2001 and 2011 we took care of 163 patients affected by LGL. Complete records were available in 152 (93%) pts. Adherence to FU was considered adequate in 127 (78%) pts (median age 58, IQR 50-67; median size 14 cm, IQR 8-19). Median FU was 117 months (95% CI 95-140). Ten-year OS, RFS and LRFS were 100%, 74% and 74%, respectively. Among the 13 (10%) relapsed pts, we observed 13 local relapses and no distant metastases. All relapses were surgically amenable. Two pts died during their FU and none because of systemic progression. The chest X-rays estimated 10-year FU cost is 450 euros per pts with an average total exposure of 0.9 mSv. **Conclusions:** Until a hardly foreseeable randomized trial on FU will be performed, our study, though retrospective, does not support the systematic use of chest imaging in ALT FU that adds apparently needless costs and low, but not negligible, ionizing radiation risks.

10571 Poster Session (Board #215), Sun, 8:00 AM-11:30 AM

Primary chest wall soft tissue sarcomas: predictors of survival following surgical resection in a large population cohort. *First Author: Sadiq Rehmani, Mount Sinai St. Luke's Hospital, New York, NY*

Background: Primary soft tissue sarcomas (STS) of the chest wall are rare entities with limited information regarding treatment and oncological outcomes. The aim of this study is to evaluate the outcomes of surgical treatment in malignant primary chest wall STS and identify factors affecting survival using the Surveillance, Epidemiology, and End Results (SEER) database. **Methods:** We conducted a retrospective analysis using the SEER database (1988 -2010) and queried for all patients with primary chest wall STS. Only adult patients with histologically confirmed single primary tumor undergoing curative surgical resection were included in the study. Primary outcome was overall survival; covariates included demographics, tumor pathology, radiation and type of surgical procedure as coded in SEER (Simple/Partial or Total/Radical). Chi-square tests were performed to analyze categorical variables. Kaplan-Meier and Cox regression analyses were used to evaluate overall survival. **Results:** A total of 1053 cases of surgically resected, histologically confirmed, primary chest wall STS were identified. Mean age was 56 years and male to female ratio was 1.33:1. Out of 1053, 57% patients underwent Simple/Partial resection while 43% underwent Total/Radical. A total of 42% patients received radiation therapy. The mean overall survival of the entire cohort was 126.6 (± 8.284) months. After adjusting for covariates using Cox's proportional hazards regression, higher tumor grade (grade3: HR = 4.934 {CI: 2.599-9.365}, $p < 0.001$; grade4: HR = 4.895 {CI: 2.629-9.117}, $p < 0.001$) and tumor size (5-10 cm: HR = 1.77 {CI: 1.216-2.560}, $p < 0.005$; > 10cm: HR = 3.72 {CI: 2.538-5.458}, $p < 0.001$) were found to be independently associated with poor survival. **Conclusions:** Primary chest wall soft tissue sarcomas are uncommon tumors. Using the SEER database, we present the largest cohort reported to date. In this analysis, both advanced tumor grade and size are poor predictors of survival. Further studies are required to validate these findings and to direct adjuvant therapy.

10572 Poster Session (Board #216), Sun, 8:00 AM-11:30 AM

Local control following resection of primary retroperitoneal sarcoma with and without preoperative radiotherapy. *First Author: Carol Jane Swallow, Department of Surgery, University of Toronto, Toronto, ON, Canada*

Background: Retroperitoneal sarcoma (RPS) represents a therapeutic challenge due to its typically advanced stage at presentation, with local failure a harbinger of death from sarcoma following resection of primary RPS. Preoperative external beam radiotherapy (Pre-op RT) offers the potential for sterilization of margins and better local control. We present mature outcomes according to histologic subtype and treatment of patients with primary RPS managed at our center. **Methods:** All patients presenting with primary RPS between 01/96 and 06/11 identified from a prospective database were eligible. Distant metastases or unresectability at presentation, receipt of pre-op chemotherapy or post-op radiotherapy were exclusion criteria. All biopsy and resection specimens were re-analysed by an expert pathologist and mdm2 status used to facilitate histologic subtyping. Cumulative-incident rate curves were constructed for local and distant recurrence (LR, DR). **Results:** All 120 included patients underwent total gross resection. In this cohort, overall survival was 75% and 64% at 5 and 10 yrs, median 206 mos, and disease specific survival was 85% and 76% at 5 and 10 yrs, median 209 mos. Pre-op RT was given to 101 patients while 19 had surgery alone. Surgical approach, histologic subtype (80% liposarcoma, LPS) and follow-up (median 59 mos) did not differ between treatment groups; median size was larger (28 vs. 19 cm) and histologic grade lower in the surgery alone group. For the 120 patients, DR occured in 12 at a median 23 mos (range 2-131) postoperatively and varied significantly by histology (4/65 DD-LPS; 0/31 WD-LPS; 7/17 LMS; 1/7 other; $p < 0.01$), but not treatment group. LR occured in 24 at a median 22.5 mos (range 2-103) and varied significantly by histology (22/65 DD-LPS; 2/31 WD-LPS; 0/24 other; $p = 0.01$). For the entire cohort, LR rate was 20% and 28% at 5 and 10 yrs. LR at 5 yrs varied significantly by treatment group (16% for pre-op RT, 51% for surgery alone, $p < 0.01$). **Conclusions:** Pre-op RT was associated with improved local control compared with a contemporaneous control. Participation in the EORTC randomized trial of pre-opRT vs. surgery alone is essential to determine the true benefit of pre-op RT in primary RPS.

10573 Poster Session (Board #217), Sun, 8:00 AM-11:30 AM

Phase 2 study of gemcitabine, docetaxel, and doxorubicin in patients with advanced, unresectable, and/or metastatic sarcoma who have failed prior therapies. *First Author: Andrew Eugene Hendifar, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Gemcitabine and docetaxel chemotherapy protocols have proven efficacy in the treatment of metastatic soft tissue sarcomas. Doxorubicin is also a commonly used treatment both as a single agent and as a part of combination therapies. This phase 2 study was designed to assess the efficacy and safety of a combination regimen of gemcitabine, docetaxel , and doxorubicin. **Methods:** This is a single institution study of advanced sarcoma pateints who were refractory to 1st line chemotherapy. Adequate performance status, organ function, and measurable disease (RECIST v1.1) were required. Patients received Gemcitabine (400 mg/m2), Doxorubicin (20 mg/m2) and Docetaxel (20 mg/m2) on days 1 and 8 of a 21 day cycle, and must have completed 2 cycles in order to be evaluable. Disease assessment was completed using the RECIST 1.1 criteria and toxicity was evaluated using the NCI CTCAE version 4.2. **Results:** A total of 32 patients were enrolled from 08/2011 - 08/2014 and 31 patients received at least 2 cycles of therapy. Pts with leiomyosarcoma (n = 7) liposarcoma (7) synovial sarcoma (2), chondrosarcoma (2), bone tumors (6), and others (8). The majority of patients (n = 21, 66%) previously received doxorubicin and many (n = 8, 25%) had previously received gemcitabine and docetaxel in combination. The average number of previous regimens was 3 previous chemotherapies (range, 1 to 7). The median age was 49 (range, 21 – 69). A median of 5 cycles of gemcitabine, docetaxel and doxorubicin were given (range, 1-12). A partial response was seen in 16 % of patients (5/31), and stable disease > 3 months in 39% (12/31). Clinical benefit (CR+PR+SD > 3months) was 17/31 55% (95% CI .36 -0.7) Grade 3 and 4 hematologic toxicities were observed in 14 patients (thrombocytopenia 12 pts, and neutropenia 2 pts) however, no patients were discontinued for toxicity. **Conclusions:** The combination of gemcitabine, doxorubicin, and docetaxel is an active regimen with a manageable toxicity profile in patients with advanced and pre-treated soft tissue and bone sarcomas.

10574 Poster Session (Board #218), Sun, 8:00 AM-11:30 AM

Metastatic Non-Uterine Leiomyosarcoma: Prognostic factors, Overall Survival and chemotherapy outcomes. *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Non-uterine Leiomyosarcoma (LMS) is an aggressive, malignant tumor of mesenchymal origin whose natural history is poorly defined. We sought to evaluate clinical and treatment outcomes in patients (pts) with metastatic (met) disease. **Methods**: In a retrospective study using an institutional sarcoma database, we identified all pts with met non-uterine LMS treated at Memorial Sloan Kettering Cancer Center between 1983-2011 and collected their correlative clinical information.Kaplan-Meier method and Cox's proportional-hazard models were used to determine overall survival (OS) from time of met and prognostic factors. Hazard ratios (HR) are listed with their 95% confidence intervals (CI). Objective responses to 1st chemotherapy were determined by RECIST 1.1. **Results:** We identified 214 pts: median age 56 (range 23-85), 80 (37%) male. Median OS was 2.6 years (yr) (range: 0.04-17 yr) with 14 yr of follow-up. Independent factors predictive of improved OS included age < 56, HR 0.70 (0.52-0.97) p = 0.03; primary tumor site in the retroperitoneum, HR 0.56 (0.34-0.93) p = 0.03; and < 3 met sites, HR 0.65 (0.47-0.9) p = .009. Most common regimens included anthracycline+alkylator (n = 47), gemcitabine-based regimens (n = 58), liposomal doxorubicin (dox) (n = 17) and dox (n = 15). Rates of complete response (CR) + partial response (PR), stable disease (SD), and progressive disease (PD) were 18%, 56% and 25%, respectively. Pts with CR/PR and SD had improved OS compared to those with PD, HR 0.25 (0.13-0.49, p < 0.001) and HR 0.46 (CI 0.28-0.76) p = 0.002, respectively. Regimen type did not impact OS. **Conclusions:** LMS is an aggressive malignancy with poor prognosis. Age < 56, primary tumors arising in the retroperitoneum and < 3 met sites were associated with improved OS. Patients with CR/PR/SD to first line chemotherapy had improved OS regardless of type of chemotherapy used. Molecular analysis of select pts with long-term OS may be warranted

TPS10575 Poster Session (Board #219a), Sun, 8:00 AM-11:30 AM

A randomized phase II/III study, comparing perioperative adriamycin plus ifosfamide versus gemcitabine plus docetaxel for operable high grade soft tissue sarcomas in extremity or trunk: JCOG1306. *First Author: Kazuhiro Tanaka, Oita University, Yufu, Oita, Japan*

Background: Based on the results of JCOG0304, which showed sufficient efficacy of perioperative chemotherapy with adriamycin plus ifosfamide (AI) for operable high-grade soft tissue sarcomas (STS), AI has been considered acceptable as standard regimen for operable STS in Japan. Recent studies have reported gemcitabine plus docetaxel (GD) is effective for advanced STS. A new clinical question has thus arisen of whether less toxic GD has a compatible efficacy to AI as perioperative therapy. Therefore, we have commenced a phase II/III trial to confirm the non-inferiority of perioperative GD to AI. **Methods:** Eligibility criteria include operable, histologically proven STS, primary tumor (T2bN0M0 or anyTN1M0) based on the 7th AJCC/UICC-TNM or first local recurrent tumor, arising in the extremities or trunk, FNCLCC grade 2 or 3, and aged 20 to 70. Patients are randomized to the AI or the GD. Patients in the AI arm receive preoperative 3 courses and postoperative 2 courses of adriamycin at 30 mg/m^2 on days 1-2 and ifosfamide at 2 g/m^2 on days 1–5, every 3weeks. Patients in the GD arm receive preoperative 3 courses and postoperative 2 courses of gemcitabine at 900 mg/m^2 on days 1 and 8, and docetaxel at 70 mg/m^2 on day 8, every 3 weeks. In the phase II part, the primary endpoint is the proportion of completion of preoperative chemotherapy without progressive disease in the GD arm. The planned sample size is 28 patients in the GD arm, which was calculated based on an expected proportion of completion of preoperative GD without progressive disease of 85% and a threshold of 65%, with a one-sided alpha of 0.1 and a beta of 0.2. In the phase III part, the primary endpoint is overall survival. The sample size was calculated as a total of 140 patients with a one-sided alpha of 0.1, power of 0.7 and a non-inferiority margin of 8% at 3 year survival, assuming 3 year survival of AI to be 85% and that of GD as 87%. The accrual period is 6 years and the follow-up period is 5 years. This trial has started in February 2014 and the current enrollment is 18 as of January 2015 (UMIN000013175). Clinical trial information: 000013175.

TPS10576 Poster Session (Board #219b), Sun, 8:00 AM-11:30 AM

EPAZ: A randomized phase II trial comparing pazopanib with doxorubicin as first line treatment in elderly patients with metastatic or advanced soft tissue sarcoma of the Working Group Medical Oncology (AIO) and German Interdisciplinary Sarcoma Group (GISG). *First Author: Viktor Gruenwald, Medical School of Hannover, Hannover, Germany*

Background: 1/3 of STS patients are 60 years and older. Single agent doxorubicin is the mainstay of therapy in metastatic disease, which is frequently associated with hematological toxicity (grade 4 neutropenia in 34%; febrile neutropenia in 9%). We assume that comorbidities in the elderly population may limit tolerability of doxorubicin and novel agents may improve health-related quality of life (HR-QoL), while maintaining efficacy. **Methods:** This is a randomized, open-label, multicenter phase II study that compares pazopanib 800 mg OD to doxorubicin 75 mg/m^{2}as first line treatment in elderly patients with metastatic or advanced STS (NCT01861951). A total of 120 patients will be recruited and randomized 2:1 to receive either pazopanib or doxorubicin, stratified by performance status (0-1 vs. 2) and histological subtype. HR-QoL (QLQ-C30) and comprehensive geriatric assessment (elderly minimal dataset of EORTC ETF) is determined throughout the course of the study, in order to assess the impact of treatment on the patient's quality of life and daily living. Key inclusion criteria: age $\geq$ 60 years; progressive intermediate or high grade STS; ECOG PS 0-2; measurable disease (RECIST 1.1); availability of archived STS tissue; adequate organ function; no prior therapy for metastatic disease. Primary endpoint: Progression free survival (PFS) based on local tumor assessment according to RECIST 1.1. Key secondary endpoints include the incidence of grade 4 neutropenia and febrile neutropenia. For the latter endpoints, sensitivity analyses will be conducted to adjust for primary prophylaxis of granulocytopenia or febrile neutropenia. Other secondary endpoints include: HR-QoL, geriatric assessment, safety and tolerability, overall survival, objective response rate, PFS rate at 12 and 26 weeks, time to onset of response, and predictive biomarkers. The first patient was randomized on October 12, 2012. Currently, a total of 85 patients have been randomized. Clinical trial information: NCT01861951.

TPS10577 Poster Session (Board #220a), Sun, 8:00 AM-11:30 AM

A study of the safety and efficacy of the combination of gemcitabine and docetaxel with ontuxizumab (MORAb-004) in metastatic soft tissue sarcoma. *First Author: Sant P. Chawla, Sarcoma Oncology Center, Santa Monica, CA*

Background: Ontuxizumab is a humanized immunoglobulin G-1-kappa monoclonal antibody (mAb) that is the first clinical stage agent to target endosialin. Endosialin (TEM-1/CD248) is a cell surface glycoprotein expressed on cells involved in the development of tumor vasculature, but has generally limited expression in normal tissue. In some tumors, such as sarcomas, endosialin is expressed directly by the tumor cells and therefore soft tissue sarcomas (STS) may be a suitable treatment target. **Methods:** This Phase 2 multicenter study in subjects with metastatic STS (0-2 prior regimens) is being conducted in two sequential parts. Part 1 was an open label, dose-escalation, safety lead in: 4, 6 and 8 mg/kg ontuxizumab (administered on days 1 and 8 of a 21 day cycle) combined with gemcitabine and docetaxel (G/D) (900 mg/m^2 on days 1/8 and 75 mg/m^2 on day 8, respectively)). Based on the observed safety profile in Part 1, 8 mg/kg was utilized in Part 2 efficacy design. In Part 2 subjects are randomized in a double-blind 2:1 ratio to G/D plus ontuxizumab (8 mg/kg) or G/D plus placebo. Using an adaptive population finder design, randomization is stratified by four histological cohorts (liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma (UPS) and myxofibrosarcoma, and other STS). An independent unblinded statistical committee (ISC) monitors the trial adaptations for futility, success, or maximal cohort sizes (60). Primary objective is progression-free survival (PFS) by RECIST1.1. Secondary objectives include overall survival (OS), overall response rate (ORR), and predictive/ response biomarkers. Enrollment ended in August 2014 with 209 subjects randomized. Primary result analysis is anticipated in December, 2015. Clinical trial information: NCT01574716.

TPS10578 Poster Session (Board #220b), Sun, 8:00 AM-11:30 AM

SARC 028: A phase II study of the anti-PD1 antibody pembrolizumab (P) in patients (Pts) with advanced sarcomas. *First Author: Melissa Amber Burgess, University of Pittsburgh Physicians, Pittsburgh, PA*

Background: Immune checkpoint inhibition with antibodies (abs) to cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) have made a significant therapeutic impact in metastatic melanoma. Abs targeting the PD-1/PD-L1 axis also exhibited clinical activity in solid tumors that are not considered "immunogenic", e.g., lung and bladder cancer. The significance of the PD-1/PD-L1 axis is currently being elucidated in sarcoma. Over 150 sarcomas of various histologic subtypes have been analyzed for PD-L1 tumor expression and the presence of PD-1+ tumor infiltrating lymphocytes (TIL): up to 65% of sarcomas expressed PD-L1 which, along with PD-1 TIL positivity, correlated with poorer overall survival and aggressive tumor features. We seek to determine the efficacy of PD-1 blockade with the anti-PD-1 ab pembrolizumab in pts with advanced soft tissue (STS) and bone sarcomas. **Methods:** This is an open label, multicenter, single stage, phase II study of P in pts with advanced STS (Arm A) or bone sarcomas (Arm B). P will be given intravenously at 200 mg every 3 weeks. The primary efficacy endpoint is objective response rate (ORR) by RECIST 1.1. 40 pts/arm will provide 82% power to detect an improvement in ORR from 10 to 25% with a one-sided type I error of 4.2%. This design will also have 87% power to detect an improvement in the 4-months progression-free survival rate from 20% to 40% with a one-sided type I error of 4%. Key eligibility criteria include $\geq$ 12 years of age, ECOG PS of 0 or 1, up to 3 prior therapies, and at least one tumor site accessible for biopsy. Exclusion criteria include low grade sarcoma, prior immunotherapies, and chronic use of corticosteroids or other immunosuppression. Secondary endpoints are safety, overall and progression free survival, and response rates by immune-related response criteria (ir-RC). Mandatory tumor biopsies pre and post-treatment will be obtained to determine PD-L1 expression as well as to perform immune monitoring in the tumor microenvironment. Peripheral blood will also be collected for immune monitoring in the circulation. Enrollment will occur at 10 SARC participating institutions and is expected to be completed in 2015. NCT02301039. Clinical trial information: NCT02301039.

11000 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Identifying somatic oncogenic mutations in leukocytes that infiltrate primary breast cancers. *First Author: Elizabeth Anne Comen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the past decade, sequencing studies have delineated somatic mutations in human cancers. Given that cancer cells interact with their microenvironment and the presence of somatic mutations in a subset of elderly individuals with clonal hematopoiesis, we hypothesized that white blood cells within tumors might be characterized by clonally selected mutations in known cancer genes. Here we provide direct evidence of the presence of clonal somatic mutations affecting known cancer genes in tumor-infiltrating leukocytes from breast cancer (BC) patients. **Methods:** We evaluated tumor infiltrating leukocytes in 17 primary BC samples: 13 patients had triple negative BC, 2 had ER+, HER2+ BC, and 2 had ER+, HER2- BC. Fluorescent activated cell sorting was employed to separate CD45-positive hematopoietic cells from CD45-negative epithelial cells. Whole exome sequencing of tumor infiltrating leukocytes revealed candidate somatic mutations in known cancer genes, including BCOR, NOTCH2, TET2, NF1, EZH2 and JAK1. To validate our findings, we expanded our sample size to 20 patients and performed targeted capture massively parallel sequencing of matched tumor-infiltrating leukocytes and germline DNA. Laser-capture microdissected cancer cells were subjected to high-depth sequencing to rule out the presence in cancer cells of the somatic mutations found in leukocytes. **Results:** In 10 of the 20 patients, we identified and validated somatic mutations, including mutations affecting genes associated with leukemia in tumor infiltrating leukocytes but not in laser-capture microdissected BC cells from the same patients. Targeted sequencing indicated that these mutations are enriched in tumor-infiltrating leukocytes as compared to circulating leukocytes. **Conclusions:** We identified clonal somatic mutations in known cancer genes in tumor infiltrating leukocytes. These data suggest a novel relationship between cancer cells and mutant infiltrating leukocytes. Studies are underway to investigate functional interactions between BC cells and hematopoietic cells harboring somatic mutations.

11001 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

White adipose tissue inflammation and breast cancer progression. *First Author: Neil M. Iyengar, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Obesity is a poor prognostic factor for breast cancer (BC) survivors. White adipose tissue (WAT) inflammation (WATi) occurs in the breasts of most obese/overweight individuals, and also in some who are normal weight. We demonstrated that breast WATi is associated with several molecular changes including activation of NF-κB and elevated aromatase expression that could contribute to tumor progression. Additionally, WATi correlates with circulating changes including hyperinsulinemia that occur in the metabolic syndrome, a poor prognostic feature for BC. Here we examine the impact of breast WATi on BC progression. **Methods:** We conducted a case-control study nested within a cohort of 610 patients (pts) with invasive BC who underwent mastectomy from 2001 – 2006. Case pts were women who developed distant relapse while control subjects remained free of disease with follow up to 2014. Controls were matched (1:1) on age at diagnosis, BMI, receptor status, grade, T stage, N stage, use of adjuvant therapy, and co-morbidities. WATi, detected by CD68 immunostain, was defined by the presence of dead/dying adipocytes surrounded by macrophages known as crown-like structures of the breast (CLS-B). Distant recurrence free survival (dRFS) was compared by CLS-B status using Cox regression. Risk of distant relapse by CLS-B status was examined by conditional logistic regression analysis. **Results:** Adequate WAT was available for 250 subjects. Among pts who developed distant relapse ($n = 127$), median dRFS was worse for pts with breast WATi (20 months [mo], range 16-26) than those without WATi (26 mo, range 20-34; hazard ratio [HR] 1.44, 95% confidence interval [CI] 1.00-2.06, $P < 0.05$). The association between WATi and shorter dRFS remained significant in multivariable analysis (HR 1.83, 95% CI 1.07-3.13, $P = 0.03$). A higher proportion of pts who developed distant relapse had breast WATi at index mastectomy (52/127, 41%) than those who remained disease free (46/123, 37%), though not statistically significant as the study was underpowered for this endpoint ($P = 0.76$). **Conclusions:** In pts with recurrent BC, breast WATi is an adverse independent prognostic variable. These findings support further study of WATi as a targetable biomarker of BC progression.

11002 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Association of inactivation of *STK11/ LKB1* with a suppressive immune microenvironment in lung adenocarcinoma (LUAC). *First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Little is currently known about how the oncogenotype of LUAC shapes its immune micro-environment. We recently identified that major subsets of *KRAS*-mutant LUAC defined on the basis of co-occurring genomic alterations in *STK11/LKB1*, *TP53* and *CDKN2A/B* display distinct immune profiles. Specifically, inactivation of the LKB1 tumor suppressor is associated with striking lack of immune system engagement. Here, we systematically assess the immune contexture of LUACs in the context of LKB1 inactivation. **Methods:** Our datasets include 431 LUACs from TCGA with available exome sequence and RNA-Seq data, as well as a cohort of 106 early stage tumors collected at MDACC (PROSPECT dataset) with available mRNA (Illumina), phospho-protein (RPPA) expression and quantitative IHC data. The un-paired t test and Wilcoxon's rank-sum test were used for comparisons of mean mRNA expression and Histo-scores respectively. PROSPECT tumors were dichotomized into "LKB1-low" and "LKB1-high" based on LKB1 protein expression. **Results:** Somatic mutation of *LKB1* was associated with wide suppression of cytolytic T cell responses. This included apparent defects in MHC class I and II antigen presentation pathways [HLA-A ($P = 0.057$), HLA-B ($P = 1.55e^{-06}$), HLA-C ($P = 1.28e^{-05}$), B2M ($P = 1.8e^{-03}$), HLA-DMA ($P = 2.8e^{-04}$), HLA-DMB ($P = 6.08e^{-07}$),HLA-DOA ($P = 6.28e^{-07}$), HLA-DOB ($P = 3.5e^{-04}$)] as well as reduced expression of co-stimulatory [CD28 ($P = 3.9e^{-03}$), CD80 ($P = 5.55e^{-07}$), CD86 ($P = 6.79e^{-06}$),CD40 ($P = 5.09e^{-09}$), CD70 ($P = 5.7e^{-04}$), TNFRSF9 ($P = 3.79e^{-05}$), TNFSF9 ($P = 0.007$), ICOS ($P = 3.3e^{-03}$),ICOSLG ($P = 1.2e^{-03}$)] and co-inhibitory [CTLA ($P = 0.034$), PDCD1 ($P = 0.0125$), CD274 ($P = 1.16e^{-08}$), PDCD1LG2 ($P = 8.66e^{-06}$), LAG3 ($P = 0.023$), LGALS9 ($P = 1.65e^{-05}$)] molecules. A number of these were further validated in PROSPECT. In the context of *KRAS*-mutant LUACs, LKB1 inactivation was associated with a lower PD-L1 IHC score ($P = 0.039$) and reduced populations of CD3+, CD8+ and CD45RO+ lymphocytes. Detailed IHC data will be presented at the meeting. **Conclusions:** LKB1 inactivation is associated with a muted tumor immune phenotype and may thus predict for resistance to immunotherapy approaches that incorporate immune checkpoint blockade.

11003 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Discordance between HER2-phenotype on circulating tumor cells and primary tumor in women with advanced breast cancer. *First Author: Amelie Schramm, Universitaetsfrauenklinik Ulm, Ulm, Germany*

Background: In the DETECT study program, women with HER2-negative metastatic breast cancer (MBC) are screened for circulating tumor cells (CTCs) to evaluate eligibility for different DETECT treatment intervention trials based on presence and HER2 phenotype of CTCs. Here we present data on the association of CTC prevalence and positive HER2-status on CTCs with patient and tumor characteristics. **Methods:** As of January 2015, number of CTCS using the FDA-cleared CellSearch System (Janssen Diagnostics, LLC) and their HER2 status have been evaluated in 1052 women with HER2-negative MBC screened for the DETECT Study program. Patients were defined as CTC positive if at least 1 CTC was detected in 7.5 ml of peripheral blood, and the cutoff for HER2 positivity was the presence of at least 1 CTC with a strong (+++) immunocytochemical HER2 staining intensity. **Results:** Overall, CTCs were detected in 661 (62.8%) of the 1052 screened patients (median 7 CTCs, range 1 – 35078). CTC prevalence was associated with a higher proportion of pN2/pN3 tumors (28.0 vs. 20.2%; $p = 0.021$) and a higher proportion of lobular carcinomas (22.4 vs. 9.5%; $p < 0.001$) compared to CTC-negative patients. Among the 661 patients with CTCs, at least one HER2-positive CTC was found in 130 patients (19.7%), indicating a discordance between primary tumor and CTCs with regard to HER2-status. Patients with HER2-positive CTCs had less often G3 tumors (27.7 vs. 39.0%; $p = 0.024$), and more often lobular carcinomas (39.2 vs. 18.3%; $p < 0.001$) compared to patients with only HER2-negative CTCs. In addition, patients with triple-negative tumors were less likely to have HER2-positive CTCs than patients with HER2-negative but hormone-receptor positive tumors (6.6 vs. 22.8%; $p < 0.001$). **Conclusions:** Our data confirm discordance in HER2-status between primary tumor and CTCs in 19.7% of patients with HER2-negative MBC. Interestingly, presence of HER2-positive CTCs was associated with hormone-receptor positive tumors. Awareness of the HER2-phenotype of CTCs may have important implications for further personalized therapy options. Clinical trial information: NCT01619111/NCT02035813.

11004 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Detection rate of actionable mutations in diverse cancers using a biopsy-free (blood) circulating tumor DNA assay. *First Author: Razelle Kurzrock, UC San Diego Moores Cancer Center, La Jolla, CA*

Background: Analysis of cell-free DNA using next generation sequencing (NGS) is a potentially powerful tool for the detection/monitoring of circulating tumor DNA (ctDNA). We report the findings of a biopsy-free NGS ctDNA assay in a series of 103 patients with advanced cancer. **Methods:** Between June 1, 2014 and January 16, 2015, plasma samples from 103 patients with a variety of cancers were analyzed for ctDNA. Single nucleotide variants (SNVs) in 54 genes and copy number variants (CNVs) in 3 genes (*EGFR*, *ERBB2* and *MET*) are reported quantitatively as the fractional mutant allele concentrations in cell-free DNA and the absolute copy numbers of the genes measured, respectively (Guardant360, Guardant Health, Inc.). This ctDNA assay has high sensitivity (detects 85%+ of the single nucleotide variants detected in tissue in advanced cancer patients) and analytic specificity (> 99.9999%). **Results:** Of the 103 patients, there were 40 with breast and 40 with lung cancer; and 23 various other malignancies. Of the total, 78 (75.7%) had at least one detectable mutation (mean = 2.1/patient). In 222 healthy volunteers used to validate that assay, only 1 had an alteration. Within the breast cancer cohort, 22% had 1 alteration; 50%, 2 or more (range 0-12; mean = 2.2/patient). *TP53* alterations were the most common, found in 32.5%. Interestingly, 25% of patients had an *EGFR* alteration (amplification or SNV), higher than previously reported. Mutations in *PIK3CA* were detected in 10 cases. In the 40 lung cancer patients, 82.5% had at least 1 alteration (mean = 2.2/patient). *TP53* alterations were present in 50%; *EGFR* alterations, in 30%; and MET amplification/variation, in 22.5%. Sixty-two of 103 patients (60% of all patients; 80% of patients with an alteration) had alterations that were conceivably actionable by an FDA approved drug and/or an agent in clinical trials. **Conclusions:** In this single institution series, 75.7% of the patients had an alteration on a 54 gene panel ctDNA assay. Importantly, of patients with at least 1 alteration, 80% had alterations actionable by existing drugs. ctDNA testing in blood identifies a high number of potentially actionable abnormalities in a broad range of cancer types.

11005 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Protein expression by genetic mutations identified in gene panels (hotspots) and efficacy of targeted treatments. *First Author: Stephen Charles Benz, Five3 Genomics, Santa Cruz, CA*

Background: Treatment decision support by next generation sequencing of gene panels is currently limited to the analysis of somatic (tumor) data from DNA sequencing without taking into consideration expression of mutated genes. We present here a supercomputer-driven, cloud-based integrated analysis of genomic (DNA) and transcriptomic (RNA) sequencing data to 1) directly identify driver variants between somatic and germline (normal) DNA and 2) to determine expression of identified mutations in a cohort of 3,784 patients, thereby establishing therapeutic relevance of the mutated genes overcoming the limitations of panels. **Methods:** This large scale 3,784 patient genomic (DNA and RNA sequencing) data set from 19 anatomical tumor types was processed to detect DNA variants (germline vs somatic) and RNA expression, and to establish not only the existence but also the expression level of hotspot mutations in the following oncogenes: PIK3CA, KRAS, NRAS, AKT1, BRAF, IDH1, CTNNB1, and IDH2. **Results:** Of the 3,784 patients in this analysis, 720 were found to have mutations in the oncogenes listed above. Remarkably, only 38 (5.3%) of these patients had better than 90% expression by RNAseq, and 36 patients (5.0%) with identified hotspot mutations had no or low (< 10%) expression. For example, mutations at position E545 in the PI3K protein encoded by the PIK3CA gene, which has been targeted by both pan-PI3K and mutant-targeted drugs in clinical trials, showed low or no expression in 12% (5/41) of breast cancer patients and not a single patient showed relatively maximal (> 90%) expression. Similarly of the 204 thyroid cancer patients with a BRAF V600 hotspot mutation, 7.5% (15/204) had low or no expression and none had relatively maximal expression. **Conclusions:** These findings illustrate that genetic mutations in gene panels (hotspots) do not always result in protein expression. Given that many gene mutations were not expressed, we conclude that an informed molecularly-driven clinical treatment decision requires insight into downstream protein expression and not just DNA alterations alone.

11006 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Safety and activity of DCR-MYC, a first-in-class Dicer-substrate small interfering RNA (DsiRNA) targeting MYC, in a phase I study in patients with advanced solid tumors. *First Author: Anthony W. Tolcher, START, San Antonio, TX*

Background: MYC, an oncoprotein deregulated in over half of all human malignancies, has thus far been considered "undruggable" with conventional approaches. RNA interference (RNAi), a therapeutic approach that can be used to silence the *MYC* oncogene, has been shown to inhibit cancer growth in animal models. Synthetic DsiRNA with specificity for *MYC* have demonstrated highly potent activity in vitro (picomolar IC_{50}), and anti-MYC DsiRNA formulated in EnCore lipid nanoparticles (DCR-MYC) have demonstrated activity in vivo across various tumor models. DCR-MYC is the first MYC-targeting siRNA to enter clinical trials. **Methods:** This phase I, dose-escalation study (3+3 design) evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD) and clinical activity of DCR-MYC in patients (pts) with advanced solid tumors, multiple myeloma or lymphoma. DCR-MYC is administered as a 2-hr IV infusion on Day 1 and 8 of a 21 day cycle. Given the role of MYC in tumor metabolism, FDG-PET is obtained after cycle 1 to assess early metabolic response, while RECIST response is assessed after every 2 cycles. **Results:** Nineteen pts have been treated across 5 dose levels (0.1, 0.125, 0.156, 0.2, 0.3 mg/kg): 8M/11F, median age 58 yrs, ECOG PS 0(5), 1(14). Tumor types include NET (4), MBC (4), CRC (3), Ovarian (2), Appendiceal (2), other (4). The most common treatment-related AEs (all grades/grade 3) include fatigue (7/0), nausea (5/0) and infusion reactions (3/1). A pt with PNET treated at 0.1 mg/kg experienced DLT (transient grade 3 AST) and fatigue. This pt experienced a complete metabolic response (based on FDG-PET) after cycle 1 which has been sustained for > 8 months without further treatment. Metabolic responses after cycle 1, as well as evidence of tumor shrinkage have been observed in multiple patients. Preliminary PK analysis from the first two dose levels shows dose proportional changes in AUC and Cmax. **Conclusions:** DCR-MYC, a novel MYC inhibitor, is well tolerated and shows promising initial clinical and metabolic responses across various dose levels. These data support early validation of MYC as a therapeutic target. Updated results from the ongoing study will be presented. Clinical trial information: NCT02110563.

11007 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Comprehensive genomic profiling (CGP) of advanced cancers to identify MET exon 14 alterations that confer sensitivity to MET inhibitors. *First Author: Garrett Michael Frampton, Foundation Medicine, Cambridge, MA*

Background: Amplifications and activating mutations in the c-MET proto-oncogene are known oncogenic drivers that have proven responsive to targeted therapy. Alterations affecting the splice sites of *MET* exon 14 have been identified, which cause exon skipping, MET activation, and predict sensitivity to MET inhibitors in vitro. We undertook comprehensive genomic profiling (CGP) of a large series of advanced cancers to identify MET exon 14 alterations. **Methods:** DNA was typically extracted from 40 microns of FFPE sections from 34,735 cases examined between April 2012 and January 2015. CGP was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of > 500x. All classes of genomic alterations (GA) were evaluated. **Results:** CGP of 34,735 patients identified 200 cases harboring METex14 alterations. The alterations had diverse sequence composition, with > 100 distinct sequence variants represented. The 200 patients had a median age of 68.2 years (range 15-83), with 86 males and 114 females. The cases were comprised of lung carcinoma (173), carcinomas of unknown primary (14), brain glioma (6), and one each of adrenal cortical carcinoma, hepatocellular carcinoma, melanoma, Merkel cell carcinoma renal cell carcinoma, rhabdomyosarcoma, sarcoma NOS, and synovial sarcoma. The majority were stage IV. Identification of this alteration via CGP in routine clinical care has led to treatment with MET inhibitors such as crizotinib, and to durable partial responses or better exceeding 3 months in histiocytic sarcoma (1), sarcomatoid lung carcinoma (1), and nsclc (1+). Multiple patients (5+) have initiated treatment on either crizotinib or MET inhibitors in clinical development, and additional outcome data will be reported. **Conclusions:** MET exon 14 alterations define a hereto unrecognized population of advanced cancers. Early reports of patients demonstrate cases harboring such alterations are responsive to multiple small molecule MET inhibitors. This finding expands the population of advanced cancer patients who can derive benefit from MET-targeted therapies.

11008 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Altering the tumor microenvironment: A phase II study of copper depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence. *First Author: Eleni Nicole Nackos, New York Presbyterian Hosp-Weill Cornell, New York, NY*

Background: Bone marrow derived endothelial progenitor cells (EPCs) and copper-dependent pathways are critical components to remodeling the tumor microenvironment and creating the pre-metastatic niche. Copper depletion (CD) inhibits tumor metastases in preclinical models. We hypothesized that TM-associated CD would reduce EPCs and other copper dependent processes in the pre-metastatic niche in BC pts at high risk for relapse. We investigated the relationship between CD and its effect on EPCs and other components of the tumor microenvironment including lysyl oxidase (LOX). **Methods:** In this single arm, phase II study, BC pts at high risk for recurrence, defined as node+ triple negative (TN), stage 3 and 4 with no evidence of disease (NED) were enrolled on a trial of CD with TM. We utilized TM to maintain ceruloplasmin (Cp) between 5-17 mg/dl until end of treatment or relapse. The primary endpoint was change in EPCs measured by flow cytometry before and during treatment with TM. Secondary endpoints included tolerability, safety, and its effect on other markers including LOX. **Results:** We enrolled 75 pts. The study treatment duration was 24 cycles (28 days each). Over 2021 cycles have been administered. The median age is 51 (range 29-66). 45 pts have Stage 2/3 BC and 30 are Stage 4 NED. 48% of pts have TNBC, and 40% of pts are Stage 4 NED. Median Cp level decreased from 28 at baseline to 16 ($p < 0.0001$) after one cycle. Copper depletion was most efficient in TNBC. TM was well tolerated and the only grade 3/4 toxicities were reversible neutropenia (2.5%) and anemia (0.04%). CD was associated with a significant decrease in EPCs ($p < 0.001$) and LOX ($p < 0.001$) in the 2 year analysis; the 5 year analysis is ongoing. The PFS for all 75 pts from the start of TM treatment was 81% including a PFS of 94% for all stage 2/3 pts with TNBC at median f/u of 5.6 yrs. The hazard ratio for relapse is zero at two years. **Conclusions:** TM is safe, well tolerated and appears to affect multiple components of the tumor microenvironment creating an inhospitable environment for tumor progression. This seems to be most striking in TNBC. Further phase III trials are warranted. Clinical trial information: NCT00195091.

11010 **Poster Discussion Session; Displayed in Poster Session (Board #222), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Next-generation sequencing to reveal somatic mutations that confer sensitivity to everolimus. *First Author: Sun Min Lim, Yonsei Cancer Center, Seoul, South Korea*

Background: Using targeted ultradeep sequencing, we aimed to explore genomic alterations that confer extreme sensitivity to everolimus. **Methods:** We collected formalin-fixed paraffin-embedded tumor/normal pairs from 38 patients (21 with exceptional clinical benefit, 17 with no clinical benefit) who were treated with everolimus across various tumor types (13 gastric cancers, 15 renal cell carcinomas, 2 thyroid cancers, 1 lacrimal gland cancer, and 7 sarcomas). Ion AmpliSeq Comprehensive Cancer Panel was used to identify alterations across all exons of 409 target genes. **Results:** Tumors were sequenced to a median coverage of 605x. Cancer genomes are characterized by 203 somatic single-nucleotide variants (186 missense, 10 nonsense, 7 splice-site) and 51 frameshift insertions/deletions, with a median of 3.9 mutations per Mb (0 to 14.8 mutations per Mb). Overall, genomic alterations with activating effect on mTOR signaling were identified in 8 of 21 patients with clinical benefit and these include *mTOR, TSC1, TSC2, NF1* and *PIK3CA* mutations. In a patient with ductal adenocarcinoma of the lacrimal gland in whom everolimus achieved a partial response (PR) for 8 months, a novel *NF1* missense mutation (D1644A) and a novel *TP53* frameshift deletion (A39fs*5) were revealed. Three *mTOR* missense mutations (K1771R, N1421D, I1973F) were found in patients with gastric cancer, renal cell carcinoma and angiosarcoma. A mutation in the helical domain of *PIK3CA* (E542K) was found in a renal cell carcinoma patient and a mutation in AKT1 (H238Y) was observed in a sarcoma patient with malignant fibrous histiocytoma. Lastly, a patient with anaplastic thyroid cancer harbored a nonsense mutation in *TSC1* (p.Trp103*) and a renal cell carcinoma patient had a *TSC1* splicing variant (c.1029+1G > A). Recurrent mutations in chromatin remodeling gene (*BAP1;* n = 2, 12%) and receptor tyrosine kinase signaling (*FGFR4;* n = 2, 12%) were noted only in patients without clinical benefit. **Conclusions:** Regardless of different cancer types, mTOR-pathway-activating mutations confer sensitivity to everolimus. Targeted sequencing of mTOR pathway genes facilitates identification of potential candidates for mTOR inhibitors.

11011 **Poster Discussion Session; Displayed in Poster Session (Board #223), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Next generation sequencing (NGS) to identify targetable recurring mutations and exceptional responders in relapsed and high-risk childhood and adolescent/young adult (AYA) malignancies. *First Author: Brian Turpin, Cincinnati Children's Hosp Medcl Ctr, Cincinnati, OH*

Background: NGS has been rapidly introduced into routine clinical care for select adult malignancies, and the National Cancer Institute genomic precision medicine initiatives (e.g. M-PACT, NCI-MATCH) seek to use genetic sequencing-based treatment to improve response rates in select adult populations. However, the applicability of this technology in pediatric and AYA tumors has yet to be established. **Methods:** In an IRB-approved retrospective analysis of focused exome sequencing of 190 relapsed and high risk pediatric and AYA malignancies, 67 hematologic malignancies, 38 sarcomas, 34 neuroblastomas, 21 CNS, 7 liver, 6 renal, and 17 "other" tumors were analyzed. DNA was sequenced to high, uniform coverage (Illumina HiSeq) and analyzed for genomic alterations (GAs) (Foundation Medicine, Cambridge, MA). **Results:** Population included 156 patients with relapsed/refractory cancer and 34 with de novo high-risk disease (median age 7 yrs; range 3 mos to 34 yrs). GAs were identified in 82% of patients (median of 2 mutations; range 0-15) and included 142 cancer related genes. TP53 was the most frequently identified GA (17% of patients). GAs were identified in multiple "actionable" pathways, including cell cycle regulation/DNA repair (36% of patients), RAS/RAF/MEK (22%), and epigenetic pathways (20%), frequently independent of histology. The number of mutaions ($p = 0.03$) and the presence of a mutation in TP53 ($p = 0.035$) or a cell cycle regulation pathway ($p = 0.004$) was associated with older age. Eceptional responses were observed with GA-based assignment of therapies with RAS/RAF/MEK and epigenetic pathway GAs. Forty percent of patients had gene mutations eligible for the adult M-PACT study. **Conclusions:** High risk and relapsed pediatric and AYA cancer patients have frequent tumor GAs amenable to targeted therapeutics, with the most common actionable pathways being cell cycle regulation/DNA repair, RAS/RAF/MEK, and epigenetic pathways. Formal prospective study of targeted therapy in pediatric and AYA cancer patients, analogous to the NCI-MATCH trial, should be feasible and informative.

11012 **Poster Discussion Session; Displayed in Poster Session (Board #224), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Skeletal tumor burden on baseline ^{18}F-fluoride PET/CT to predict bone marrow failure after radium-223. *First Author: Elba Etchebehere, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The purpose of this study is to evaluate if skeletal tumor burden on whole-body 18F-sodium fluoride PET/CT (Fluoride PET/CT) is able to predict bone marrow failure Radium-223 therapy (Ra-223). **Methods:** We retrospectively reviewed 76 histologically confirmed hormone-refractory prostate cancer patients (43-89 y old; mean 71 ± 9 yrs.) with bone metastases who underwent Fluoride PET/CT either prior to, during and/or 3 months after therapy with Ra-223. Bone marrow failure (BMF) was the primary end point. BMF was defined as: (1) the development of hematologic toxicity (WHO Grades 3 or 4) associated with no recovery after 6 weeks, or (2) death due to BMF after the last Ra-223 dose. The following parameters were evaluated: Fluoride PET/CT skeletal tumor burden (TLF_{1O} < 12,000 *vs* ≥ 12,000), the total number of Ra-223 doses the patients received (Ra_{Tot}), the use of chemotherapy during and after Ra-223, serum hemoglobin concentration (HBG < 10 *vs* ≥ 10g/dl), serum alkaline phosphatase (AP < 147 *vs* ≥ 147UI/L), and serum PSA (< 10 *vs* ≥ 10 ng/ml). **Results:** Forty-one patients underwent a baseline Fluoride PET/CT prior to Ra-223 and were eligible for analysis. The number of Ra-223 administrations ranged from 2 to 6 (mean = 5). Of the 41 patients, 16 developed BMF (G3 = 12; G4 = 4). A significant increased risk of developing BMF was observed for patients with $TLF_{1O} \geq 12{,}000$ (OR = 40.0; p = 0.0013), fewer Ra_{Tot} (OR = 0.51; p = 0.0190), HGB < 10 g/dl (OR = 51.0; p = 0.0137) and AP ≥ 147UI/L (OR = 9.50; p = 0.0025). Chemotherapy used concomitant to or after Ra-223 was not found to increase risk of BMF (OR = 0.79; p = 0.71), nor was PSA (OR = 1.17; p = 0.83). Moreover, in a multivariable analysis including all evaluated parameters, TLF_{1O} was the only independent predictor of BMF (OR = 8.74; p = 0.0450). **Conclusions:** Bone marrow failure may occur after Ra-223 treatment, and high skeletal tumor burden as quantified by Fluoride PET/CT is a significant risk factor.

11013 **Poster Discussion Session; Displayed in Poster Session (Board #225), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Imaging peritoneal metastasis of gastric cancer with PET/CT and the radiotracer ^{18}F-fluorothymidine (^{18}F-FLT):Proof-of-concept study. *First Author: Yoshitaka Honma, Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan*

Background: Peritoneal metastasis (PM) is the most frequent form of metastasis in gastric cancer (GC), especially in diffuse type adenocarcinoma (DTAC). Microscopic PM can be identified accurately only in laparoscopic staging. The utility of metabolic imaging for GC is limited because DTAC are not 18F-fluorodeoxiglucose (FDG) avid, and the sensitivity of detecting PM by FDG/PET is known to be low in GC.18F-fluorothymidine (18F-FLT) was developed for imaging cellular proliferation, and its physiological accumulation to the intestinal tract is known to be less than FDG. In previous reports, 18F-FLT-PET had higher sensitivity than FDG and could visualize primary lesion or lymph node metastasis of GC with sufficient contrast, even in DTAC. In this proof-of-concept study, we explored the capability of 18F-FLT PET/CT for detecting macroscopic PM of GC. **Methods:** The key eligibility criteria were: (i) histologically proven gastric adenocarcinoma; (ii) PM detected by CT imaging; (iii) PS: 0-2; and (iv) sufficient organ function. 18F-FLT PET/CT was performed at the National Cancer Center Hospital, and the PET/CTs were interpreted by two independent radiologists who were not informed of the patient background. Detection sensitivity (DS) was defined as proportion of patients for whom 18F-FLT PET/CT noted at least one of the lesions detected in CT. **Results:** Twenty patients were enrolled in this study. One patient was diagnosed as gastric lymphoma by pathological review, who was excluded from the analysis. Fifteen of 19 patients (78.9%) had DTAC. PM was detected by 18F-FLT PET/CT in 14 of 19 patients (SUVmax: 1.697-13.21, DS = 73.7%). Classifying the patterns of PM into omental-cake-type (oPM) and nodule-type (nPM), seven of 19 patients (36.8%) had oPM, all of which were detected by 18F-FLT PET/CT (SUVmax: 1.771-13.21, DS = 100%). Meanwhile, in a total of 42 nodules detected by CT in the 12 patients with nPM, 20 nodules were detected by 18F-FLT PET/CT (SUVmax for positive cases: 1.697-6.524, DS = 47.6%). **Conclusions:** This proof-of-concept study clear the criteria of DS by 18F-FLT PET/CT for proceeding to the future study investigating clinical utility of 18F-FLT PET/CT for PM of GC. Clinical trial information: UMIN000009329.

11014 **Poster Discussion Session; Displayed in Poster Session (Board #226), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Phenotypic correlation of tumor uptake of exogenous glutamine radiotracer versus tumor mutational status. *First Author: Mark Dunphy, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Fluoroglutamine (FGln) is a positron emission tomography (PET) clinical tumor imaging radiotracer now in a first in human trial. Glutamine metabolism in several cancer models has been linked both to aggressive tumor phenotype and specific oncogenic mutations. **Methods:** Adults with advanced solid tumors or lymphoma with adequate end organ function are eligible for this phase 1 trial. Microdose radiotracer is given by IV bolus, followed by serial PET scans over a 3-hour period. The primary endpoint is safety, pharmacokinetics, metabolism and bio-distribution of FGln, to be reported separately. Secondary endpoint analysis compares tumor uptake of exogenous glutamine tracer versus tissue-derived tumor biomarkers. **Results:** 20 pts: median age 75 (range 21-75); male 40%; primary tumor site: brain (6), pancreas (3), breast (3), kidney (2), stomach (2), lung (1), large bowel (1), lymph node (1), adrenal gland (1); histology: adenocarcinoma (11), neuroendocrine (2), lymphoma (1), astrocytoma/oligodedriglioma/GBM (6); mean tumor size 2.8cm (range 1.1 to 11.5). Tumor uptake of exogenous glutamine tracer varied between pts with PET-positive tumors (n = 12) and PET-negative (n = 8); tumor uptake expressed as tumor/blood ratio of tracer concentrations, ranged 0.8-4.4. Uptake did not correlate with pre FGln-injection serum glutamine levels (R^2= 0.005); median serum glutamine concentration 610 (range 425-982). 14 pts with tumoral DNA sequencing available or pending were identified. Mutations in TCA cycle genes occurred in 6 of 14 pts (2 with IDH R132H, 1 with FH F402L, 3 with SDH-A/B alterations). Highest observed tumor uptake of exogenous glutamine radiotracer and the longest retention of tracer were observed in 2 pts with tricarboxylic acid (TCA) cycle mutations. **Conclusions:** Fluoroglutamine PET detected tumors in a variety of cancer types, including patients with known mutations affecting tumor metabolism. Clinical trial information: NCT01697930.

11015 **Poster Discussion Session; Displayed in Poster Session (Board #227), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Subjects' views on compensation for donating biospecimens. *First Author: Rebecca D. Pentz, Emory University School of Medicine, Atlanta, GA*

Background: Biobanking for research is an increasingly common practice. Ethical concerns regarding ownership of tissue and compensation for donation have arisen as the prevalence of biobanks has increased. **Methods:** Patients eligible for surgical removal of tumors or other tissues at the Winship Cancer Institute were asked to donate tissue by physicians during a surgical oncology clinic as well as by tissue donation staff carrying out a national, multisite NCI biobanking study. We surveyed 101 of these patients, regardless of whether they donated tissue, about informed consent issues surrounding broad future research use of donated tissues. One question queried participants on their preferences regarding compensation for biospecimen donation. Once consented, participants had the option of completing the interview on-site or over the phone. We did not collect any Protected Health Information, other than contact information, which was destroyed upon completion of the interview. **Results:** Of the 140 patient approached, 101 (72%) participated, with 94 (93%) completing the interview over the phone. 19 (14%) patients refused to participate and 20 (14%) were lost to follow up. 52 (51%) were male, 74 (73%) white, and the median age was 62 years. 50 (50%) had a college degree, and the average income bracket was $60,000 - $80,000. Seventy-five (74%) did not think they should be paid for donating tissue. When probed as to their reasons for not wanting payment, most subjects [46 (61%)} provided altruistic reasons. Five noted that biobank participants were not subjected to any additional burden, and three mentioned that the tissue would be destroyed if they had not participated. Seven of the 75 said payment would be appreciated though not expected. Nine (9%) said donors should be paid, with five citing ownership of the tissues. 14 (14%) believed they should only be paid under certain conditions, most commonly referring to tissue use by for-profit companies. Three (3%) had no opinion. **Conclusions:** The majority of subjects did not feel that they should be compensated for tissues provided, viewing it as an opportunity to help others. A small minority believed compensation was due, especially in the case of tissue use by private researchers in for-profit companies.

11016 **Poster Discussion Session; Displayed in Poster Session (Board #228), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Progesterone receptor isoform ratio to define the molecular signature of luminal breast cancers and their antiprogestin responsiveness. *First Author: Maria May, IBYME-CONICET, Buenos Aires, Argentina*

Background: Current therapies for hormone receptor (+) breast carcinomas target the estrogen receptor. Evidence indicates that the progesterone receptor (PR) also participates in cancer growth. In experimental models, we showed that mifepristone (MFP) inhibits the growth of mammary carcinomas when the predominant isoform is PR-A. The aim of our study was to confirm these observations and explore the molecular signatures of breast cancers overexpressing isoforms PR-B or PR-A. **Methods**: Tissue sections from 100 surgical samples were cultured with MFP (10 nM) or vehicle for 48 hs, and embedded in paraffin for Ki-67 staining. Frozen samples were processed for Western blotting (n = 360) or RNAseq (n = 16). Patients were considered PR-A(+) if PR-A/PR-B $\geq$ 1.2, or PR-B(+) if PR-A/PR-B $\leq$ 0.83. The sample size required to detect a 50% difference in MFP response between PR-A+ vs. non PR-A+ samples (type I error: 5%; type II error: 10%) was 19 patients/group. **Results**: MFP only inhibited Ki-67 expression in PR-A+ samples ($p < 0.001$). The 9 ductal HER2 (-) cancer samples analyzed by RNA-Seq with the EBseq algorithm showed 140 transcripts (FC $> \pm 2$; FDR < 0.05); 55 up-regulated in PR-A, and 85 in PR-B. Gene ontology showed functional modules associated with cancer cell proliferation such as 'Aurora B signaling' and the 'FOXM1 transcription factor network' ($p < 0.01$) linked with PR-B up-modulated genes. Intrinsic subtypes and risk score (ROR-S) predicted by the 50-gene PAM50 model were associated with each PR isoform group; 4/4 PR-B cases were Luminal B and 4/5 PR-A were Luminal A ($p < 0.01$). Studies of 140 deregulated transcripts discriminating PR-A from PR-B (TCGA RNASeq breast cancer dataset) demonstrated that a large number of genes up-regulated in PR-B group, remained up-regulated in luminal B and basal-like cancers, compared with PR-A associated genes that are expressed in normal-like and luminal A subtypes. The gene expression signatures associated to each PR isoform are now under validation using an independent cohort of breast cancer samples. **Conclusions:** The PR isoform ratio may define subgroups within the luminal breast cancers: those with PR-A/PR-B $\geq$ 1.2 are candidates for MFP treatment.

11017 **Poster Discussion Session; Displayed in Poster Session (Board #229), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

A head-to-head comparison of Mammaprint and Oncotype Dx: A McGill University Health Center Experience. *First Author: Ralph Maroun, Department of Oncology, McGill University Health Center, Montreal, QC, Canada*

Background: The Objective of our study was to investigate the concordance of patient results from a single university centre tested with the 21-gene recurrence score assay, Oncotype DX (ODX) when compared to the 70-gene signature Mammaprint (MP), the 80 gene signature of BluePrint (BP) and TargetPrint (TP). **Methods:** Eighty-six consecutive patient-slides node negative hormone positive breast cancer tissue tested with the ODX were enrolled. Based on the ODX recurrence scores (RS) patients were placed either on Chemotherapy and hormonal therapy or hormonal therapy alone. MP was performed on all of the slides previously tested with ODX, and results were reported as either Low or high recurrence risk and were compared with those of the ODX. **Results:** Of the 50 ODX low RS cases, 33 were low risk by MP (66 % agreement) and of the 9 ODX high RS, 7 were high risk by MP (78 % agreement). Of ODX intermediate risk cases (27), 14 of were MP Low risk (52 %), (48 %) 13 were MP high risk. Of BP low risk luminal tumors, 33/49 (67%) were ODX low, 14/49 (29%) ODX intermediate, and 2/49 (4%) ODX high risk (Table). BP class was correlated with ER, PR and HER2 results. Overall agreement between clinical ER, PR, HER2 (IHC+FISH) results with TP results were 98% (81/83), 83% (69/83), 99% (82/83), and percent positive agreement for HER2 was 0/1 (of unequivocally HER2 positive cases identified correctly by TP). **Conclusions:** Results from our institution show that they are real differences in risk assignments between MP and ODX that may affect treatment decisions. There was close correlation between pathologic variables and MP and BP. These results underscore the need for a proper validation of the ODX and MP genetic signatures with outcomes in order to avoid misclassification of both low and high risk patients.

ODx vs. MP.

Oncotype					
Mammaprint	**Blueprint**	**High**	**intermediate**	**Low**	**Total**
High risk MP	Basal-like	0	0	0	0
	ERBB2	1	1	0	2
	Luminal-like	6	11	18	35
High risk total		7	12	18	37
Low risk MP	Basal-like	0	0	0	0
	ERBB2	0	0	0	0
	Luminal-like	2	14	33	49
Low risk total		2	14	33	49
Grand total		10	25	52	86

11018 **Poster Discussion Session; Displayed in Poster Session (Board #230), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Circulating tumor cell (CTC) EMT and stem cell biomarker expression predict overall survival (OS) in mCRC by a combined immunomagnetic qRT-PCR approach. *First Author: Yan Ning, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: CTCs harboring epithelial, mesenchymal and stem cells direct the metastatic process. CTC enumeration and biomarker expression have been associated with clinical outcomes in mCRC patients (pts). We developed and validated a combined immunomagnetic qRT-PCR protocol for colorectal CTC characterization based on epithelial, EMT, and stem cell biomarkers with sufficient sensitivity, specificity, and efficiency. The goal of this study was to test whether molecular characterization of CTCs will more effectively predict OS. **Methods:** CTCs were obtained from 94 pts with mCRC [Median age: 56.5 years, Median follow up: 17.3 (1.3, 39.5) mos and OS: 11.4 (9.0, 21.1) mos]. All pts were refractory to standard treatments and were enrolled in clinical trials at USC from 2009 to 2014. Prior to treatment initiation, peripheral blood was collected for CTC isolation. Immunomagnetic qRT-PCR was used for CTC detection based on the presence of CK20 and survivin gene expression. We then selected, based on functional roles and reliability of detection in CTCs, and quantified markers of EMT (PI3Kα, Akt-2) and stem cell (ALDH1) pathway activation in CTC-positive mCRC pts with AdnaGen primer mixture. Cut-off values were determined by Receiver-operating characteristic (ROC) curves. **Results:** 74 of 94 (79%) pts with CTCs based on CK20 and/or survivin gene expression (CTC-positive group) had a significantly worse OS (10 mos v. not yet reached;) compared with the CTC-negative group (21%) in both univariate (HR:3.383 [1.04, 11.01], $P = 0.001$) and multivariate analyses (HR : 4.557 [1.097, 18.926], $P = 0.037$). All CTC-positive pts, which had PI3Kα(57%), Akt-2(56%) and ALDH1(80%) mRNA expression, independently predicted OS based on cut-off values of each marker. Higher gene expression associated with significantly worse OS compared to those with lower gene expression: PI3Kα: 6.4 *v.* 10.4 mos; Akt-2: 8.6 *v.* 23.6 mos; ALDH1: 7.8 *v.* 10.3 mos ($P < 0.001$ for all comparisons). **Conclusions:** Our study is the first to demonstrate the prognostic and predictive significance of this CTC EMT and stem cell gene signature in mCRC pts. This technology may allow real time molecular monitoring of drug efficacy.

11019 **Poster Discussion Session; Displayed in Poster Session (Board #231), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Prospective study comparing outcomes in patients with advanced malignancies on molecular alteration-matched versus non-matched therapy. *First Author: Jennifer J. Wheler, Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: With the paradigm shift to precision medicine, we hypothesized that matching patients to therapy based on molecular profile could significantly improve outcomes. **Methods:** Archival tissues from patients treated in MDACC's Phase I clinic were sent to Foundation Medicine, where next-generation sequencing (NGS)-based comprehensive genomic profiling (236 genes) was performed. Patients with actionable molecular alterations were preferentially treated on pathway-matched therapies. A direct match was defined when the drug targeted an alteration or its immediate downstream effector; an indirect match, when the drug targeted a protein > 1 effector removed from the alteration. Based on matching and the number of alterations in patients' tumors, an exploratory scoring system was evaluated; each direct match was given a 1, each indirect match 0.5, and no match a value of zero, normalized by the number of alterations per patient. Progression-free survival (PFS) and overall survival (OS) were analyzed (Kaplan-Meier method; log-rank test). **Results:** Molecular profiling was performed for 339 of 500 patients (68%) consented on the study. Ninety-five percent of those tested (322/339) had ≥ 1 molecular alteration on NGS. Patients (n=175) were treated either on pathway-matched (n = 110, 63%) or non-matched therapy (n = 65, 37%). Matched/non-matched patient characteristics were similar. The most common reasons for not profiling or not treating were inadequate tissue or early death/hospice. Outcomes are shown below. **Conclusions:** Patients treated on matched therapy had significantly improved PFS and OS versus those on non-matched therapy. An exploratory scoring system that included the number of matched therapies in the regimen and molecular alterations in the tumor confirms the above results. Further analyses of response rates and multivariate analyses of factors impacting outcomes are ongoing.

Outcome by therapy and scoring system.

Basis	**Treatment**	**Patients (n = 175)**	**Median PFS (months)**	**p-value**	**Median OS (months)**	**p-value**
Matching	Matched	110	3.9	0.002	10.8	0.018
	Unmatched	65	3.3		7.5	
Scoring system	≥ median score (≥ 0.13)	92	3.8	0.013	11.1	0.026
	< median score (< 0.13)	83	3.3		7.5	

11020 **Poster Discussion Session; Displayed in Poster Session (Board #232), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM**

Comprehensive genomic profiling of sarcomas from 267 adolescents and young adults to reveal a spectrum of targetable genomic alterations. *First Author: Deborah Morosini, Foundation Medicine, Inc., Cambridge, MA*

Background: Sarcomas comprise nearly 10% of all cancers (CA) in adolescents and young adults (AYA, age 15-39). Despite high unmet clinical need for better treatments, comprehensive genomic profiling (CGP) of AYA sarcomas has not been reported. To identify the genomic alterations (GA) and potential therapeutic targets, we performed CGP on 267 AYA sarcomas. **Methods:** DNA and RNA were extracted from 267 AYA sarcomas. CGP was performed on hybridization-captured libraries to a mean coverage depth of $>$ 500X for 405, 315, or 265 (DNA) and 333 (RNA) CA-related genes, plus select intronic regions frequently rearranged in CA. Results were analyzed for base substitutions, insertions/deletions, copy number alterations, and fusions/rearrangements. We compared pediatric (peds) (n = 51), AYA (n = 267) and $>$ 39yo (n = 853) patients and complex karyotype driven (CKD) versus fusion driven (FD) subtypes. **Results:** In AYA sarcoma, the most common GAs were in *TP53* (25%), *CDKN2A* (16%), and *EWSR1* (12%). An average of 3 GAs/sample was found (range 1-12). Clinically relevant GAs (associated with approved drugs or mechanism based trials) were present in 60% of cases. Cell cycle alterations (*CCND1,2,3, CCNE1, CDK4/6, CDKN2A/B, RB1*) were enriched in $>$ 39 yo (53%) vs AYA sarcomas (33%, $p < 0.001$, Fisher's exact test). Comparison of CKD and FD AYA sarcomas revealed differing frequency by age grouping. CKD sarcomas were less frequent in the AYA group (15%) compared to either the peds (20%) or $>$ 39 yo (22%). FD sarcomas seem more frequent in AYA tumors (5%) vs $>$ 39 yo (0.5%), but less frequent than in the peds (35%). FD tumors were enriched for GA in *EWSR1* and *SS18* corresponding to the frequency of Ewing and synovial sarcoma, respectively, seen in AYA CA. Novel fusions were also found, such as a *LMNA-NTRK1* fusion in a YA with metastatic sarcoma, enabling enrollment in a clinical trial of NTRK-specific therapy. **Conclusions:** A combined DNA and RNA CGP assay can characterize tumor specific GA in AYA sarcomas and guide novel treatment decisions. Further use of CGP in these patients can potentially increase AYA enrollment in clinical trials of targeted therapies and lead to improved outcomes for these aggressive forms of CA.

11021 Poster Session (Board #233), Sun, 8:00 AM-11:30 AM

Comparison of tumor-infiltrating lymphocytes between primary and metastatic tumors in breast cancer patients. *First Author: Rin Ogiya, Tokai University, School of Medicine, Isehara Kanagawa, Japan*

Background: The assessment of tumor-infiltrating lymphocytes (TILs) in primary breast cancer allow to predict prognosis and chemotherapy benefit, particularly in triple-negative (TN) and HER2-positive breast cancer. In the latter, it predicts also benefit from HER2-targeted agents. A little is known about the change of TILs during the metastatic progression. We compared TILs in paired samples from primary and metastatic TN and HER2-positive tumors. **Methods**: We retrospectively identified 25 patients with triple-negative or HER2-positive early breast cancer diagnosed between 1990 and 2010 at a single institution and subsequently experienced a distant recurrence confirmed by tumor biopsy/resection. Hematoxylin- and eosin-stained slides for these paired match cases were evaluated for stromal-TILs as recently recommended (Salgado R Ann Oncol 2014). We defined three groups according to : low-TILs (≤ 5), intermediate-TIL (10-50), Lymphocyte Predominant Breast Cancer (LPBC) ($\geq 60\%$). **Results**: We evaluated 25 breast cancer patients (n = 11 TN; n = 14 HER2+). Primary tumors had 28% (LPBC), 52% (intermediate-TIL) and 20% (low-TIL). Corresponding first metastatic recurrences had 44% (intermediate-TIL) and 56% (low-TIL). Overall, TILs in primary tumors were significantly higher (average 34.6%) than at metastatic recurrences (average 15.7%) (paired t-test, $p = 0.004$). This difference was similar in HER2+ ($p = 0.036$) and TN ($p = 0.06$). In 13/25 (66%) cases the percentage of TILs decreased and in 3/25 increased (difference $> 10\%$). We performed an exploratory analysis of post-progression overall-survival according to TIL at distant site of recurrence. The group with low-TIL had a significantly lower overall-survival than intermediate-TIL (HR = 3.77, CI 95% 0.99-14.9; logrank test $p = 0.038$). **Conclusions**: Tumor at first metastatic recurrence in TN and HER2+ breast cancer have lower infiltrating-lymphocytes compared to primary tumors, supporting a role for immune escape in tumor progression. Low-TIL at recurrences seemed to be associated with worst overall survival suggesting a more aggressive phenotype. These findings warrant independent confirmation.

11022 Poster Session (Board #234), Sun, 8:00 AM-11:30 AM

Complications following immediate breast reconstruction and influence on breast cancer recurrence rates. *First Author: Suzanne M Beecher, University Hospital Galway, Galway, Ireland*

Background: The rate of immediate breast reconstruction has risen over the past number of years. Post-operative infections are more frequent in patients who undergo reconstruction. The inflammatory response to a postoperative infection can increase the risk of tumour recurrence in other forms of cancer through the release of pro-inflammatory mediators. The aim of this study was to assess the relationship between complications and breast cancer recurrence in patients who undergo immediate breast reconstructive surgery. **Methods:** A review of a prospectively maintained database of allpatients who had immediate breast reconstruction between 2004 & 2009 was conducted. All patients had a minimum 5-year follow up. Univariate & multivariate Cox Regression analysis was performed using SPSS v21. **Results:** 229 patients who underwent immediate breast reconstruction were identified. The overall 5-year disease-free survival was 86%. 53 (23%) patients had wound complications. 43 (19%) had a wound infection. There was a significantly greater risk of developing systemic recurrence in patients who experienced a post-operative wound complication compared to those without (HR: 4.94; 95% CI: 2.72 - 8.95; $P < 0.0001$). The five-year disease free survival rate for patients who had a wound complication was 64% compared to 91% in patients without a complication ($p < 0.0001$). **Conclusions:** This study demonstrates that wound complications after immediate breast reconstructive surgery may have survival implications for breast cancer patients. Further research is warranted to confirm this relationship. In addition, strategies are required to minimize the risk of post-operative wound complications in breast cancer patients undergoing reconstruction.

11023 Poster Session (Board #235), Sun, 8:00 AM-11:30 AM

Inhibition of AKT3 to increase migration and metastasis by upregulation of S100A4 protein expression. *First Author: Florian Ewald, University Medical Center Hamburg Eppendorf, Hamburg, Germany*

Background: The treatment of patients with distant metastases represents one of the biggest challenges in modern oncology, and the occurrence of metastases often determines the prognosis of the disease. Therefore, understanding the mechanisms facilitating the development of metastasis is of paramount importance. It was previously shown that activation of the PI3K/AKT pathway is a requirement for the ability of tumour cells to disseminate and form metastases. However, single AKT isoforms (AKT1, AKT2 and AKT3) were shown to have different, and even opposing functions regarding the regulation of cancer cell migration *in vitro*, giving rise to the hypothesis that inhibition of distinct AKT isoforms might have undesirable effects on cancer progression. The aim of this project therefore is to investigate the functions of the specific AKT isoforms regarding migration and metastasis of cancer cells. **Methods:** Three cell lines were used to generate single and double AKT isoform knockdown cells. Migration and invasion of these cells was analysed *in vitro* using live imaging migration, chemotaxis, and invasion assays. Metastatic potential of AKT isoform knockdown MDA-MB-231 cells was evaluated in a subcutaneous xenograft mouse model *in vivo*. **Results:** Knockdown of AKT3, but not AKT1 or AKT2, results in increased migration and scattering *in vitro*, and this effect was even more pronounced in AKT2/AKT3, and AKT1/AKT3 double knockdown cells. Furthermore, we were able to demonstrate that knockdown of AKT2/AKT3 and AKT1/AKT3 results in an increased number of lung metastasis, as detected by Alu PCR and upon histological examination. We found that AKT3 specifically regulates the expression of the metastasis promoting protein S100A4 via regulation of NFAT5 in MDA-MB-231 cells, and knockdown of S100A4 or NFAT5 were able to reverse the AKT3 induced increase in migration. **Conclusions:** Our study provides novel insight into the specific contribution of each AKT isoform to the regulation of migration and metastasis, and our results indicate that inhibition of AKT3 might cause adverse effects on cancer dissemination and progression. Therefore, our results provide a rationale for the development of AKT isoform specific inhibitors.

11024 Poster Session (Board #236), Sun, 8:00 AM-11:30 AM

Evaluation of a novel c-MET based circulating tumor cell (CTC) biomarker in patients with gastrointestinal (GI) and genitourinary (GU) malignancies. *First Author: Tian Zhang, Duke University Medical Center, Durham, NC*

Background: Genetic alterations in the *MET* oncogene exist in many GI and GU malignancies. *MET* amplification is associated with poor prognosis and can arise as a resistance mechanism to EGFR targeting therapies. We aimed to capture and identify CTCs expressing c-MET. **Methods:** We modified the Cellsearchplatform by using nanomagnetic particles conjugated to antibodies against c-MET to capture c-MET-expressing CTCs and stained for c-MET-PE, DAPI, and pan-CK-FITC. CD45 + cells were excluded. The method was validated by spiking *MET*-amplified gastric cancer cells, c-MET-overexpressing, nonamplified cancer cells, and *MET*-negative cancer cells into peripheral blood from healthy volunteers (HVs). Peripheral blood samples were obtained from patients (pts) with refractory metastatic gastric, pancreatic, colorectal, bladder, renal, and prostate cancers. CTC enumeration with c-MET capture was compared to EpCAM capture. After CTC isolation, DNA FISH for *MET* amplification was performed. **Results:** The novel c-MET CTC assay was 80% sensitive for *MET*-amplified cells, 40-80% sensitive for c-MET-overexpressed cells, and 100% specific for c-MET negative cells and in 20 HVs. Of 50 pts tested thus far, we captured c-MET CTCs in duplicate samples from 3 pts, with gastric adenocarcinoma (90 and 52 c-MET CTCs), colorectal adenocarcinoma (7 and 2 c-MET CTCs), and renal cell carcinoma (RCC; 3 and 1 c-MET CTCs). CTC FISH demonstrated polysomy 7 and *MET* amplification in both gastric and colorectal cancer pts and trisomy 7 with gain of *MET* gene copies in the RCC pt. **Conclusions:** The c-MET CTC assay is rapid, non-invasive, sensitive and specific. c-MET expressing CTCs can be detected in gastric, colorectal, and renal cancers but not negative controls. *MET* amplification can be detected using FISH after CTC capture, leveraging this technology as a potential minimally invasive liquid biopsy. This approach may be clinically useful to identify and follow patients who may be candidates for c-MET directed therapies.

11025 Poster Session (Board #237), Sun, 8:00 AM-11:30 AM

Circulating tumor DNA (ctDNA) as a prognostic marker for recurrence in resected pancreas cancer. *First Author: Judy Sing-Zan Wang, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Despite aggressive therapeutic interventions with pancreaticoduodenectomy and adjuvant chemo/chemoradiotherapy, recurrence rates remain high for patients with resectable pancreas cancer. Additionally, current post-operative surveillance methods including tumor marker CA19-9, clinical symptoms, and CT scans lack sensitivity and specificity for early recurrence. Hence, a practical, blood-based biomarker that could identify cancer at an earlier time point, and prompt a change in management, would be clinically important. **Methods:** Using a highly sensitive digital DNA quantification approach, we measured *KRAS* mutation-associated circulating tumor DNA (ctDNA) in the archived sera of 46 resected pancreas adenocarcinoma patients taken 8-10 weeks post-operatively, after confirming the mutational presence in the primary tumor. Approximately 10 years of patient data were available from chart review and clinical databases to assess disease recurrence. A mutant allele fraction $>$ 0.02% was considered positive. **Results:** In a subgroup analysis, patients whose tumor had a p.G12V *KRAS* mutation and who did not have detectable levels of ctDNA had significantly longer time to disease recurrence than did patients with detectable ctDNA ($p = 0.02$; CI 1.037 to 12.77). Amongst patients whose tumor harbored a p.G12R *KRAS* mutation, those with undetectable ctDNA also had significant longer time to disease recurrence as compared to those with detectable ctDNA ($p = 0.01$; CI 1.241 to 36.99). In combination, 14 of the total 46 patients who had undetectable ctDNA following their resection trended, though statistically insignificant, towards longer time to disease recurrence (median time 545 to 471 days; HR = 0.58; $p = 0.3$) including 3 ctDNA-negative patients who still remain disease free. **Conclusions:** This retrospective analysis demonstrates that ctDNA can be detected in peripheral blood, and may be a valuable clinical marker for specific tumor mutations. Additional larger, prospective studies are needed to validate the clinical utility as a prognostic biomarker for recurrence in resected pancreas cancer.

11026 Poster Session (Board #238), Sun, 8:00 AM-11:30 AM

Emergence of *KRAS* mutation in detection of circulating tumor DNA during treatments for metastatic gastrointestinal cancer patients. *First Author: Yuji Takayama, Saitama Medical Center, Jichi Medical University, Saitama, Japan*

Background: It has been reported that molecular alterations in *KRAS* status were observed during treatment in colorectal cancers. The aim of this study was to explore change in *KRAS* status during various treatments for metastatic gastrointestinal cancer patients. **Methods:** One hundred and nineteen plasma samples were collected prospectively in 2014 from 52 patients who underwent chemotherapy due to metastatic gastrointestinal cancer including 46 colorectal and 6 pancreatic cancer patients. *KRAS* mutant circulating tumor DNA (ctDNA) was detected by digital PCR. Less than 0.1% of positive *KRAS* mutant is estimated as negative. **Results:** *KRAS* assessment in tumor tissues showed 22 patients with *KRAS* mutation (MT), 18 without *KRAS* mutation (WT) and 12 patients without *KRAS* information (NI). Among 22 patients with MT, KRAS assessment in ctDNA displayed 10 patients with KRAS mutant ctDNA and 12 patients without mutant ctDNA. While 18 patients with WT did not show any mutant ctDNA before chemotherapy, 3 patients exhibited *KRAS* mutant ctDNA after treatments. They are treated with different regimens such as CapeOX+BEV, CPT+Cmab and Regorafenib, respectively. *KRAS* mutant ctDNA was detectable in the blood of these three patients prior to radiographic detection of disease progression (PD). Among 12 patients with NI, there were 4 patients with *KRAS* mutant ctDNA and 8 patients without mutant ctDNA. Concerning response to chemotherapy, poor outcome was found in patients with *KRAS* mutant ctDNA regardless of *KRAS* status in tumor tissues. **Conclusions:** These results indicated that blood monitoring of *KRAS* status could be required not only to predict outcome of treatments but also to choose optimal regimes.

KRAS status		Change in KRAS ststus		Tumors		Treatments				Response		
Tissue	ctDNA	Number		Colon	Pancreas	Chemotherapy	Chemo+ BEV	Chemo+ Cmab or Pmab	Regorafenib	CR+PR+SD (%***)	PD	Not determined
Mutant (n = 22)	Mutant	10	0	7	3*	3	6	0	1	0 (0%)	10	0
	Negative	12	0	10	2*	5	7	0	0	5 (50.0%)	5	2
WILD (n = 18)	Mutant	0	0	0	0	0	0	0	0	0 (0%)	0	0
	Negative	18	3(Negative→MT)	17	1*	2	7(1**)	6(1**)	3(1**)	10 (58.8%)	7	1
Unknown (n = 12)	Mutant	4	0	4	0	2	2	0	0	0 (0%)	2	2
	Negative	8	0	8	0	1	7	0	0	2 (66.6%)	3	3

*, FOLFIRINOX; **, Negative→MT; ***, CR+PR+SD/CR+PR+SD+PD

11027 Poster Session (Board #239), Sun, 8:00 AM-11:30 AM

Subclassification of prostate cancer circulating tumor cells (CTCs) by nuclear size reveals very-small nuclear CTCs in patients with visceral metastases. *First Author: Yi-Tsung Lu, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: In prostate cancer (PCa), morphologic classification remains a standard clinical practice in pathology. It has been shown that nuclear size and shape in tumor sections correlate with distant metastasis and death, but this relationship has not been explored in emerging tissue sources such as CTCs. Using NanoVelcro chip, our group sub-classified CTCs in PCa patients by shape features focusing on nuclear size and related this to clinical information, particularly the lethal progression to visceral metastasis (VM). **Methods:** A total of 148 blood samples were obtained from 57 PCa patients across the spectrum of metastatic states: no metastases, non-visceral (osseous and/or nodal) metastases, and visceral (hepatic and/or pulmonary) metastases. CTCs captured and enumerated on NanoVelcro Chips were subjected to pathologic review including nuclear size. The distribution of nuclear size was analyzed using a Gaussian Mixture Model. Correlations were made between CTC subsets and metastatic status. **Results:** Statistical modeling of nuclear size distribution revealed 3 distinct subsets: large-nuclear ($>$ 15 μm), small-nuclear (snCTCs, 8.54 - 15 μm), and very-small-nuclear CTCs (vsnCTCs, $<$ 8.54 μm). The proportions of the 3 CTC nuclear subsets varied significantly among different metastatic states ($p < 0.001$). snCTC + vsnCTC identified patients with metastatic disease from those without (0.35 $\pm$ 0.66 versus 2.02 $\pm$ 3.36 cells per mL of blood, $p < 0.001$). vsnCTC counts alone were elevated in patients with VM when compared to those without (0.36 $\pm$ 0.69 vs. 1.95 $\pm$ 3.77 cells/mL blood, $p < 0.001$). Serial enumerations suggested the emergence of vsnCTCs prior to radiographic detection of newly developed VM. **Conclusions:** There are morphologic subsets of CTCs that can be identified by fundamental pathologic approaches, such as nuclear size measurement. Our observation strongly suggests that they contain relevant information on disease status. In particular, the detection of vsnCTCs correlated with the presence of VM and should be explored as a putative blood-borne biomarker to identify patients at risk for developing this lethal progression event of PCa.

11028 Poster Session (Board #240), Sun, 8:00 AM-11:30 AM

Molecular profiling of circulating tumor cells in non-metastatic breast cancer. *First Author: Victoria Forte, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Circulating tumor cells are prognostic in all stages of breast cancer (BC), yet few studies have examined their molecular biology in non-metastatic BC. We have previously reported a method for isolation and gene expression profiling of pure CTCs that permits gene expression profiling without background subtraction of leukocytes. We hypothesized that transcriptional profiling of CTCs prior to therapy may predict for pathologic complete response (pCR) to neoadjuvant chemotherapy (NC) in Stage II-III breast cancer. **Methods:** We are currently enrolling patients to a prospective, observational clinical study in which CTCs are enumerated and captured from 20 mL peripheral blood (PB) via immunomagnetic enrichment based on EpCAM followed by fluorescence-activated cell sorting (IE-FACS). CTCs and tumors are profiled with RNA Seq via the Illumina HiSeq (primary predictor); NanoString PAM50 and real-time polymerase chain reaction will be used as validation studies. **Results:** To date, we have isolated CTCs from 29/33 patients (88%). No CTCs were found in 23 healthy controls. The median number of CTCs isolated was 7 (range 0-65). We will analyze our primary endpoint when $n = 20$ and $n = 40$ NC treated patients. Currently 12/33 patients had NC and 21 had no NC; 10/12 patients had CTCs isolated and 5/10 patients had a pCR. RNA Seq of the first 17 patients CTCs shows clear differentiation between CTCs and PB with 253 differentially expressed genes with a fold-change of at least 2 (false-discovery rate adjusted $p < 0.001$). A gene set enrichment analysis of the 17 CTC samples demonstrated up-regulation of cancer related pathways ($p < 0.001$). RNA Seq and validation studies of additional CTC and tumor samples is currently in progress. **Conclusions:** RNA Seq of rare CTCs is feasible in Stage II-III breast cancer and shows evidence of oncogenes and tumor suppressor genes.

11029 Poster Session (Board #241), Sun, 8:00 AM-11:30 AM

Applying a mitotic index to circulating tumor cells and its prognostic significance: A cytological approach to patient stratification. *First Author: Daniel L Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: It has been well documented that enumeration of Circulating Tumor Cells (CTCs) isolated from the peripheral blood of breast cancer patients can be used as a prognostic indicator of survival. Typically, CTC identification relies on immunohistochemical stains used in an absent/present method (i.e. CK+/CD45-). However, the methodology for identification of CTCs is highly subjective, and histological cytology remains the standard identifier of cancer cells. We expand upon our work regarding the cytological criteria of CTCs, Adams et al, Cytometry 2015, to determine if pathological grading criteria can be applied to CTCs. We report the assessment for overall survival of late stage breast cancer in relation to CTC number and presence of active mitosis. **Methods:** A prospective pilot study of 30 single blinded Stage III/IV breast patient samples were provided by Fox Chase Cancer Center and University of Maryland Baltimore. 7.5mL whole blood was diluted in pre-fixation solution and filtered by CellSieve microfiltration. Cells were fixed, permeabilized, and stained with DAPI, an antibody cocktail against CK 8/18/19, EpCAM, and CD45. CTCs were enumerated and identified as described by Adams et al. Cytometry 2015. CTCs were further subtyped by 1) number of pathologically definable CTCs (PDCTCs) and 2) presence of mitotic events, identified by standard visual cues (e.g. prophase, anaphase, etc.). Kaplan-Meier plots and Hazard ratios were determined at 24 months. **Results:** PDCTCs were found in 87% (26 of 30) of patient samples tested. Of the 14 patients who had $\geq$ 5 CTCs/7.5mL, 36% (5 of 14) survived 24 months. Of the 16 patients who had $<$ 5 CTCs/7.5mL, 81% (13 of 16) survived 24 months. By contrast, 12 of the 30 patients who had $\geq$ 1 CTC with a mitotic event, 17% (2 of 12) survived 24 months. Of the 18 patients who had no mitotic CTCs, 89% (16 of 18) survived 24 months. **Conclusions:** Stratification of breast cancer patients based on number of CTCs is a prognostic indicator of patient survival. Our data suggests that prognostic value is increased by subtyping CTCs based on their mitotic index as assessed by overall survival over a 24 month period.

11030 Poster Session (Board #242), Sun, 8:00 AM-11:30 AM

Exploring the intra-patient *PIK3CA* mutational heterogeneity of circulating tumour cells by massive parallel sequencing in patients with metastatic hormone receptor-positive breast cancer. *First Author: Bram De Laere, Center for Oncological Research (CORE) - campus Sint-Augustinus - University of Antwerp, Antwerpen, Belgium*

Background: Circulating tumour cells are a real-time reflection of the *ad hoc* relevant subpopulation in patients with progressive disease. The study comprises the clinical application of a liquid biopsy to assess the *PIK3CA* genotype at a single cell level. **Methods:** Using CellSearch and DEPArray we purified single and groups of CTCs and WBCs from peripheral blood in 29 patients with metastatic hormone receptor-positve breast cancer. Recovered cells were subjected to Ampli1 whole genome amplification (WGA). Temporally-matched circulating cell-free DNA (cfDNA) was purified from plasma. Additionally, gDNA from archival primary tumour (PT) tissue sections was extracted as comparator. Mutation analysis was performed via targeted amplicon sequencing (TAS) of exons 9 and 20. **Results:** Archival PT tissue section showed a high frequency of mutant *PIK3CA* (16/27 (59,2%)), with a poor and fair agreement with cfDNA (n = 21; 43% disparity; κ = 0,113) and CTCs (n = 22; 27% disparity; κ = 0,394), respectively. A concordant *PIK3CA* status between different compartments was observed in 10/18 (56%) samples. At the used sequencing depth, cfDNA failed to the detect *PIK3CA* mutations in 4 cases (22%), of which three were present in the respective PT and corresponding CTCs. Gain of mutation was observed in 4/18 patients (22%), with a wild type PT and mutant CTCs at progression (cfDNA confirmed the MT genotype in three cases). A wild-type *PIK3CA* sequence in recovered WBCs indicates a high specificity and tumorigenic nature of the picked up variants. Intra-CTC analysis reveals *PIK3CA* mutational heterogeneity with the presence of both mutant and wild-type CTCs. Additionally, unique double-mutated CTCs were detected in 10/26 (38%) cases as well. **Conclusions:** PIK3CA mutations are frequent in metastatic HR^+ breast cancer. Intra-patient *PIK3CA* mutational heterogeneity was observed with cases of concordance and discordance when comparing early to advanced disease. The study presents the utilization of a liquid biopsy, thereby paving the way towards the application of a more personalized medicine in the management of patients with metastatic cancer.

11031 Poster Session (Board #243), Sun, 8:00 AM-11:30 AM

Vemurafenib to eliminate BRAF-mutated circulating epithelial tumor cells (CETCs) from blood of patients with malignant melanoma. *First Author: Dorothea Zimon, Transfusion Center Bayreuth, Bayreuth, Germany*

Background: Almost 50% of melanomas harbor mutations in BRAF, mainly V600E. The mutations are usually identified in the primary tumor. However, the primary tumor is often no longer available and metastases not always reflect the characteristics of the primary tumor. In melanoma it is not clear at what stage epithelial antigen is expressed. CETCs are present in peripheral blood in a significant proportion of patients with malignant melanoma. The aim of the present study was to analyze whether these cells belong to melanoma clone due to the presence of the BRAF gene mutation in these cells. For this reason, the analysis of multiple isolated CETCs from individual patients for BRAF gene mutations was performed. **Methods:** Blood from patients with malignant melanoma was analyzed for cells positive for the EpCAM and Melan-A using the maintrac approach, avoiding cell selection and using an image analysis system for detection. Subsequently, between 8-20 EpCAM and Melan-A positive cells from each patient were isolated individually using a semi-automated capillary approach and deposited one by one into micro cups. The DNA of individual cells was amplified by whole genome amplification and assayed using the cobas BRAF V600 mutation test. Furthermore, we performed mutation analysis of cells after magnetic bead enrichment which is known to contain a mixture of CETCs and leukocytes. **Results:** DNA could be amplified from all individually isolated cells. In addition, we analyzed the presence of V600 mutation after magnetic bead enrichment. A BRAF mutation was detected in 20 - 75 % of evaluable cells in patients with BRAF mutation in primary tumor. In advanced stage or metastatic patients under Vemurafenib therapy, we were not able to find mutated CETCs. **Conclusions:** Individually isolated CETCs from the peripheral blood from patients with melanoma allow not only to detect mutations but also to determine the frequency of mutated cells. This proves that at least part of the CETCs is originated from the primary tumor. Furthermore, detection of BRAF mutation in CETCs may be crucial for a successful molecular-targeted therapy.

11032 Poster Session (Board #244), Sun, 8:00 AM-11:30 AM

Folate Receptor-Positive Circulating tumor cell detected by LT-PCR based method as a diagnostic biomarker for non-small cell lung cancer. *First Author: Xiaoxia Chen, Tongji University Medical School Cancer Institute, Shanghai, China*

Background: To investigate the diagnostic performance of folate receptor (FR) positive circulating tumor cells (CTCs) in distinguishing non-small cell lung cancer (NSCLC) from lung benign disease by using a novel ligand-targeted polymerase chain reaction (LT-PCR) detection technique. **Methods:** CTCs were enriched from 3ml peripheral blood by immune-magnetic depletion of leukocytes and then labeled with a conjugate of a tumor-specific ligand folic acid and a synthesized oligonucleotide. After washing off free conjugates, the stripped bound conjugates were analyzed by quantitative PCR. **Results:** 756 participants (473 patients with NSCLC, 227 patients with lung benign disease, and 56 healthy donors) were randomly assigned to a training set and a test set. The CTC levels in patients with NSCLC were significant higher than those with lung benign disease ($P < 0.001$) and healthy donors ($P < 0.001$). Compared with CEA, NSE, and Cyfra21-1, CTCs displayed the highest area under curve (AUC) (training set: 0.815; validation set: 0.813) in the diagnosis of NSCLC, with a markedly sensitivity (training set: 72.46%; validation set: 76.37%) and specificity (training set: 88.65%; validation set: 82.39%). The model combining CTCs with CEA, NSE, and Cyfra21-1 was more effective for the diagnosis of NSCLC than tumor makers alone (sensitivity and specificity in the training set: 84.21%, 83.91%; validation set: 88.78%, 87.36%). In addition, the CTC levels were higher in patients with stage III/IV NSCLC compared with those with stage I/II disease. **Conclusions:** LT-PCR technique was feasible and reliable for detecting FR-positive CTCs in NSCLC patients and CTC levels could be used as a useful biomarker for the diagnosis of NSCLC.

11033 Poster Session (Board #245), Sun, 8:00 AM-11:30 AM

ERCC1 induction after oxaliplatin exposure may depend on KRAS mutational status in colorectal cancer patient: preliminary data from liquid biopsy. *First Author: Mariantonietta Di Salvatore, Medical Oncology Unit, Catholic University of the Sacred Heart, Rome, Italy*

Background: Basing on preliminary observations of OPUS and PRIME studies, our group retrospectively suggested that KRAS mutational status could affect response to oxaliplatin. We further confirmed this evidence in vitro demonstrating that KRAS mutated cell lines were more sensitive to oxaliplatin due to their inability to induce ERCC1 after drug exposure. Using CTCs as a surrogate, dynamic tissue, in this study we sought to confirm in vivo the relationship between KRAS mutational status, ERCC1 inducibility and clinical outcome in oxaliplatin-treated colorectal cancer patients. **Methods:** We collected blood samples from colorectal cancer patients treated with oxaliplatin-based regimen at 0 and 48 hours during the first cycle of chemotherapy. The presence of CTC was detected by AdnaGene system followed by multiplex RT-PCR including ERCC1 transcript. In CTC-positive ERCC1-positive patients, ERCC1 mRNA expression was measured using a quantitative real time RT-PCR method, before and after drug exposure. We evaluated the relationship between ERCC1 induction and KRAS mutational status and we tried to correlate this association with clinical outcome **Results:** On a total of 38 patients enrolled, 19 were KRAS wild type and 19 KRAS mutated. CTCs were detected in 12 (31,5 %) patients. ERCC1 was expressed in 8/12 CTCs-positive patients, 5 KRAS wild type and 3 mutated. After Oxaliplatin exposure, among ERCC1-positive patients, only 3 showed a significant induction of ERCC1 expression; interestingly all of them were KRAS wild-type and experimented a rapid progression of disease. The median PFS of patients with ERCC1 induction was shorter than that observed in patients with stable or reduced ERCC1 (2,5 months vs 7,2 months). Notably none of the KRAS mutated ERCC1-positive CTCs was able to induce ERCC1 and median PFS was 11,6 months. **Conclusions:** Although based on a small sample size,this study could support the relationship between KRAS mutational status, ERCC1 inducibility, and clinical outcome, corroborating our hypothesis that KRAS mutational status could be a surrogate marker of efficacy of oxaliplatin therapy. Further studies are warranted to study this association.

11034 Poster Session (Board #246), Sun, 8:00 AM-11:30 AM

EpCAM-independent isolation of EMT- circulating tumor cells in patients with primary breast cancer who receive primary systemic therapy. *First Author: Fanny Le Du, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tumor cells with amesenchymal phenotype and/or cancer stem-like cells (CSCs) are known to contribute to metastasis. Circulating tumor cells (CTCs) undergoing epithelial-mesenchymal transition (EMT) may not be detected using an anti-EpCAM antibody. We have developedan antibody-independent CTC enrichment platform, *Apostream* that does not rely on EpCAM-based capture, assessing morphologic and dielectric properties gated on CD45- cells. We used this instrument to determine the feasibility and clinical relevancy of measuring EMT-CTCs in breast cancer patients who received primary systemic chemotherapy (NST). **Methods:** Blood samples from newly diagnosed breast cancer patients were prospectively collected before NST (T0), after NST (T1), and after definitive surgery (T2) and processed using the *Apostream* system. Isolated cells were stained with antibodies to leukocytes (anti-CD45), and the DAPI nuclear stain, to identify CTCs. These CTCs were also stained with additional markers and examined on a laser scanning cytometer to measure protein expression levels of various markers to define 4 CTC-phenotypes: epithelial (CK+, EpCAM+, E-cadherin+), EMT (β-catenin,+ vimentin+), combined epithelial and EMT (CK+, EpCAM+, E-cadherin+, vimentin+), and CSC (CD44+, CD24low). Pathological complete response (pCR) was correlated to CTCs and marker expression. **Results:** Of the 15 patients enrolled, 5 patients achieved pCR. Epithelial-CTCs were detected in 60%, 67%, and 77% of the T0, T1, and T2 samples, respectively. EMT-CTCs were detected in 80%, 87%, and 85% of these samples, respectively. The mean number of CTCs with epithelial and EMT phenotype was 32.8 (range, 0-434) and 68.7 (range, 0-687) respectively. Number ofCTCs with epithelial phenotype and CSC phenotype were more likely to decrease, after NST, if N stage (nodes) > or equal 3 ($P = 0.014$) or T stage (primary tumor) > or equal 4 ($P = 0.066$), respectively. Neither EMT ($P = 0.505$) nor epithelial ($P = 0.580$) phenotypes of CTCs seem to predict pCR. **Conclusions:** A*postream* was successful in detecting both epithelial and EMT-CTCs. We will present the final data analysis of 50 patients to conclude on their predictive impact.

11035 Poster Session (Board #247), Sun, 8:00 AM-11:30 AM

Intra-patient genomic heterogeneity of single circulating tumor cells (CTCs) associated to phenotypic CTC heterogeneity in metastatic castrate resistant prostate cancer (mCRPC). *First Author: Mark Landers, Epic Sciences, Inc., San Diego, CA*

Background: Analysis of somatic genomic alterations in primary tumors is often used to define mutational status and guide therapeutic decisions. Selective pressures (including multiple lines of therapy) can lead to tumor evolution through step-wise accumulation of genomic alterations. CTCs from mCRPC pts have shown phenotypic heterogeneity in size, shape, CK expression (exp) and AR exp. Heterogeneity increases with multiple lines of therapy and is associated with treatment resistance. Defining CTC genotype to phenotype correlation may enable identification of emerging resistant clones for which a change in tx may be needed. We performed NGS whole genome CNV analysis at the single CTC level to detect driver somatic alterations associated with CTC epithelial & AR exp profiles. **Methods:** 147 CTCs were individually sequenced from 9 mCRPC pt blood samples and classified as traditional, CK-, or small CTCs and analyzed for AR exp. CTCs were individually isolated, lysed, WGA, library constructed, sequenced, aligned, parsed, normalized, and subtracted from germline CNV. Each pt CTC CNV profile was used to identify distinct sub-clonal populations and characterize CTC genomes. The genomic alterations were associated with CTC phenotypes. **Results:** Within each pt, 2-5 clonal populations were identified. On average, 11 CNV events were detected per CTC, with an intra-patient CTC correlation of 30-59%. The correlation increased 33% within a CTC specific phenotype ($p = 0.013$). The presence of mCRPC driver alterations (Amp- AR, cMYC; Del- TP53, PTEN, RB1) were predominantly in CTC subpopulations of pts not responding to tx. Overall, 59% of CTCs had a single driver alteration. **Conclusions:** Tracking all CTC populations is important to assessing genomic driver alterations. Intra-patient CTC genomic heterogeneity is common and statistically associated with heterogeneity of size, shape, CK & AR exp. CK- & small CTCs, unlike traditional CTCs, often possess loss of tumor suppressors, and are associated with resistance. Actionable alterations may only be observed in rare CTC subtypes and represent a potential new target to delay disease progression.

11036 Poster Session (Board #248), Sun, 8:00 AM-11:30 AM

Centrosome amplification and prognosis in breast cancer. *First Author: Ryan Austin Denu, University of Wisconsin School of Medicine and Public Health, Madison, WI*

Background: Centrosome amplification (CA) has been reported in all human cancers and is thought to result in aneuploidy and chromosomal instability (CIN). CA is associated with deleterious clinical factors such as higher grade and stage, but these reports have not shown how CA affects survival. Here we analyzed centrosome abnormalities in a cohort of 362 patients. **Methods:** A tissue microarray was constructed using triplicate punch biopsies from each patient. Centrosomes were recognized by immunohistochemistry as the overlap of pericentrin and polyglutamylated tubulin, which represent pericentriolar material (PCM) and centriole markers, respectively. We assessed centrosome number, size, shape, and clustering in at least 30 cells from 3 different regions of each patient's tumor. Ploidy and CIN were assessed using 6-chromosome FISH. Survival was analyzed using the Kaplan-Meier method and Cox proportional hazards modeling. Correlations were assessed using Spearman's rank correlation coefficient. **Results:** CA was associated with worse overall survival, both all-cause and breast cancer-specific mortality, as well as recurrence-free survival. Further, greater centrosome size and centrosome clustering were also associated with worse survival. CA was more pronounced in triple negative and HER2-positive subgroups, and also increased with increasing stage and histological grade. Cox proportional hazards modeling using CA, stage, grade, HER2 status, and hormone receptor status revealed that stage and hormone receptor status were the only independent predictors of survival in this cohort. Further, CA correlated with increased ploidy and chromosomal instability in these tumors. Lastly, the presence of acentriolar centrosomes was higher in cases of higher grade and stage. **Conclusions:** CA, centrosome clustering, and increased centrosome size are associated with worse survival and adverse clinical factors in breast cancer and provide important insight and possibly a direct biologic explanation for the clinical behavior of some aggressive cancers. The presence of acentriolar centrosomes was associated with higher grade and stage, which suggests that PCM fragmentation may be one cause of CA, particularly in more aggressive tumors.

11037 Poster Session (Board #249), Sun, 8:00 AM-11:30 AM

***SOD2* rs4880 CT/CC genotype to predict poor survival for Chinese gastric cancer patients received platinum and fluorouracil based adjuvant chemotherapy.** *First Author: Zhi Xu, Department of Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China*

Background: Adjuvant chemotherapy is a standard therapy for gastric cancer patients, however, treatment response is quite heterogeneous. Molecular biomarkers will be highly valuable to guide the therapy. The antioxidant enzymes superoxide dismutase 2 (SOD2) and glutathione S-transferase pi 1 (GSTP1) are involved in oxidative stress and drug detoxification, which modulate the efficacy of anticancer drugs. Here, we investigated the clinical associations of two single nucleotide polymorphisms of *SOD2* and *GSTP1* in stage II-III postoperative gastric cancer patients. **Methods:** *SOD2* rs4880 and *GSTP1* rs1695 were genotyped in 207 patients received postoperative platinum and fluorouracil based chemotherapy and 304 patients who did not. The genotyping were examined in DNA samples extracted from paraffin-embedded tumor tissue. Association of the 2 SNPs with each clinicopathologic feature was analyzed using the Pearson chi square test. Gastric cancer-specific overall survival was analyzed using Kaplan-Meier curves and log-rank tests. Multivariate Cox regression analyses of these SNPs also were performed. **Results:** *SOD2* rs4880 CT/CC significantly associated with decreased median overall survival time of 23 months when compared to the TT genotype (mean overall survival time of 65.2 months, $P = 0.002$) only for patients received adjuvant chemotherapy. Stratification analysis showed *SOD2* rs4880 CT/CC affected most significantly the clinical outcome for patients with tumor arising at gastric body (HR, 5.707, $P = 0.002$), well to moderately differentiated adenocarcinoma (HR, 4.900, $P < 0.001$), tumor of intestinal type (HR, 4.398, $P < 0.001$), or tumor size less or equal to 5 cm (HR, 2.490, $P = 0.004$); while *GSTP1* rs1695 GA/GG was significant decreased overall survival time among patients with tumor arising at fundus or cardia (HR, 3.001, $P = 0.004$), or mucinous or signet-ring cell carcinoma (HR, 4.750, $P = 0.042$). **Conclusions:** The present study suggested the two polymorphisms would affect the adjuvant chemotherapy outcome in specific subtype of gastric cancer. *SOD2* rs4880 could be used as a biomarker to predict the prognosis and response to therapy.

11038 Poster Session (Board #250), Sun, 8:00 AM-11:30 AM

Clinical impact of expanded *BRAF* mutational status on the outcome for metastatic colorectal cancer patients with anti-EGFR antibody: An analysis of the BREAC trial (Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer Genomics). *First Author: Satoshi Yuki, Hokkaido University Hospital, Sapporo, Japan*

Background: $BRAF^{V600E}$ mutation has been recognized as a prognostic marker in patients (pts) with metastatic colorectal cancer (mCRC). Several studies have consistently shown a significant association between the presence of $BRAF^{V600E}$ mutation and resistance to anti-EGFR antibody therapy in pts with previously treated mCRC while there are few reports on the clinical impact of minor *BRAF* mutations. **Methods:** The BREAC trial was a multicenter, retrospective study to investigate the novel biomarkers of anti-EGFR antibody therapy. *RAS and BRAF* mutations were detected by targeted sequencing using FFPE materials of mCRC pts who received anti-EGFR antibody after a failure to standard therapies. Progression-free survival (PFS), overall survival (OS), and response rate (RR) were evaluated according to expanded *RAS/BRAF* mutational status. **Results:** Of 184 pts enrolled in the study, *RAS/BRAF* testing was succeeded in 150 pts. Patients characteristics were as follows; male/female 87/63, median age 63.5 years (range, 28-85), PS 0/1/2 81/65/4. Median PFS, OS, and RR were 4.0 months, 12.4 months, and 21%, respectively. Expanded *RAS* and *BRAF* mutations were detected in 40 pts (26.7%, *KRAS/NRAS* 29/11) and in 16 pts (10.7%, $BRAF^{V600E}$/other 9/7), respectively. Observed *BRAF* mutations other than $BRAF^{V600E}$ were located at kinase domain. The clinical outcomes of other *BRAF* mutations were worse similar to those of $BRAF^{V600E}$ and expanded *RAS* mutations (Table). **Conclusions:** Expanded *BRAF* mutations might predict a lack of response for mCRC pts who received anti-EGFR antibody. Further investigation is warranted to confirm the clinical impact of expanded *BRAF* mutations.

	***RAS/BRAF* all wild**		***RAS/BRAF* any mut**	***RAS* any mut**	***BRAF* V600E mut**	***BRAF* other mut**
n	94		56	40	9	7
Median PFS (months)	5.9	**HR=3.49 p <0.0001**	2.1	2.1	1.6	2.3
Median OS (months)	14.5	**HR=2.14 p <0.0001**	6.4	6.3	4.6	8.1
RR (%)	31.9		1.8	2.5	0.0	0.0

11039 Poster Session (Board #251), Sun, 8:00 AM-11:30 AM

TLR6 polymorphism associated with overall survival in metastatic colorectal cancer (mCRC) patients treated with FOLFIRI/bevacizumab enrolled in FIRE3. *First Author: Satoshi Okazaki, University of Southern California/ Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Toll-like receptors (TLRs) play crucial roles in carcinogenesis and evolution of tumor microenvironment. Recent studies have shown that TLR6 dependent stimulation of the mesenchymal stem cells promotes angiogenesis. We tested the hypothesis that genetic variations of TLR6 will predict outcome in patients treated with bevacizumab based chemotherapy. **Methods:** Genomic DNA was isolated from tissue samples from 543 mCRC patients enrolled in the FIRE3 trial and treated in first-line with either FOLFIRI+bevacizumab (n = 265) or FOLFIRI+cetuximab (n = 278) was obtained from tissue samples. Two single nucleotide polymorphisms (SNPs) in the *TLR6*gene, rs5743810 G/A and rs3821985 G/C, were analyzed by PCR-based direct sequencing. These SNPs were tested for the association with tumor response, progression free survival (PFS) and overall survival (OS). Subgroup analyses by gender, tumor location, and Kras status were also analyzed. **Results:** In the FOLFIRI+bevacizumab treated patients, *TLR6*rs3821985 G/G variant showed a trend toward longer PFS (10.5 vs. 10.0 months, HR: 1.24, logrank p = 0.11) and OS (24.8 vs 24.7 months, HR: 1.28, logrank p = 0.10) compared to other variants (C/G and C/C). In the subgroup of Kras-wild type patients treated with FOLFIRI+bevacizumab, the same variant was significantly associated with longer PFS (10.7 vs. 9.9 months, HR 1.34, logrank p = 0.046) and OS (26.1 vs. 23.8 months, HR: 1.45, logrank p = 0.026) which remained significant (HR: 1.42, p = 0.041,) in a multivariate analysis. In the FOLFIRI+cetuximab treated patients, there was no association with outcome. **Conclusions:** This is the first report showing that *TLR6*SNP is associated with outcome in patients with wild type Kras mCRC treated with bevacizumab based chemotherapy.

11040 Poster Session (Board #253), Sun, 8:00 AM-11:30 AM

Stratification markers for the risk of recurrence after curative resection of stage II or III gastric cancer and potential clinical applications. *First Author: Takashi Oshima, Gastroenterological Center, Yokohama City University, Yokohama, Japan*

Background: Standard treatment for stage II or III gastric cancer is curative resection followed by adjuvant chemotherapy. Treatment outcomes are expected to be further improved by individualized therapy based on biomarker analysis. We extracted mRNA from frozen specimens of gastric cancer to establish a cDNA bank and then analyzed markers for stratifying the risk of recurrence after curative resection of stage II or III gastric cancer. We report our currently available findings. **Methods:** The study group comprised 255 patients with stage II or III gastric cancer who underwent curative resection and were followed up for ≥ 5 years after surgery. The patients were divided into 2 groups: a training set consisting of 145 patients and a validation set consisting of 110 patients. A total of 104 genes were selected as candidate biomarkers on the basis of comprehensive screening by DNA microarray, extraction by SAGE library analysis, and the identification of target molecules and related families, including the results of preclinical studies. The relative expression levels of target genes in gastric cancer tissue were measured by quantitative polymerase chain reaction. Genes identified be independent predictors of poor outcomes in the training set were verified in the validation set by Cox proportional-hazards analysis. **Results:** In the training set of stage II or III gastric cancer, 38 genes were evaluated to be independent predictors of poor outcomes. Verification analysis was then performed using the validation set, and the following 12 genes were selected as candidate markers for recurrence risk stratification ($P < 0.2$): SPARC, INHBA, HRBB2, VSNL1, CXCR4, EZH2, CCR7, PDGFRB, P53, MMP11, MRP1, and CEACAM7. Good reproducibility was obtained for 5 of these genes: SPARC, INHBA, HRBB2, VSNL1, and CXCR4 ($P < 0.05$). **Conclusions:** Promising candidate markers for stratification of recurrence risk after curative resection of stage II or III gastric cancer were identified. These candidate markers are now being analyzed at the protein level by tissue microarray, using specimens from about 500 patients each at two high-volume centers, with the goal of developing clinical applications.

11041 Poster Session (Board #254), Sun, 8:00 AM-11:30 AM

Effect of mutant TP53 genotypes on the outcome of breast cancer (BC) patients in different clinical tumor subtypes. *First Author: George Fountzilas, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece*

Background: Comprehending the clinical utility of the massively produced BC genomic data remains a challenge. Here, we examined the impact of BC genotypes on patient outcome with respect to clinical (immunohistochemical) tumor subtypes and treatment. **Methods:** Paraffin DNA from 1664 tumors (556 Luminal A, 439 Luminal B, 291 Luminal-HER2, 157 HER2-enriched and 221 triple-negative [TNBC]) yielded informative results upon targeted parallel sequencing for 58 genes. Patients had operable BC and had been treated in 4 prospective trials with adjuvant anthracycline-based chemotherapy in the pre- and post-trastuzumab (T) era. Analysis was performed in training and validation sets and in the entire cohort. **Results:** Eligible mutations (mut, n = 3086) were observed in 56 genes and were distributed in various combinations (1 to > 20 mutant genes) in 1043 tumors (63%). PIK3CA mut were found in 466 (44%); TP53 in 420 (40%); GATA3 in 128 (12%); and, CDH1 in 121 (11.5%) tumors. PIK3CA mut were more common in Luminal A/B tumors (49%), while TP53 in HER2-positive (57%) and TNBC (73%) (all $p < 0.001$). Both PIK3CA and TP53 mut were observed in 7% of all tumors. TP53 mut conferred increased risk for relapse in patients with Luminal A/B (HR = 2.00; 95% CI 1.42-2.82; Wald $p < 0.001$) and TNBC (HR = 1.82; 95% CI 1.04-3.20; Wald p = 0.037). In the same context, PIK3CA mut were associated with favorable prognosis in the absence of TP53 mut; this effect disappeared in tumors with mut in both genes. In HER2-positive patients in the pre-T era, TP53 mut alone or in combination with PIK3CA mut did not interfere with outcome. By contrast, these mutant genotypes tended to confer decreased risk for relapse in patients treated with T (HR = 0.51; 95% CI 0.23-1.14; Wald p = 0.101). All described effects were equally significant in the training and validation sets. **Conclusions:** TP53 mutant genotypes are unfavorable prognosticators in Luminal A/B and TNBC patients, but may predict benefit in HER2-positive patients with operable BC treated with T. PIK3CA mut do not seem to interfere with patient outcome in the latter context. If validated in independent large studies, these findings may have important clinical implications.

11042 Poster Session (Board #255), Sun, 8:00 AM-11:30 AM

PI3K/PTEN/Akt/mTOR pathway aberrations and co-incidence of hormone receptors and HER2 in 19,784 diverse solid tumors. *First Author: Sherri Z. Millis, Caris Life Sciences, Phoenix, AZ*

Background: Molecular aberrations in the phosphatidylinositol 3-kinase (PI3K) pathway have been documented across cancers, especially *PIK3CA*mutations and mutation or loss of PTEN. These alterations may be relevant to therapies targeting the PI3K/PTEN/Akt/mTOR signaling pathway. **Methods:** Molecular profiling was performed on 19,784 tumors (> 40 cancer types) at a CLIA-certified laboratory. Tests included next generation sequencing (NGS), protein expression (immunohistochemistry), and gene amplification (FISH or CISH). **Results:** Frequency and type of *PIK3CA, AKT1* and *PTEN* mutations were collated across cancers. Aggregate gene mutation rates (47 genes), protein expression rates (18 proteins), and copy number (5 biomarkers) were measured. Comparison of frequencies and correlations across cancers identified lineage-specific differences, and co-incidences of associated biomarkers, which will be described. Of note, endometrial, breast, cervical, anal squamous cell, and bladder cancers had the highest *PIK3CA* mutation rate (37%, n = 1600; 31%, n = 2282; 29%, n = 284; 28%, n = 67, 22%, n = 303, respectively). Patterns in *AKT1* and *PTEN* mutation rates differed by cancer, as did PTEN loss - hepatocellular, 57%, prostate, 52%, and endometrial 50% loss. Co-mutation of *PTEN* and *PIK3CA* occurred in 1.5% of breast, 0% of prostate, and 12% of endometrial cancers. Of interest, PIK3CA mutations and PTEN loss co-occurred frequently, e.g. 31% of *PIK3CA*mutated patients also have a PTEN loss. PIK3CA mutations across cancers were distributed 43% in exon 9, 33% in exon 20, and 24% in other exons. Distribution of *PIK3CA* mutations by cancer type varied and occurred more frequently in the absence of HER2 protein expression or copy number increase (p= 0.0001) and more frequently in the presence of hormone receptor overexpression (androgen receptor (AR), progesterone receptor (PR), and estrogen receptor (ER)) (p= 0.0335). PTEN loss was seen in 27% of patients with and 30% without HER2 overexpression or amplification (p= 0.004). **Conclusions:** Patterns of biomarker co-alterations across cancers may provide new insights relevant to targeted therapy and may be crucial to optimizing combination treatments.

11043 Poster Session (Board #256), Sun, 8:00 AM-11:30 AM

piRNA-651 as a prognostic marker in surgically resected non-small-cell lung cancer. *First Author: Nuria Vinolas, Hospital Clinic, Barcelona, Spain*

Background: Piwi-RNAs (piRNAs) are small non-coding RNAs (24-32 nt) required to protect the genome in germline cells. Initially they were thought to be expressed only in germline cells, but they have recently been found to be expressed in several tumours. piRNA-651 has been identified as an oncogene in gastric cancer. However, its role in non-small-cell lung cancer (NSCLC) as well as its potential as a prognostic marker have not yet been examined. **Methods:** piRNA-651 expression levels were assessed in tumour and paired normal tissue samples from NSCLC patients. piRNA-651 expression was analyzed from formalin-fixed paraffin-embedded samples by real-time PCR and by chromogenic *in situ* hybridization. Disease-free survival (DFS) and overall survival (OS) were studied by means of Kaplan-Meier, Log Rank and Cox methods. **Results:** A total of 70 patients with stage I-III surgically resected NSCLC between March 1996 and June 2007 in a single institution were prospectively registered. The median follow-up of living patients was 79 months. None of these patients received preoperative or adjuvant treatment. piRNA-651 was overexpressed in tumour tissue compared to normal tissue, and tumour cells showed a marked cytoplasmic expression. Low piRNA-651 expression was associated with shorter disease-free survival (86.8 *Vs* 25.4 months, p = 0.045) and shorter overall survival (116 *Vs* 59.1 months, p = 0.044). The multivariate analysis identified piRNA-651 as an independent prognostic factor for DFS (p = 0.031) and for OS (p = 0.050). **Conclusions:** piRNA-651 expression may well influence prognosis in NSCLC. To our knowledge, this is the first study to find evidence for a prognostic role for piRNAs in cancer.

11044 Poster Session (Board #257), Sun, 8:00 AM-11:30 AM

Does age influence the intrinsic biology of breast cancer? *First Author: Tomo Osako, Department of Molecular Oncology, BC Cancer Agency, Vancouver, BC, Canada*

Background: The incidence of breast cancer and its molecular subtype are age-related. Patient age may be associated with breast cancer biology through subtype-determining genetic factors (e.g. BRCA1 germline mutation) or aging of the tissue of origin (e.g. telomere shortening or epigenetic modifications in breast epithelium). EZH2 catalyzes trimethylation of histone H3 at lysine 27 (H3K27me3), an epigenetic change playing a role in breast cancer development and progression. We investigated if biomarkers including EZH2 and H3K27me3 display age-associated expression in breast cancer and if non-malignant breast epithelium reflects any age-dependent associations. **Methods:** Two independent sets of breast cancer tissues (n = 3,464 and n = 1,537) and a set of normal breast tissues of non-cancer patients who underwent reduction mammoplasty surgery (n = 537) were used to construct tissue microarrays for protein expression analysis using immunohistochemistry (42, 19 and 12 markers analyzed, respectively). A set of breast cancer tumour samples (n = 1,992) was assayed for global gene expression analysis using Illumina HT-12 gene chips. The associations of biomarker expression with patient age were statistically investigated. **Results:** In breast cancer,EZH2 protein and mRNA expression decreased and H3K27me3 marks increased with age at diagnosis. Gene expression analysis showed that more than 10% of genes (2,708 of about 25,000 genes) showed significant age-associated expression, and gene set enrichment analysis showed that these were enriched in 34 pathways. In non-malignant breast epithelium, EZH2, H3K27me3, ER, Ki67, EGFR and FOXA1 showed age-associated trends, which were similar to the trends seen in breast cancer. **Conclusions:** Patient age may influence the biology of breast cancer, and age-associated gene expression data leads us to hypothesize a mechanism involving histone modification by EZH2. Understanding the age-associated biology offers hope for age-specific preventive and therapeutic options.

11045 Poster Session (Board #258), Sun, 8:00 AM-11:30 AM

Identification of novel prognostic markers of glioblastoma using computational strategies on four genomic datasets. *First Author: Haruka Itakura, Stanford Univ Medcl Ctr, Stanford, CA*

Background: We sought to discover novel biomarkers using computational strategies on four genomic/epigenomic datasets to improve prognostication in glioblastoma (GBM). **Methods:** We obtained survival, clinical, gene expression, copy number variation (CNV), microRNA, and methylation data from The Cancer Genome Atlas on GBM subjects. Our study design was to fit Cox proportional hazards regression models using penalized maximum likelihood on the four datasets to predict overall survival, our analysis endpoint. We trained and tested our Cox models using 10-fold cross-validation on combined datasets created by three different integration strategies: concatenation, partial integration with double penalized maximum likelihood, and combination of weighted predictions from each dataset. We compared three, final Cox regression models using: 1) molecular features selected by the highest-performing integration strategy, 2) established risk factors (age, performance status (KPS), IDH1, MGMT, CIMP), and 3) combined molecular and established features. **Results:** 243 subjects, who possessed survival and all four genomic datasets, were included for analysis. Selecting the top 25% varying genes, gene expression data contained 4453, CNV 5770, microRNA 534, and methylation data 4643 features. The integration strategy based on weighted predictions produced the highest performing prediction model ($p = 0.0006$). The final molecular feature-only model yielded a multivariate combination of 17 prognostic features ($p = 3.89x10^{-10}$). The established features model produced three prognostic features ($p = 5.0x10^{-08}$): age, gender, and KPS. In the combined molecular-established risk model, 11 molecular features (one gene expression, three CNV, four microRNA, and three methylation features) and three clinical features (age, CIMP status, and KPS) were prognostic ($p = 1.79x10^{-08}$). **Conclusions:** Using four genomic datasets and novel computational strategies, we identified 11 molecular features that could improve GBM prognostication beyond the current set of established risk factors. These features warrant closer investigation as novel markers for disease prognostication and targets for therapy.

11046 Poster Session (Board #259), Sun, 8:00 AM-11:30 AM

Assessment of circulating free DNA concentration as a prognostic and predictive biomarker in a large cohort of non-small cell lung cancer treated by platinum-based chemotherapy. *First Author: Claire Tissot, Acute Respiratory Medicine and Thoracic Oncology Department Lyon Sud Hospital and Lyon University Cancer Institute, International Agency for Research on Cancer, Molecular Mechanisms and Biomarkers Group, Pierre Benite, France*

Background: Plasma circulating free DNA (cfDNA) has raised interest in oncology because it has been shown to contain tumor DNA and may thus be used as liquid biopsy. In non-small cell lung cancer, cfDNA quantification has been proposed to be useful as prognosis biomarker and for monitoring. However, available studies are limited and need to be confirmed. Our objective was to assess the predictive and prognostic value of plasma cfDNA concentration in a large series of patients with non-small cell lung cancer and treated with a standard chemotherapy regimen. **Methods:** Our study included samples from lung cancer patients who have been recruited in the French PHARMACOGENOSCAN study. CfDNA of 218 patients has been extracted and quantified by fluorometry before and after 2 or 3 cycles of platinum-based chemotherapy. The correlations between baseline or post-chemotherapy concentrations and treatment response assessed by RECIST 1.0 criteria or patient survival were analyzed. **Results:** 176 patients had stage IV disease and 42 patients had stage IIIb disease. We found that patients with high cfDNA concentration (highest tertile) at baseline had a significant poorer median progression free and overall survivals (OS) than those with lower concentrations (lowest and middle tertile) (10 months (95% CI 10.7-13.9) versus 14.2 months (95%CI 12.6-15.8) for median OS respectively, (P 0.001)). In multivariate analysis, increased baseline concentration in cfDNA was significantly associated to OS independently of Performance Status at diagnosis, stage, age, and response rate. However, we did not find any association between cfDNA concentration and response to treatment. **Conclusions:** These results show that cfDNA may be a useful non-invasive marker for prognosis assessment in NSCLC. However, total concentration of cfDNA is not a good biomarker to assess chemotherapy response.

11047 Poster Session (Board #260), Sun, 8:00 AM-11:30 AM

APC mutations in myeloid malignancies: Incidence and impact on leukemogenesis. *First Author: Aziz Nazha, Leukemia Program, Department of Hematology and Oncology, Cleveland Clinic, Cleveland, OH*

Background: Adenomatous polyposis coli (APC) gene is a tumor suppressor gene that plays an integral role in the WNT-signaling pathway. Germline mutations in *APC* are responsible for the autosomal dominant familial adenomatous polyposis, while somatic mutations are are linked to the initiation and progression of colorectal cancer (CRC). Haploinsufficiency of *APC* impairs hematopoiesis in animal models suggesting that loss of *APC* function contributes to the development of myelodysplasia (Wang J,et al. Blood 2010); however, patients (Pts) with germline *APC* mutations are not predisposed to develop myeloid malignancies. It is not known whether somatic mutations in *APC* gene can drive leukemogenesis. **Methods:** We screened our genomic database for the presence of somatic mutations in *APC* genes in pts with myeloid malignancies. A panel of 62 gene mutations obtained by NG targeted deep sequencing was included. Variant allele frequencies adjusted by zygosity were used to define clonal architecture. **Results:** Among 886 pts with myeloid malignancies, 15 (2%) had somatic mutations in *APC*. Of these, 8 had MDS, 4 AML, and 3 MDS/MPN; with median age of 69 years (range 39-84); none had a documented family history or personal history of CRC. In metaphase cytogenetic (MC) analyses, 11 pts had normal karyotype, 2 del(7q), 1 (-7), 1 inv(1q), and none had chr 5 abnormalities by either MC or SNP. Mutations in *APC* included: 8 missense, 3 nonesense, and 4 non-frameshift in/dels. Majority of *APC* mutations showed heterozygous configuration, resulting in the same consequences with hemizygous deletion of the locus. We then compared these mutations to germline variants recorded in the GEO database. No variants matched our data. Clonal architecture analysis showed that *APC* mutations can be either founder or subclonal. In founder cases, *APC* mutations were always accompanied by subclonal mutations described in myeloid malignancies e.g. *SF3B1, TET2, DNMT3A,* and *RUNX1,* etc. suggesting that *APC* alone is not sufficient to drive leukemogenesis. **Conclusions:** Somatic mutations in *APC* gene are rare in myeloid malignancies. They can be either founder or subclonal. In founder cases, a second hit with recurrent myeloid mutations is required to drive leukemogenesis.

11048 Poster Session (Board #261), Sun, 8:00 AM-11:30 AM

Low frequency *KRAS* G12/13 mutations in urine cell-free (cf) DNA from patients with *BRAF* V600E-mutant advanced cancers. *First Author: Filip Janku, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tumor heterogeneity and clonal selection contribute to resistance to molecular targeted therapies. Dynamic tracking of urine cfDNA mutations can offer a noninvasive tool for monitoring therapeutic efficacy. **Methods:** cfDNA was isolated from single or sequential urine samples from patients with advanced cancers and archival tumor tissue with *BRAF* V600E from a CLIA-certified laboratory. Assays for quantitative detection of *BRAF* V600E and *KRAS* G12/13 mutations in urine cfDNA were developed using digital droplet (dd) PCR and next generation sequencing. Analytical sensitivity of *BRAF* V600E and *KRAS* G12/13 assays is 0.03% and 0.006% mutant alleles in wild-type DNA background. **Results:** Urine cfDNA was examined in 34 patients (melanoma, $n = 11$; colorectal cancer, $n = 8$; papillary thyroid carcinoma, $n = 5$; non-small cell lung cancer, $n = 5$; other, $n = 5$) with *BRAF* V600E in tumor tissue. 32 of 34 patients (94%) had the same mutation in urine cfDNA (mutant, $n = 22$; low-mutant, $n = 10$). Longitudinal analysis in 25 (74%) patients (treated with: BRAFi, $n = 23$; MEKi, $n = 1$; none, $n = 1$) showed that changes in *BRAF* V600E cfDNA amounts correlated with percent changes in target lesions on imaging ($r = 0.68$, $p < 0.001$). Patients with decreased *BRAF* V600E cfDNA ($n = 16$) compared to others ($n = 8$) had a trend to a longer median time-to-treatment failure (8.8 months, 95% CI 8.1-9.5 vs. 2.2 months, 95% CI 0.0-5.1; $p = 0.07$) on BRAF or MEK therapy. Moreover, 22 (65%) patients had a low frequency *KRAS* G12/13 mutation (median 3.4 copies/10^5 genome equivalents) in urine cfDNA that was previously undetected in tumor by CLIA, except in one case. 9 of 9 patients with urine examined at the time of progression had detectable cfDNA *KRAS* G12/13. Re-analysis of the retrieved archival tumor tissues from 8 patients found a previously undetected low frequency (1.3%) *KRAS* mutation in one sample by ddPCR. **Conclusions:** Our results suggest that 65% of patients with advanced cancers and *BRAF* mutation in tumor tissue have low frequency *KRAS* G12/13 mutations in urine cfDNA undetected in tumor samples by standard CLIA technologies. Low frequency *KRAS* mutations can plausibly drive resistance to BRAF targeting agents, and these may be detected in urine cfDNA.

11049 Poster Session (Board #262), Sun, 8:00 AM-11:30 AM

Prosigna (PAM50) to predict response to neoadjuvant chemotherapy (NAC) in HR+/HER2- early breast cancer (EBC) patients. *First Author: Begona Jimenez Rodriguez, Hospital Regional Universitario y H. Universitario Virgen de la Victoria, Málaga (Spain), Malaga, Spain*

Background: Prosigna has been clinically validated in 2 large randomized studies to predict the risk of distant and late recurrence in HR+/HER2- patients treated with endocrine therapy.NAC efficacy is evaluated through pathological surrogates such as residual cancer burden(RCB) and pathologic complete response(pCR), and this response has been correlated to improved survival.HR+/HER2- tumors typically have low rates of pathologic response, however,genomic tests may be able to differentiate between patients who would or would not respond to NAC. We evaluate the correlation between ProsignaROR score and response to NAC. **Methods:** Retrospective analysis was performed on FFPE HR+/HER2- breast tumors from EBC patients who were treated with a contemporary NAC regimen (anthracyclines+taxanes)in a multi-center Spanish cohort. The Prosigna assay was performed on the NanoString nCounter Dx Analysis System at HU Virgende la Victoria de Málaga/CIMES-UMA. Univariate analysis was used to evaluate the correlation of ProsignaROR score and intrinsic subtype to pathologic response. RCB was determined centrally and used as the primary endpoint. **Results:** 95.8% (207/216) ofcore biopsy samplesyielded passing results of which 180 had anRCB classification. Medianage was48y.o.(27-75), initial mammographic tumor size was 3.4cm(1-10), and 27% of patients had G3 tumors. The overall rate of RCB-0/Iwas 18.9%. Prosigna subtypes observed: LuminalA n = 54; LuminalB n = 105; Basal-liken = 14;Her2En = 7. Rate of response RCB-0/I(%) according to PAM50 subtypes was LumA = 9.3%, Her2E = 14.2%, LumB = 20%, Basal = 50%. Prosigna ROR was a significant predictor of response to NAC ($p = 0.047$).Luminal A tumors were unresponsive to NAC relative to the other intrinsic subtypes (Odds RatioLumA vs. non-LumA = 0.341, $p = 0.037$). **Conclusions:** Prosigna ROR reliably predicted response to NAC in this HR+/HER2- population. High-risk tumors were significantly more likely to respond to NAC than lower-risk tumors. The intrinsic subtypes were also predictive of chemo-sensitivity with Luminal A tumors being resistant to NAC,supporting the current St. Gallen consensus guideline where intrinsic subtype determines chemotherapy use.

11050 Poster Session (Board #263), Sun, 8:00 AM-11:30 AM

Evaluation of invasive breast cancer using a 12-chemokine gene expression score (CS): Correlation with clinical outcomes. *First Author: Sangeetha Prabhakaran, Moffitt Cancer Center, Tampa, FL*

Background: We derived a unique CS from a metagene grouping with high enrichment for immune-and inflammation-related genes that in various tumors including breast cancer, accurately predicts the degree and type of lymphoid infiltrate close to tumor aggregates and areas of tumor necrosis and shows improved overall survival (OS) in Stage IV melanoma. (Messina JL et. al Scientific Reports 2012). We analyzed the correlation between the CS, clinicopathologic variables and survival in breast cancer patients (pts). **Methods:** A retrospective review was performed on selected Stage I - III breast cancer pts treated at our institution from 1978 to 2011. CS were calculated by principal component analysis. Pts given neoadjuvant chemotherapy were excluded. Pts were divided into 2 groups at the median into high or low CS. Descriptive and survival analyses were performed. **Results:** 366 pts were included, median age at diagnosis was 54.5 years. Pts mainly presented with Stage II disease (51.8 %) with ductal histology (77.6 %) and were ER/PR positive (63.5%). 86.5% received adjuvant therapy after surgery. Mean CS was 0.23 (range -2.2 to 2.1). Median follow-up period was 66.3 months (mths) (range 2.5 - 212.9). 263 pts were alive and 82.5% disease free at analysis. 88 (37 vs. 51) pts recurred in high vs. low CS groups. In comparison with the low CS group, patients with high CS were more likely to be white (172 vs. 159) ($P = 0.03$), with poorly differentiated tumors (112 vs. 59) ($P < .0001$), ER/PR negative (41 vs. 26) and Her2 positive (36 vs. 19) ($P = 0.001$). They had better OS (median 17.5 vs. 13) ($P = 0.88$) and recurrence free survival (RFS) (median not reached vs.11.1) mths ($P = 0.128$) compared to low CS. Higher scores in Her2 positive pts correlated with increased RFS (12.4 vs. 4.4 mths) that trended towards significance ($P = 0.058$). **Conclusions:** Higher scores are associated with high grade tumors and aggressive subtypes. They also correlate with improved OS and RFS. Further studies using larger datasets to repeat these observations and select tumor subtypes could extend the predictive value of this novel CS and potentially identify candidates for immunotherapeutic treatment.

11051 Poster Session (Board #264), Sun, 8:00 AM-11:30 AM

Prognostic significance of stromal versus intratumoral infiltrating CD8+ lymphocytes in resected non-small cell lung cancer. *First Author: Malaka Ameratunga, Austin Health, Heidelberg, Australia*

Background: The prognostic significance of tumor infiltrating lymphocytes (TILs) in non-small cell lung cancer (NSCLC) remains unclear. Immunotherapies in NSCLC have recently shown therapeutic promise. Assays predicting response to PD1/PDL-1 inhibitors have utilized expression of its ligand PDL-1 on tumor cells or the surrounding immune infiltrate. In other tumor types, stromal CD8+- TILs have been reported to be prognostic. We sought to characterize the immune infiltrate in a large series of resected NSCLC to determine their prognostic significance, focusing on intra-tumoral and stromal TILs. **Methods:** A tissue microarray (TMA) was constructed with triplicate cores of primary tumor from 507 NSCLC lobectomy or pneumonectomy cases. Immunohistochemistry was performed for CD8, CD4 and FoxP3. PDL1 was performed using a proprietary assay from BMS. CD8+ TILs were manually counted and assigned global tumoral and stromal scores based on TIL density, with the scorer blinded to clinical outcomes. Cases were categorized: stromal (S), tumoral (T) or other (equal proportions of tumoral:stromal CD8+-TILs). Disease-specific survival (DSS) was correlated with TIL characteristics. **Results:** Most patients were male (69%). Histologically, 50% were adenocarcinoma (AC) and 42% squamous (SQ). Comparisons were stratified by nodal stage: node negative (N0, n = 354) and node positive (N+, n = 153). In N0 there were 24(7%) T, 40(11%) S and 290(82%) other, compared to 16(11%), 11(7%) and 126(82%) respectively in N+ ($p = 0.16$). There were no differences in CD8+ TILs based on histology ($p = 0.73$). In the N0 population, there was no significant difference in DSS, based on TIL characteristics. In the N+ population, the presence of an S infiltrate was associated with significantly increased DSS compared to a T infiltrate (HR 0.36, 95% CI 0.14-0.96; $p = 0.05$) or other (HR 0.36, 95% CI 0.26-0.92; $p = 0.03$). **Conclusions:** In this large patient cohort, the presence of stromal CD8+ TIL infiltrates was not prognostic in N0 NSCLC but was associated with significantly improved survival in node positive NSCLC. Correlation of PDL-1, FOXP3 and CD4+ stains may further define the TILs and will be reported.

11052 Poster Session (Board #265), Sun, 8:00 AM-11:30 AM

Analysis of the prognostic value of the tumor immunologic profile in resectable NSCLC. *First Author: Marta Usó, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia, Spain*

Background: The analysis of immune features of tumor microenvironment is leading to the development of new immunotherapies and the identification of new biomarkers. In this study, we have investigated the prognostic value of immune markers, especially those related to immune-regulation in resectable NSCLC. **Methods:** RNA was isolated from fresh-frozen lung specimens (tumor and normal lung) (n = 178). RT-PCR was performed to analyze the expression of 20 genes: CCL2, CCL22, CD1C, CD127, CD209, CD25, CD4, CD8, CLEC4, CTLA4, FOXP3, IDO1, IL10, IL23A, LGALS1, LGALS2, NRP1, PD1, PDL1 and TGFB1, by the use of hydrolysis probes. Relative gene expression was assessed by Pfaffl formula and normalized by the use of ACTB, GUSB and CDKN1B as endogenous genes. Statistical analyses were considered significant at $p < 0.05$. **Results:** Unsupervised hierarchical analysis according to gene expression levels classified patients in two clusters. Cluster I (n = 70) was composed by samples showing lower expression levels of the analyzed genes, whilst cluster Cluster II (n = 84) grouped samples that, in general have higher gene expression levels. Survival analysis showed that patients in Cluster II had better OS (NR vs 46.6 months, $p = 0.040$) and longer PFS (81.22 vs 26.28 months, $p = 0.027$) than patients in Cluster I. In order to obtain a more clinically valid biomarker, an expression score based on the regression coefficients from a multivariate model was built: (IL23A x 0.016) + (IL10 x 0.077) + (CCL2 x 0.154) + (PD1 x 0.132) + (CTLA4 x 0.173). Patients with high expression score have longer OS (NR vs 42.9 months, $p = 0.007$) and longer PFS (82.6 vs 23.4 months, $p = 0.011$). Multivariate analysis, including all significant variables found in the study, indicated that the expression score, along with KRAS status, was an independent biomarker of prognosis for OS [HR: 0.368; 95%CI, 0.190-0.715; $p = 0.003$] in our cohort. **Conclusions:** We identified a unique immune-reaction related profile associated with survival which leaded to the creation of an expression score composed by five genes. Furthermore, this expression score was found to be an independent prognostic biomarker in resectable NSCLC. Supported by grants PI1202838 and RD12/0036/0025 from ISCIII.

11053 Poster Session (Board #266), Sun, 8:00 AM-11:30 AM

Wild type *VHL* clear cell renal cell carcinomas: A distinct morphological and clinical entity with PD-L1 expression. *First Author: Laurence Crouzet, Center of Oncology Eugene Marquis, Rennes, France*

Background: Clear cell renal cell carcinoma (ccRCC) is an aggressive tumor and in most of cases, is characterized by an inactivation of the tumor suppressor gene *VHL (Von Hippel-Lindau).* This inactivation causes an overexpression of the target genes of HIF-dependent transcription factor. VHL/HIF/VEGF pathway thus has a major role in oncogenesis and is currently targeted by anti-VEGF therapy. The emergence of resistance leads to the development of immunotherapy. The interaction of programmed death-1 ligand (PD-L1) with its receptor (PD-1) on T cells inactivates antitumor immune responses. PD-L1 expression appears to be associated with poor outcome in ccRCC. The correlation between complete *VHL* status and the expression of PD-L1 has not yet been investigated. **Methods:** In this study, we correlated the complete status of the *VHL* gene in 98 ccRCC cases with pathological criteria, expression of PDL1 and clinical outcome. For these patients, we had 64 months median follow-up. From frozen tumor sections, *VHL* gene deletion, mutation and promoter hypermethylation were screened. PD-L1 expression was analyzed by immunohistochemistry on the highest Fuhrman nuclear grade and considered positive when any membranous tumor cell staining was detected. **Results:** 33.6% of ccRCCs had 0 or 1 alteration (non inactivated *VHL*) *versus* 66.3% with 2 inactivating events (inactivated *VHL*). Non inactivated *VHL* ccRCCs were associated with a higher Fuhrman grade 4 ($p = 0.02$), metastases ($p = 0.04$), sarcomatoid component ($p = 0.01$) and dense lymphocyte infiltrate ($p = 0.013$). Furthermore, in this group, wild type *VHL* tumors (no alteration of the *VHL* gene, 11,2%), were particularly associated with PD-L1 expression ($p < 0,0001$), and had a worse outcome with a median specific survival of 33 months ($p = 0.016$). **Conclusions:** This long-term study is the first to analyze complete *VHL* gene status in ccRCC in association with PDL1 expression. Wild type *VHL* ccRCCs represent a distinct entity with probably different involved oncogenic pathways. Interestingly, they overexpress PD-L1 and may benefit therapies inhibiting PD-L1/PD-1.

11054 Poster Session (Board #267), Sun, 8:00 AM-11:30 AM

Immune response triggered by a novel molecular crosstalk of major hallmarks of cancer: Angiogenesis, mismatch repair, and immune pathways. *First Author: Shannon Graver, University of Wuerzburg Biocenter, Wuerzburg, Germany*

Background: The development of bevacizumab to inhibit VEGF has resulted in extended PFS, however OS has failed to show significant clinical benefit in a number of cancer types. Recent data however, has shown bevacizumab to prolong OS in a subset of patients with MMR deficient tumors in adjuvant CRC. **Methods:** Isolated macrophages were treated with tumor-conditioned media from MMR proficient and MMR deficient tumor cells. Furthermore tumor cells were co-cultured with human monocyte-derived macrophages for analysis of phagocytic activity. Treatment regimens *in vitro* attempted to mimic the clinical setting by inducing DNA damage in tumor cells, and then allowing cells to recover with or without VEGF using bevacizumab treatment for 24 hrs before co-culture or collection of tumor-conditioned media. **Results:** Gene expression changes in macrophages induced by tumor-conditioned media showed *CCL18* to be a bevacizumab regulated gene. MMR deficient tumor cell conditioned media after DNA damage showed a 68% increase in *CCL18* expression compared to the untreated control that was not evident in MMR proficient cells. *CXCR4* expression may demonstrate negative regulation as MMR proficient tumor cells treated with bevacizumab after DNA damage, promoted a 1.4 fold increase in *CXCR4* expression in macrophages with no functional enhancement of macrophage activity detected. The results of this study also showed an increase in the phagocytic activity of macrophages in the presence of bevacizumab that was significantly more apparent in MMR deficient cells and may be attributed to CCL18. DNA damage in MMR deficient cells in addition to bevacizumab treatment reinforced phagocytosis by a further 16.5% ($\pm$3.9%) compared the controls. Moreover, after DNA damage MMR deficient cells treated with bevacizumab released a cytokine mix that reduced monocyte migration in a bevacizumab dependent manner, showing a functional response with the combination of MMR deficiency and bevacizumab. **Conclusions:** CCL18 is a potential marker for the administration of bevacizumab in a clinical setting that is specific to bevacizumab treatment in combination with MMR deficient tumor cells via immune cell modulation.

11055 Poster Session (Board #268), Sun, 8:00 AM-11:30 AM

Detection of rare somatic mutational profiles in metastatic colorectal cancer (mCRC) during routine *RAS* sequencing using next generation sequencing (NGS). *First Author: Jean-Louis Merlin, Institut de Cancérologie de Lorraine, Service de Biopathologie, CNRS UMR 7039 CRAN Université de Lorraine, Nancy, France*

Background: In most patients with mCRC who are being considered for anti-EGFR antibody therapy, *RAS* mutation testing i.e. *KRAS* and *NRAS* exon 2, 3 and 4, is routinely assessed using PCR-based assays only detecting major hotspot mutations of exon (ex) 2 (codon 12 and 13), 3 (codon 59 and 61) and 4 (codon 117 and 146). We performed deep sequencing of the entire exons using NGS as an alternative to detect additional rare mutations profiles with significant frequency of mutated allele (FMA). **Methods:** 188 formalin-fixed paraffin-embedded tumor samples from primary or metastatic lesions of patients (M/F sex ratio 1.27, mean age 69 years, range 32-90) with mCRC (150 colon, 38 rectum) were analyzed. DNA was extracted from macrodissected slides (mean tumor cell content 43.3%, range 5-80). **Results:** *RAS* mutation testing was routinely assessed using NGS in 177 mCRC samples. NGS could not be performed in 11 cases (6.2%) due to the insufficient quantity or quality of DNA. NGS sensitivity was 1% at X1000 depth. *RAS* mutations were found in 103 samples (62%) and relatively distributed as 69.9% *KRAS* ex2, 3.9% *KRAS* ex3, 14.6% *KRAS* ex4, 4.8% *NRAS* ex2, 1.0% *NRAS* ex3, 1.0% *NRAS* ex4 and 4.8% multiple mutations. Uncommon mutational profiles were detected in 10 cases (9.7%): 2 *KRAS* ex2 c.37G > T p.G13C single mutation with FMA > 30%, 5 silent mutations (4 with FMA > 25%), alone ($n = 2$) or combined with other rare mutations ($n = 3$) with lower but significant FMA (> 1%), and 6 multiple mutation profiles among which 2 double hotspot mutation (*KRAS* ex2 c.34G > A p.G12S and *NRAS* ex3 c.181C > A p.Q61K, *KRAS* ex2 c.34G > A p.G12S and *NRAS* ex2 c.38G > T p.G13V), 1 secondary rare mutation associated with a *KRAS* ex2 c.35G > A p.G12D hotspot mutation, and 3 multiple mutations only with rare but potentially deleterious mutations located around the loops responsible for nucleotide (GTP) binding. In only 1 case, the FMA of the secondary mutations was < 1%. As a whole, 7 cases (6.8%) had *RAS* mutations out of hotspots. **Conclusions:** NGS proved accurate, sensitive and suitable for routine *RAS* genotyping in mCRC. It can detect uncommon *RAS* mutation profiles with significant FMA that can potentially impair the patient response to anti-EGFR antibody.

11056 Poster Session (Board #269), Sun, 8:00 AM-11:30 AM

[^{18}F]FMAU for PET imaging in breast cancer patients. *First Author: Peter Conti, University of Southern California, Los Angeles, CA*

Background: To develop a practicable method of synthesizing ^{18}F-labeled 2'-deoxy-2'-fluour-5-methyl-1-β-*D*-arabinofuranosyluracil ([^{18}F]FMAU) for clinical investigation and study [^{18}F]FMAU in patients with known breast cancer to obtain data on safety, circulating metabolite, tumor imaging feasibility, and radiation dosimetry. **Methods:** Various reaction factors, such as time, temperature, and solvent effect, were explored to optimize [^{18}F]FMAU synthesis. A total of nine breast cancer patients were scanned. [^{18}F]FMAU, 10 mCi i.v. injection in saline was administered to the patient through venous line. Multi-bed position PET scans over tumor-bearing region(s) were obtained, along with attenuation correction images, throughout the time period between 1 and 120 minutes post injection. Throughout the procedure, study staff monitored and recorded patient vital signs. **Results:** A simplified synthesis of [^{18}F]FMAU with shorter synthesis time and higher radiochemical yield was achieved as compared to previously reported methods. The total synthesis time was about 90 min from the end of bombardment.Radiochemical purity was > 99% and specific activity was > 400 mCi/μmol. The PET imaging showed excellent primary breast tumor as well as metastatic disease uptake of [^{18}F]FMAU. No adverse reactions were observed for all studied patients. No major circulating metabolites were identified in human blood at 1 h post injection of [^{18}F]FMAU. The preliminary dosimetry of [^{18}F]FMAU was estimated as 5.0 rem in liver (primary organ), 4.2 rem in kidneys (secondary organ), 0.76 rem in whole body, 0.60 rem in active blood forming organs, and 0.45 rem in gonads per single administration. **Conclusions:** A simplified one-pot synthesis of [^{18}F]FMAU has been developed, which is well suitable for clinical investigations. Our pilot trial achieved its goals of obtaining data on safety, circulating metabolite, breast tumor imaging feasibility, and radiation dosimetry of [^{18}F]FMAU in humans. The data provided a solid foundation for proceeding to larger clinical trials to confirm the utility of [^{18}F]FMAU as an *in vivo* cell proliferation marker for non-invasively and serially estimating DNA synthesis in patients with cancer.

11057 Poster Session (Board #270), Sun, 8:00 AM-11:30 AM

Clinical impact of high-throughput sequencing in patients with advanced cancer: Lessons learned from the Michigan Oncology Sequencing Center. *First Author: Erin Frances Cobain, University of Michigain Health System, Ann Arbor, MI*

Background: The molecular aberrations that drive cancer are diverse and multiple defects are often present. Next generation sequencing permits detection of numerous aberrations within a tumor, which may identify targets for therapy. **Methods:** From 5/2011-12/2014, 452 patients (pts) underwent comprehensive next generation sequencing (Illumina) of a primary or metastatic tumor at the University of Michigan under an IRB approved protocol. Somatic and germline mutations, copy number alterations, gene fusions, and gene expression findings were reviewed at an institutional tumor board. Clinically actionable alterations were categorized as follows: rationale for use of an investigational targeted agent, rationale for off-label use of therapy approved in another condition, information predictive of treatment efficacy and germline mutations known to confer increased cancer risk. We report subsequent treatment information for the first 200 patients enrolled. **Results:** Sequencing was successful in 183 samples (92%). Somatic alterations of biological relevance were identified in 176 cases (96%). 100 pts (55%) had potentially actionable results. 79 pts (43%) had alterations providing rationale for use of an investigational targeted therapy and 7 enrolled in a trial informed by results. Somatic alterations provided rationale for off-label use of a drug in 13 cases (7%) and 5 pts received off-label therapy. 22 pts (12%) had alterations predictive of treatment efficacy, prompting treatment change in 3 pts. 5 pts (3%) were found to have germline mutations conferring increased cancer risk. 48 pts (26%) died within 5 months of enrollment. **Conclusions:** These data demonstrate that comprehensive tumor genome analysis can identify potentially actionable somatic aberrations, indicating this approach is useful as a screening tool for clinical trial participation. Early in the course of the study, many pts died shortly after enrollment. This experience led us to employ this strategy earlier in the therapeutic algorithm.

11058 Poster Session (Board #271), Sun, 8:00 AM-11:30 AM

Allowance of tumor-educated platelets for multiclass liquid biopsy-based diagnosis of cancer. *First Author: Myron Best, Department of Neurosurgery, VU University Medical Center, Amsterdam, Netherlands*

Background: Cancer diagnosis is frequently hampered by limited access to adequate tissue of the primary tumor or metastatic lesions. To overcome such limitations, the use of blood-based liquid biopsies has been suggested. Blood represents a biosource of tumor-educated platelets (TEPs) that sequester biomolecules during tumor growth, thereby altering the platelet mRNA profile. **Methods:** Blood platelet samples of 188 cancer patients covering six tumor types (40 non-small cell lung cancer, 39 glioblastoma, 37 colorectal cancer, 35 pancreatic cancer, 24 breast cancer, and 13 hepatobiliary cancer) and of 52 healthy donors were isolated from whole blood by differential centrifugation. RNA was isolated, subjected to SMARTer mRNA amplification and submitted for whole transcriptome mRNA sequencing on the Illumina platform. Healthy donors, pan-cancer, and individual cancer classes were distinguished by a self-learning support vector machine (SVM) algorithm, using transcripts with moderate to high expression. **Results:** The 240 blood platelet samples were successfully sequenced and demonstrated a good intersample correlation of the detected mRNAs. Based on mRNA profiles, all tumor samples were clearly distinguished from healthy donors: the pan-cancer SVM-supported classification test reached a sensitivity of 97% and a specificity of 90% to distinguish cancer patients from healthy donors. Also, all patients without overt metastases were correctly predicted as cancer patients. Moreover, a multiclass cancer diagnostics TEP-test, to distinguish multiple tumor subclasses and healthy donors provided an overall accuracy of 73%, far exceeding random classification. In addition, we distinguished HER2-positive, and mutant KRAS and EGFR tumors from their wild-type counterparts. Also, patients with metastatic tumors in lung, brain, and liver were accurately diagnosed according to the tumor in the tissue of origin. **Conclusions:** Molecular interrogation of TEP-based liquid biopsies may leverage cancer diagnostics. TEPs provide a circulating biosource for pan-cancer, multiclass, and molecular cancer classification. Of interest, this tool might also allow for blood-based highly sensitive early-stage cancer screening.

11059 Poster Session (Board #272), Sun, 8:00 AM-11:30 AM

Improvement in imaging of metastatic breast cancer (BC) with a novel pretargeted immuno-PET targeting CEA: First clinical results. *First Author: Caroline Rousseau, ICO Cancer Center, Nuclear Medicine Department, Saint Herblain, France*

Background: New phenotypic imaging with noninvasive antibody imaging methods targeting membranous antigens have been tested in BC trials. A new generation of immuno-PET comprising anti-CEA x anti-HSG humanized trivalent TF2 bispecific MAb and ^{68}Ga-IMP288 HSG peptide is being assessed. This study aimed to compare the sensitivity of anti-CEA immuno-PET/CT comparing this immune-PET to morphological imaging and FDG-PET/CT in metastatic BC patients. **Methods:** Thirteen patients with metastatic BC enrolled in an optimization immuno-PET study had whole-body immuno-PET/CT at 1h and 2h after injection of 150 MBq of ^{68}Ga-IMP288 pretargeted by 120 nmol of unlabeled TF2 binding CEA and the HSG peptide injected 24h to 30h before. Thoracic-abdominal-pelvic CT and FDG-PET/CT were also performed. The gold standard was determined by follow-up and a lesion detected by at least 2 imaging modalities was considered as positive. **Results:** Median serum CEA was 46.15 μg/L (9.5 to 1359.0). To date, 515 lesions were confirmed as pathologic by the gold standard: 18 in LN, 4 in lung, 94 in liver, 399 in bone, 1 in skin, and 4 in brain. Overall sensitivity of immuno-PET was 93.8%, with 100% sensitivity for bone, liver, skin, and brain, 94% for LN, and 37.5% for lung. Overall sensitivity of CT and FDG-PET/CT was 74.6% and 84.7%, respectively. Bone MRI had 94% sensitivity. Brain lesions were only detected by immuno-PET/CT and confirmed by MRI. Median tumor SUVpeak on immuno-PET at 1h and 2h was 9.58 (3.52 to 24.55) and 11.04 (3.09-34.27), respectively. In half of patients (7/13) an increased tumor uptake between 1h and 2h was observed and no lesion was detected only at 2h. **Conclusions:** These results demonstrate the high accuracy of anti-CEA pretargeted immuno-PET/CT for staging pts with metastatic BC, especially for bone, liver and brain evaluation. Immuno-PET allowed detection of bone lesions in areas not explored by MRI. Clinical trial information: NCT01730612.

11060 Poster Session (Board #273), Sun, 8:00 AM-11:30 AM

Predictive value of coexisting KRAS and TP53 mutations on response to chemotherapy in non-small cell lung cancer (NSCLC). *First Author: Pascale Tomasini, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada*

Background: *KRAS* and *TP53* are among the most common mutations in NSCLC. The LACE-Bio group evaluated coexisting *KRAS/TP53* mutations in resected NSCLC and found chemotherapy to be deleterious in patients with double mutations. **Methods:** In an attempt to validate these results,NSCLC patients from Princess Margaret Cancer Centre who were tested for *KRAS* & *TP53* mutations and received chemotherapy for any stage NSCLC were selected. Mutation status was analyzed using Mi-SEQ or Sequenom platforms. *TP53* analysis was added for DNA sequenced by Sequenom. Mutation status was correlated with clinical and demographic data. Relapse- or progression-free survival (RFS, PFS) was the main endpoint. **Results:** Among 186 patients identified, 24 had coexisting *KRAS/TP53* mutations, 67 *TP53*, 27 *KRAS;* 68 had no *KRAS* or *TP53* mutation (WT/WT). No difference was seen in age, sex or stage among the 4 populations ($p = 0.09$, $p = 0.23$, $p = 0.36$, respectively). There were significantly more Caucasians (96 *v* 65%, $p = 0.009$), smokers (29 *v* 14%, $p = 0.007$) and adenocarcinoma (96 *v* 73%, $p = 0.046$) in the *KRAS/TP53* group. 5-year overall survival (OS) was higher in the WT/WT group (68%) compared to *KRAS/TP53* 48%, *KRAS* 42%, *TP53 41%* (log-rank $p = 0.02$). However, no significant OS difference was seen for *KRAS/TP53* compared to the other groups (HR 1.41, CI 0.81-2.45, $p = 0.23$). Among 98 patients who received *adjuvant* chemotherapy, there was no significant difference in RFS for the *KRAS/TP53* group *v* all others (HR 1.47, CI 071-3.08, $p = 0.3$). For 30 stage III patients who received concurrent chemo-XRT, there was no PFS difference for the *KRAS/TP53* group *v* all others (HR 0.80, CI 0.30-2.15, $p = 0.65$). For 85 patients who received 1st-line palliative chemotherapy, there was no difference in PFS in the *KRAS/TP53* group *v* the others (HR 1.05, CI 0.59-1.87, $p = 0.87$). Similarly, in 43 patients who received 2nd-line chemotherapy, there was no difference in PFS comparing the *KRAS/TP53* group to the others (HR 1.18, CI 0.45-3.13, $p = 0.73$). **Conclusions:** We could identify no significant difference in OS, RFS or PFS for patients with NSCLC harboring coexisting *KRAS/TP53* mutations who received chemotherapy for any stage compared to patients with *KRAS* or *TP53* mutation or WT/WT tumors.

11061 Poster Session (Board #274), Sun, 8:00 AM-11:30 AM

Detection of low abundant somatic mutations in circulating exosomal RNA and cfDNA with next-generation sequencing. *First Author: Vincent J. O'Neill, Exosome Diagnostics, Cambridge, MA*

Background: Circulating nucleic acids (NA) in the bloodstream of cancer patients are of interest because of their potential to provide tumor mutation status without requiring a tissue sample. Blood plasma contains at least two sources of circulating cell-free NA: circulating free DNA (cfDNA), from apoptotic/necrotic cells, and RNA enclosed in exosomes (exoRNA), which are secreted by living cells through active metabolic processes. However, tumor derived mutated sequences are often of very low abundance against a background of wildtype. Therefore, efficient extraction of all available circulating NA as well as a highly sensitive mutation detection method, are paramount to development of clinically relevant liquid biopsies. **Methods:** We used a single-step isolation platform for both exoRNA and cfDNA from plasma (EXO52) in combination with a quantitative NGS method detecting a panel of actionable mutations (EXO1000). The assay uses a PCR-based selection of 9 mutation hotspots from 6 genes, a custom library preparation protocol and bioinformatics pipeline. We analyzed mutations present in nucleic acids from plasma of patients with various types of cancer including NSCLC, mCRC and melanoma. **Results:** EXO52 columns simultaneously isolate both cfDNA and exoRNA from plasma samples up to 4 mL with close to 100% efficiency, allowing somatic mutations to be readily detected in both exoRNA and cfDNA. The combination of both was found to provide a superior mutation signal and yield compared to cfDNA alone. The EXO1000 actionable mutation panel and associated bioinformatics pipeline were demonstrated to be quantitative, reproducible and highly sensitive. The assay faithfully detected low copy numbers of mutations using clinical plasma samples from 102 patients with different types of cancer. **Conclusions:** We demonstrate the superiority of isolating both cfDNA and exoRNA from plasma for the purpose of detecting circulating somatic mutations in cancer patients. The EXO52 isolation method combined with the EXO1000 actionable mutation panel overcomes current technical limitations by maximizing mutation signal from all sources of circulating NA, thereby enhancing assay sensitivity.

11062 Poster Session (Board #275), Sun, 8:00 AM-11:30 AM

Assessing HER2 testing quality in breast cancer (BC): Variables that influence HER2-positivity from a large, multicenter, observational study in Germany. *First Author: Josef Ruschoff, Institut für Pathologie Nordhessen, Kassel, Germany*

Background: Despite $>$ 10 years of routine HER2 testing in BC, quality is still an issue. It is often assumed that inter- and intra-laboratory variations in testing quality can be assessed by HER2-positivity rates. However, the extent to which patient- or tumor-related factors influence HER2-positivity rates has not been systematically studied. **Methods:** This observational, prospective study in Germany monitored routine HER2 testing to identify patient- or tumor-related factors that influence HER2-positivity rates, and to identify centers with HER2-positivity rates that could not be explained by these factors. Data collected from eligible BC specimens included test result, patient- and tumor-related factors, sample source, and method of retrieval. Factors influencing HER2-positivity rates were identified by multiple logistic regression (MLR) analysis. Center effects were assessed in an extended MLR model by their statistical significance after adjusting for the combined effect of covariates and multiple testing. **Results:** From Jan 2013 to Aug 2014, data were collected from 16,528 BC specimens and 57 centers. Final analyses included 15,332 invasive BC specimens. Tumor grade showed the highest correlation with HER2-positivity, followed by hormone receptor status, carcinoma subtype, age, and nodal status (all $P<$ .0001). No significant correlation was found for specimen source. Overall HER2-positivity rate across centers was 14.4%. Adjusting for patient- or tumor-related covariates and multiple testing, a statistically significant center effect on HER2-positivity rate was identified for three centers and a significant trend toward center effect for a further three. **Conclusions:** This study is the first of its kind, reporting on the multifactorial parameters that can impact on routine HER2-positivity rates. Results highlight that assessing HER2 testing quality by comparing positivity rates only, as recommended, may be insufficient, and that patient characteristics should be considered to assess HER2 testing quality effectively. As therapy options for HER2-positive BC continue to evolve, identifying the right patients is key.

11063 Poster Session (Board #276), Sun, 8:00 AM-11:30 AM

Towards rapid and cost-effective point-of-care detection of TMPRSS2:ERG fusion transcripts in urine via a novel methodology. *First Author: Eugene J.H. Wee, The University of Queensland, Australian Institute for Bioengineering and Nanotechnology, Brisbane, Australia*

Background: The TMPRSS2:ERG gene fusion is a highly-specific prostate cancer biomarker which is present in about 50% of all prostate cancer cases. The present use of serum PSA for prostate cancer screening is controversial due to its lack of specificity as a screening biomarker. In contrast, the presence of TMPRSS:ERG fusions could offer better screening potential. However, current detection methodologies of TMPRSS2:ERG, such as RT-PCR or FISH, are time consuming, expensive and require specialized equipment. Therefore, a new rapid and cost-effective point-of-care detection methodology is needed to enhance and enable the clinical utility of TMPRSS2:ERG and other cancer-related fusion transcripts. **Methods:** We developed a methodology by combining robust isothermal amplification with a novel readout based on amplified DNA-mediated bridging flocculation. This instrument-free visual evaluation of successful amplification complements the binary biomarker characteristic of TMPRSS2:ERG to give a simple positive/negative outcome. **Results:** The method is sensitive to as few as 10^5 copies (single cell level) of TMPRSS2:ERG fusion transcripts. We were also able to detect fusion transcripts in both whole urine and urinary sediments. Finally, to demonstrate clinical utility, the method was applied to 10 metastatic, castration-resistant prostate cancer urine specimens and results were validated with standard PCR-based methods. **Conclusions:** A simple, rapid ($\leq$ 90 min) and inexpensive ($\leq$ $5 USD) assay was developed to detect TMPRSS2:ERG fusion transcripts in urine. The approach may have broader applications in detecting other gene fusion events in prostate cancer or other cancers to enable quick and convenient clinical decisions.

11064 Poster Session (Board #277), Sun, 8:00 AM-11:30 AM

Preliminary direct evidence of a dose-response relationship for [Y-90]-microsphere selective internal radionuclide therapy (SIRT) in hepatic malignancy. *First Author: Dale L Bailey, University of Sydney, Lidcombe, Australia*

Background: [Y-90]-SIRT has an established role in managing patients with primary and secondary hepatic neoplasia. Recently, imaging of the regional distribution of the implanted [Y-90]-microspheres with positron emission tomography (PET), usually imaged on a hybrid device incorporating X-ray CT (PET/CT), has been implemented. Aims: #1 - To determine SIRT dose (in Gy) to liver lesions identified on FDG PET/CT; #2 – to use early follow-up FDG PET/CT to examine metabolic response; and, #3 – to relate metabolic response to SIRT dose. **Methods:** Prospective data collection of baseline and early follow-up FDG PET/CT as well as Y-90 images within 24 hrs of SIRT (SIR-Spheres microspheres, Sirtex Medical, Sydney, AUS) between January 2013 and June 2014. Within a PET-defined volume of interest (VOI) we measured Total Lesion Glycolysis (TLG = lesion volume on FDG PET $\times$ average SUV_{VOI}) for up to 5 target lesions. Fractional change (%) in TLG between baseline and follow-up was determined and compared to the average dose within the FDG-defined target lesion VOIs applied to the Y-90 PET images converted to dose maps. A positive change in TLG reflects a decrease in uptake (*i.e.*, positive response). **Results:** Fifteen patients containing 32 measurable lesions (CRC = 18,HCC = 6,other = 8) were examined. Mean time from treatment to follow-up FDG PET/CT was 62 ± 15 days. The data were fitted with a log function and showed a good correlation between dose and response (R^2= 0.79). A significant metabolic response, defined as change in TLG of $\geq$ 50%, was seen in all lesions receiving a mean dose of $\geq$ 30 Gy. No relationship was observed between site of origin of the malignancy/pathology and response. **Conclusions:** Dose to tumour and normal tissue can be determined using Y-90 PET/CT imaging. The dose delivered correlates with the metabolic response seen. The dose maps can be used to immediately (with 24 hrs) determine if a therapeutic dose of Y-90 SIRT has been delivered on a lesion-by-lesion basis and, if sub-therapeutic, further action can be instigated.

11065 Poster Session (Board #278), Sun, 8:00 AM-11:30 AM

Development of a PD-L1 immunohistochemistry (IHC) assay for use as a companion diagnostic for pembrolizumab (MK-3475) in non-small cell lung cancer (NSCLC). *First Author: Marisa Dolled-Filhart, Merck & Co., Inc., Kenilworth, NJ*

Background: Tumors express PD-L1 to contribute to escape from immunosurveillance. We developed a PD-L1 IHC assay to investigate whether it could predict response to pembro in NSCLC patients (pts) and be used as a companion diagnostic. **Methods:** The assay uses the 22C3 anti–PD-L1 murine monoclonal antibody on the Dako platform. One pathologist scored each tumor sample by 4 methods: percentage of cells staining at any intensity (PS1), percentage of cells staining at moderate/strong intensity (PS2), percentage of cells staining at strong intensity (PS3), and H-score (HS = PS1 + PS2 + PS3). Only cells with at least partial membrane staining were counted. Receiver operating characteristic analysis was used to compare scoring methods and determine a cutoff using data from 146 NSCLC pts treated with pembro in KEYNOTE-001 who had tumor evaluable for PD-L1 expression by IHC and data for response (immune-related response criteria, investigator review). Samples from the first 31 pts were also tested with a prototype assay by a different pathologist who scored the presence or absence of a regional, primarily inflammatory cell or "interface" pattern in addition to the above. PFS and OS were assessed in the 146 pts with measurable disease (RECIST 1.1, central review). **Results:** The various scoring methods are summarized in the table. Incorporating the interface pattern did not improve scoring. Using PS1, 19 (43%) of 44 pts with $\geq$ 50% tumor cell staining responded, versus only 8 (8%) of 102 pts with $<$ 50% tumor cell staining (odds ratio = 8.93). Median PFS and OS were 4.0 mo and not yet reached, respectively, for pts with $\geq$ 50% staining and 2.1 and 6.1 mo, respectively, for pts with $<$ 50% cell staining. **Conclusions:** The PD-L1 IHC assay is potentially useful to enrich trial populations and as a companion diagnostic in NSCLC. While all 4 scoring methods assessed performed similarly, the percentage of cells staining at any intensity with a cutoff of 50% is the simplest and easiest method to implement in practice. Clinical trial information: NCT01295827.

	Area Under Curve	Youden Index	Cutoff	False Positive Rate, %	True Positive Rate, %
PS1	0.743	0.494	50	21.0	70.4
PS2	0.758	0.462	11	16.8	63.0
PS3	0.736	0.445	1	18.5	63.0
HS	0.758	0.502	63	20.2	70.4

11066 Poster Session (Board #279), Sun, 8:00 AM-11:30 AM

[^{18}F]AA-7: PET imaging in patients with suspected glioma. *First Author: Satoshi Nozaki, Novel PET Diagnostics Laboratory, RIKEN Innovation Center (RINC), Kobe, Japan*

Background: Positron emission tomography (PET) imaging with [^{11}C]methionine provides valuable information about amino acid metabolism in brain tumors. In surgical resection or radiotherapy of gliomas, precisely detecting the normal brain tissue–tumor boundary is critically important. However, as [^{11}C]methionine accumulates not only in tumor tissues but also in normal and inflamed tissues, it cannot detect precisely the normal brain tissue–tumor boundary. Hence, the purpose of this study was to develop a tumor-specific PET tracer, targeting the amino acid transporter LAT1, to assess the safety, biodistribution, and dosimetric properties of the novel PET radiopharmaceutical agent, and to preliminarily evaluate its application in the diagnosis of glioma. **Methods:** We have developed the novel LAT1-specific tracer, [^{18}F]AA-7. In preclinical studies, PET imaging with [^{18}F]AA-7 was performed in mice bearing LNZ308 human glioblastoma cell line and also in two mice models of inflammation (turpentine oil-induced myositis model and collagen-induced arthritis model mice). In a clinical study, dosimetry estimations for [^{18}F]AA-7 in healthy volunteers were determined. Patients with glioma received 185 MBq of [^{18}F]AA-7 and underwent PET scan for 45 minutes after the injection. [^{11}C]methionine and [^{18}F]FDG were used as control tracers in both preclinical and clinical studies. **Results:** In preclinical studies, [^{18}F]AA-7 was highly accumulated in LAT1 positive tumors as compared with [^{11}C]methionine[tumor to muscle ratio: 3.3$\pm$0.2 vs 2.1$\pm$0.4]. Moreover, although [^{18}F]FDG was also highly accumulated in inflamed regions, noticeable accumulation of [^{18}F]AA-7 was not observed in the two mice models of inflammation. In a clinical study, three healthy volunteers and five patients were enrolled in the "first-in-human" trial. All subjects had no significant problem. Upon visual examination, PET imaging using [^{18}F]AA-7 resulted in extremely clear images in patients with suspected glioblastoma. **Conclusions:** [^{18}F]AA-7 may be useful as a novel PET tracer for LAT1-positive tumor imaging and imaging for the efficacy evaluation of therapies, which has low accumulation in inflamed tissues. It may be suitable for PET imaging in patients with suspected glioblastoma. Clinical trial information: UMIN000015271.

11067 Poster Session (Board #281), Sun, 8:00 AM-11:30 AM

Non-invasive determination of HER2-expression in metastatic breast cancer by using ^{68}Ga-ABY025 PET/CT. *First Author: Henrik Lindman, Department of Oncology, Uppsala University, Uppsala, Sweden*

Background: In contrast to biopsies, PET imaging gives a complete and quantitative image of all the patient's tumors and all parts of individual lesions. PET imaging of HER2 could select patients for HER2-targed therapy, predict response based on uptake and be used for monitoring. In this pivotal phase I/II study the HER2-binding Affibody molecule ABY025 was labeled with ^{68}Ga for PET to study effect of peptide mass, test-retest variability and correlation of quantified uptake in tumors to histopathology. **Methods:** Sixteen women with known metastatic breast cancer and on-going treatment were included and underwent FDG PET/CT to identify viable metastases. After iv injection of 212$\pm$46 MBq ^{68}Ga-ABY025 whole-body PET was performed at 1, 2 and 4 h. In the first 10 patients, ^{68}Ga-ABY025 PET/CT with two different doses of unlabeled peptide was performed 1 week apart. Six had HER2-positive primary tumors and 4 were included as HER2-negative controls. In the last six patients (5 HER2-pos and 1 HER2-neg primary tumor), repeated ^{68}Ga-ABY025 PET were done as a test-retest of uptake at 2 h in individual lesions. Primary tumors and biopsies from metastases were collected for verification of HER2 expression. **Results:** Scanning with the higher peptide dose at 2-4h provided better discrimination of HER2-pos metastases in all tissues ($p < 0.01$). Sixteen metastases in 12 patients were biopsied and evaluated by immunohistochemistry and in-situ hybridization. Uptake (SUV, mean $\pm$ SD) at 2h in these metastases was 10.9 $\pm$ 5.1 in HER2-pos (n = 7) vs 3.4$\pm$2.1 in HER2-neg (n = 9) ($p = 0.001$). SUV at 4h was 15.0 $\pm$ 3.4 in HER2-pos (n = 6) vs 2.9$\pm$1.9 in HER2-neg (n = 6) ($p < 0.001$, no overlap). The test-retest intra-class correlation was R = 0.996. ^{68}Ga-ABY025 PET led to change in HER2-targeting treatment in 3 of the 16 patients due to receptor up- or down-regulation. Moreover, the PET data indicates occurrence of intra-patient heterogeneity of HER2-expression in several cases. **Conclusions:** ^{68}Ga-ABY025 PET accurately quantifies whole-body HER2-receptor status in metastatic breast cancer. Clinical trial information: NCT01858116.

11068 Poster Session (Board #282), Sun, 8:00 AM-11:30 AM

A prospective evaluation of cell free DNA (cfDNA) genotyping and circulating tumor cells (CTC) in *EGFR* mutant NSCLC patients (pts) treated with erlotinib. *First Author: Masahiko Yanagita, Dana Faber Cancer Institute, Boston, MA*

Background: Genotype directed therapy is now standard of care for advanced NSCLC pts. However, adequate tumor tissue for comprehensive genotyping remains a challenge. Recent research suggests that CTC capture or cfDNA analysis allows for non-invasive diagnosis and monitoring of treatment. This prospective trial was designed to quantify the predictive value of CTC and cfDNA analyses of *EGFR*-mutant NSCLC pts treated with first-line erlotinib. **Methods:** TKI naïve *EGFR* mutant NSCLC pts were enrolled in a phase II trial of erlotinib treatment. Paired blood for cfDNA and CTC analysis was collected at baseline prior to therapy and every 2 months during follow ups. Plasma genotyping was performed by ddPCR for *EGFR*19del, L858R, T790M while CTCs were isolated by CellSearch and analyzed by IF and *MET*-FISH. Repeat biopsies at progression were performed when feasible. **Results:** Between 2/10 and 1/15, 60 *EGFR*mutant pts (L858R:17, 19del:38, other:5) were enrolled. As of 1/15, 44 patients have discontinued therapy (39 for RECIST progression; 5 for adverse events). Blood was available for cfDNA analysis on 53 and 33 pts at baseline and progression respectively, and *EGFR* mutations were detected in 25/53 pts (47.1 %, median: 57 copies/mL plasma, range: 2-1649) and 10/33 pts (30.3% median, 71 copies/mL plasma, range: 5-2530). Blood was available for CTC analysis on 47 and 33 pts and CTCs were detected in 17/47 pts (36.1%, median: 3 CTCs/7.5 mL blood, range: 1-1145) at baseline and 15/33 pts (45.4%, median: 6 CTC/7.5 mL blood, range: 1-328) at progression. *MET*amplification was identified in CTCs of 2 pts. For 18 pts with detectable cfDNA at baseline and $>=$ 3 follow up blood draws, treatment reduced cfDNA levels to non-detectable for $>=$ 4 months in 83.3 % (15/18). In contrast, for 17 pts with detectable CTCs at baseline, CTCs continued to be intermittently detected on treatment in 58.9% (10/17) of pts. **Conclusions:** cfDNA and CTCs are complementary non-invasive assays for *EGFR*mut NSCLC although the low yield of CTCs may preclude genotyping. Serial cfDNA monitoring may be a better predictor of treatment efficacy than CTCs. Funding: R01-CA135257, P50-CA090578, Conquer Cancer Foundation, Genentech

11069 Poster Session (Board #283), Sun, 8:00 AM-11:30 AM

Contrast-enhanced spectral mammography (CESM) compared with breast MRI for breast cancer detection. *First Author: Lydia Liao, MD Anderson Cancer Center at Cooper, Cooper Breast Imaging Center, Voorhees, NJ*

Background: Contrast-enhanced spectral mammography (CESM) is a new study to detect contrast enhancing malignancy that may not be visible on conventional mammogram. Limited studies have shown that adding CESM to diagnostic workup in adjunct with mammogram and breast ultrasound does increase sensitivity for breast cancer detection. More studies are needed to compare the sensitivity of CESM to BMRI to further define the role of CESM in breast cancer diagnosis. **Methods:** This study involved 60 malignant breasts in 58 women retrospectively chosen from of 1020 patients in our institution during the period of October 2012 to October 2014. Both CESM and BMRI were done for each patient within 30 days. The positive findings were confirmed by pathology reports. The number of malignant lesions was quantified. The size of lesions was classified into three categories based on standard of breast cancer stages. The enhancement intensity on both studies has been quantified based on a scale of 0-3. The scores of each case were calculated for average size of index lesion and statistical analysis. Sensitivity and positive predictive value (PPV) were calculated for each study. Morphology consistence was evaluated by the percentage of the consistent findings between CESM and BMRI. The mean study time for each test was recorded and analyzed for statistical significance. **Results:** Both CESM and BMRI are shown to have sensitivity of 98% for breast cancer detection. No statistical significance was identified on the mean size of index cancer ($p = 0.39$). The enhancement intensity of breast parenchyma is significantly lower on CESM than on BMRI ($p < 0.01$). The mean score of enhancement intensity of index lesions on CESM was significantly less than that for BMRI ($p < 0.01$). The smallest cancer can be detected by both CESM and BMRI is less than 0.5 cm. Morphology consistence was 59/60 (98.3%). CESM has a higher PPV than BMRI (98.0% versus 92.6%). The average test time for CESM is significantly shorter than BMRI (10 minutes versus 25 minutes). **Conclusions:** CESM and BMRI are consistent on morphology and equal sensitivity for detection of breast cancer lesions. CESM has less enhancement intensity than BMRI and higher PPV (reflecting a higher specificity) than BMRI.

11071 Poster Session (Board #285), Sun, 8:00 AM-11:30 AM

Identification of novel and potentially targetable receptor tyrosine kinase alterations in colorectal carcinoma using a 341 gene hybrid capture-based next-generation sequencing assay. *First Author: Jaclyn Frances Hechtman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The current mainstay of clinical molecular testing for advanced colorectal carcinoma (CRC) is mutation analysis for *KRAS*, *NRAS*, and *BRAF* to determine anti-EGFR therapy eligibility. However, the growing number and potential of targeted therapies has led to the need for broader molecular panels to triage patients. Here, we report our experience with a next-generation sequencing (NGS) assay that enables the detection as well as molecular characterization of CRC with rare and potentially targetable receptor tyrosine kinase (RTK) alterations. **Methods:** We use a hybrid capture-based NGS assay encompassing all exons of 341 cancer genes (MSK-IMPACT) to sequence tumor against matched normal to detect potentially actionable somatic alterations including point and indel mutations, copy number alterations, and selected structural rearrangements. CRC with hotspot mutations in *KRAS*/ *NRAS* exons 2-4 and *BRAF* exons 11 and 15 were excluded from further analysis as these downstream mutations often lead to primary resistance. **Results:** Seventy four of 164 CRC had wild type *RAS*/*RAF*. Twelve cases (16%) of this subgroup harbored RTK alterations previously reported to be activating and potentially targetable. Hotspot mutations commonly seen in other tumor types were also identified, including one each of *EGFR* p. L858R in a patient also harboring an *ERBB2* p. S310F, *EGFR* p. L861R, and *ERBB2* p. V842I a patient with *ERBB2* amplification. One each of in-frame fusions of RTKs were also detected: *ERBB2-GRB7* in a patient with *ERBB2* amplification, *RET-NCOA4*, and *ETV6-NTRK3*. Additional RTK amplifications were also observed in the absence of other oncogene alterations, including *FGFR1* (n = 3), *ERBB2* (n = 2), *MET* (n = 1) . No *ALK* or *ROS1*fusions were detected in any of the 164 CRC. Of these 12 patients with potentially targetable RTK alterations, 3 have already enrolled in 'matched' targeted therapies. **Conclusions:** Using a broad molecular assay to interrogate potentially actionable mutations, approximately 16% of *RAS*/ *RAF* wild type CRC harbor RTK alterations that are known to be activating and potentially responsive to inhibition.

11072 Poster Session (Board #286), Sun, 8:00 AM-11:30 AM

Analysis of cell-free circulating tumor DNA in patients with glioblastoma and other primary brain tumors. *First Author: David Eric Piccioni, UC San Diego Moores Cancer Center, San Diego, CA*

Background: Glioblastoma is the most aggressive type of primary brain tumor with a median survival of 15 months and limited therapy options. Trials of genomically targeted matched therapies for brain tumors requiring recent tissue samples for next generation sequencing (NGS) has limited progress. Recently, a cell-free circulating tumor DNA (ctDNA) NGS panel of 54 genes has become available. We sought to evaluate whether this biopsy-free approach would allow us to interrogate genomic alterations in glioblastoma and other primary brain tumor patients. **Methods:** Fifty-nine consecutive patients with primary brain tumors were tested prospectively with the Guardant360 ctDNA panel at a CLIA-certified, CAP-accredited clinical laboratory. Single nucleotide variants (SNVs) in 54 genes and copy number variants (CNVs) in 3 genes (EGFR, ERBB2 and MET) are reported quantitatively as the fractional mutant allele concentrations in cell-free DNA and the absolute copy numbers of the genes measured, respectively. The test is sensitive to a single DNA fragment of mutated ctDNA in a 10 ml blood sample and analytic specificity is 99.999%. **Results:** Average patient age was 53 (range 24-87) and 61% were male. Histopathological subtypes tested were glioblastoma (34), astrocytoma (9), meningioma (6), oligodendroglioma (5), glioma NOS (4) and ependymoma (1). 22 (37.3%) of patients had at least one genomic alteration detected and 4(6.8%) had two genomic alterations detected. SNVs detected included *TP53* (7), *NOTCH* (4), *JAK2* (2), and *KIT*, *ERBB2*, *ALK*, *APC*, *ATM*, *EGFR*, *AR* and *HNF1A* (1 each). A single copy number amplification in *MET* was reported. Cell-free DNA was sufficient to complete the sequencing assay in 100% of cases. **Conclusions:** Contrary to other ctDNA studies where it was postulated that ctDNA would not cross the blood-brain barrier and reach the systemic circulation, we found that over one-third of primary brain tumor patients, including glioblastoma patients, had detectable ctDNA with the Guardant360 assay.

11073 Poster Session (Board #287), Sun, 8:00 AM-11:30 AM

Raise and decline of KRAS mutant clones in colorectal cancers (CRCs) treated with multiple rounds of anti-EGFR antibodies. *First Author: Giulia Siravegna, Istituto di Candiolo, Fondazione del Piemonte per l'Oncologia-IRCCS, Candiolo, Italy*

Background: We previously reported that acquired resistance to anti-EGFR antibodies (moAbs) is associated with the emergence of *KRAS* mutations that can be detected in the blood before disease progression (PD) is clinically manifest (Misale S et al. Nature 2012). It is unknown whether and how subsequent therapies affect KRAS clones, which were selected during treatment with anti-EGFR moAbs. **Methods:** We studied blood samples of 16 patients (pts) who responded and then progressed upon anti-EGFR therapy. For all pts, samples were available at baseline, at the time of first PD and at different time-points across subsequent lines of treatment. At least 4 longitudinal blood draws were available for each case. We analyzed the effect of drug withdrawal in populations of CRC cells (DiFi), which had acquired resistance to cetuximab (cmab). **Results:** In 11/16 pts, mutated *KRAS* alleles were detected in blood samples obtained at PD (2 exon 2 and 8 exon 3 mutations; 1 amplification). Mutant fractional abundance (MFA) varied from 0.09 to 23.46%. *KRAS* mutant clones (1 G12D, 1 G13D, 2 Q61H and 3 Q61L) were tracked in the blood of 7 pts who initially achieved benefit and then experienced PD after treatment with an anti-EGFR moAb (partial response maintained for 3-12 months). Mutant *KRAS* alleles, which rise in blood during EGFR blockade, decline upon withdrawal of anti-EGFR moAbs (from 7.3% MFA to undetectable levels) indicating that clonal evolution continues beyond clinical progression. In the blood of pts who benefit from multiple challenging with anti-EGFR moAbs the levels of *KRAS* mutations are dynamic. They raised during the first anti-EGFR treatment, declined and became undetectable when the anti-EGFR moAb was suspended and raised again during re-challenge with EGFR blockade (from 0.31 to 1.27% MFA). Pharmacogenomic analysis of CRC cells (DiFi), which acquired resistance to cmab, revealed that upon antibody withdrawal, KRAS clones decay while the population regains sensitivity to cmab. **Conclusions:** These results reveal that the CRC genome adapts dynamically to intermittent drug schedules and provide a molecular explanation for the efficacy of re-challenge therapies based on EGFR blockade.

11074 Poster Session (Board #288), Sun, 8:00 AM-11:30 AM

The Prospective Epidemiologic Risk Factor (PERF I) Study: A serum biomarker reflecting collagen type I degradation as an early detection tool for cancer. *First Author: Cecilie Liv Bager, Techinical University of Denmark, Lyngby, Denmark*

Background: Matrix metalloproteinase (MMP) mediated degradation of the extracellular matrix (ECM) play an important role in the development of cancer. One of the most abundant ECM proteins is type I collagen, which is commonly dysregulated and degraded in early stages of tumorigenesis. However, MMP mediated tissue destruction has not been quantified in larger prospective cancer outcome studies. The aim of this study was to investigate if a biomarker reflecting MMP-mediated degradation of type I collagen (C1M) could be used for early detection of cancer, in a large prospective study. **Methods:** From 1999-2001, 5,856 women aged 60-85 participated in the Prospective Epidemiologic Risk Factor (PERF I) stud, which addresses age-related diseases. Demographics and serum samples were collected at time of enrollment. Cancer diagnoses were collected from the Danish Cancer Registry ultimo 2014. Serum C1M levels were measured by ELISA and compared to time of diagnosis and to non-cancer diagnosed and non-diseased women (healthy). Women diagnosed with cancer prior to PERF1 enrollment were excluded from analysis. Data was analyzed using one way ANOVA on log transformed data and by Pearson's correlation coefficient. **Results:** A total of 1,154 women were diagnosed with cancer following PERF I enrollment. C1M, at baseline, was significantly elevated in women diagnosed less than 6 months after blood draw compared to healthy women (p=0.016) and to women diagnosed more than 48 months (p=0.016) after blood draw (see table). Furthermore, C1M correlated with time to diagnosis up to 3 years after blood draw (r = -0.143, p=0.0146, n=289). **Conclusions:** The levels of MMP-degraded type I collagen (C1M) were significantly elevated in serum from women diagnosed up to 6 months after enrollment in PERF I and correlated with time to diagnosis up to 3 years after blood draw. Further investigations into C1M as an early detection tool for cancer could be highly relevant.

	Healthy (95% CL) n=3051	<6 months (95% CL) n=81	6-24 months (95% CL) n=121	24-48 months (95% CL) n=176	>48 months (95% CL) n=776
C1M (ng/ml)	50.1 (38.1-39.3)	63.6 (38.9-52.2)	51.0 (45.9-56.1)	53.0 (46.5-59.5)	49.4 (47.1-51.8)

11075 Poster Session (Board #289), Sun, 8:00 AM-11:30 AM

A phase I, first-in-human dose study of the dual PI3K/mTOR inhibitor LY3023414 (LY) in patients (pts) with advanced cancer. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: The phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway is dysregulated in many malignant diseases. LY3023414 (LY) is an oral ATP competitive inhibitor of the class I PI3K isoforms, mTOR and DNA-PK. Based on preclinical results, we investigated LY in patients with advanced solid tumors. **Methods:** In this 3+3 dose escalation phase I study, patients with solid tumors refractory to standard therapies received LY once daily (QD) or twice daily (BID). The primary objective was to determine a recommended phase II dose (RPTD). Additional objectives were to assess LY dosing safety, pharmacokinetic/pharmacodynamic (PK/PD) profiles, drug-drug interaction with midazolam, and to document anecdotal antitumor activity. **Results:** As of September 2014, 47 pts have received LY either QD (at 20, 40, 80, 150, 225, 325, 450 mg) or BID (at 150, 200, 250 mg). Dose-limiting toxicities (DLTs) have been observed for LY QD only at 450 mg and consisted of grade [G] 4 thrombocytopenia, G4 hypotension, G3 hyperkalemia in 3/3 patients treated. For BID dosing, DLTs were observed in 3/4 patients at 250 mg (G4 hypophosphatemia, G3 fatigue, G3 mucositis) and in 1/15 patients at 200 mg (G2 nausea). Common treatment-related adverse events (all grades) included nausea (38%), fatigue (31%), vomiting (27%), and diarrhea (17%). PK analyses showed a dose-proportional increase in LY exposures (AUC) at tolerated dose levels with a half-life of 1.9 hours and a body clearance of 85 L/hr. Midazolam PK data indicated that LY is a weak inhibitor of CYP3A4. Biomarker assessment demonstrated dose-related target inhibition in peripheral mononuclear cells at LY doses $\geq$ 150 mg. Durable partial response according to RECIST was observed in an endometrial cancer patient harboring PIK3R1 and PTEN mutations and 22 additional patients (47%) had stable disease as their best response. **Conclusions**: LY appears to be safe when administered as single agent up to 325 mg QD or 200 mg BID. The RPTD of single-agent LY is 200 mg BID based on safety, tolerability, and PK/PD data. LY is currently studied in tumor-specific expansion cohorts for mesothelioma, breast cancer, indolent Non-Hodgkin Lymphoma and squamous NSCLC. Clinical trial information: NCT01655225.

11076 Poster Session (Board #290), Sun, 8:00 AM-11:30 AM

Lung cancer patients with HER2 mutations treated with chemotherapy and HER2 targeted drugs: Results form the EUHER2 cohort study. *First Author: Julien Mazières, Hôpital Larrey CHU Toulouse, Toulouse, France*

Background: *HER2* mutations are identified in about 2% of non-small cell lung cancer (NSCLC) and behave as an oncogenic driver. Little is known about the efficacy of chemotherapy and of HER2 targeted drugs in this population. We aimed to study therapeutic outcomes of patients harboring *HER2* mutations (HER2+) in order to establish the efficacy of various drug regimens and to orient future clinical trials. **Methods:** We conducted a retrospective cohort study in European centers testing NSCLC patients for HER2. Eligible patients had advanced stage NSCLC, known HER2 exon 20 insertions by local testing, and treatment with chemotherapy and/or targeted drugs. Clinicians had to obtain informed consent and IRB approval according to local regulations, and response were assessed according to RECIST version 1.1. Data were anonymized and analyzed centrally. **Results:** We identified 101 eligible patients from 38 centers. Our population was characterized by a median age of 61 yrs (30-87), a high proportion of women (63 *vs.* 38 men, 62.4%), and of never smokers (61, 60.4%). All tumors were adenocarcinomas. Concomitant EGFR mutation, ALK translocation and ROS translocation were observed in 5, 1 and 1 patients respectively. The median number of treatment lines was 3 (1-11). Overall survival of the whole population (n = 101) was 24 months (m.). Response rate (RR) and median progression free survival (PFS) for patients treated with conventional chemotherapy (excluding targeted therapy) were 43.5% and 5.9 m. in first line (n = 93) and 10% and 4.2 m. in second line (n = 52) respectively. RR to EGFR-TKI (n = 27) was 7.2% and PFS was 3 m. Eighty-six targeted treatments against HER2 were given to 65 patients including trastuzumab (n = 57), neratinib (n = 14), afatinib (n = 9), lapatinib (n = 5) and T-DM1 (n = 1). RR was 18% and PFS 3.9 months for afatinib. RR was 50% and PFS 5.1 m. for trastuzumab (given with vinorelbine n = 24, docetaxel n = 12, paclitaxel n = 12, cisplatinum based combination n = 7, alone n = 2). **Conclusions:** This series, the largest to date, underlines the chemosensitivity of HER2 + NSCLC and the potential interest of anti-HER2-antibodies that deserve to be further evaluated in clinical trials.

11077 Poster Session (Board #291), Sun, 8:00 AM-11:30 AM

Protein tyrosine phosphatase non receptor 11 (*PTPN11*/Shp2) as a driver oncogene and a novel therapeutic target in non-small cell lung cancer (NSCLC). *First Author: Yasir Elamin, Education Centre Beaumont Hospital, Dublin, Ireland*

Background: *PTPN11*/Shp2 somatic mutations occur in 25% of Juvenile myelomonocytic leukemias (JMML) and less commonly in adult solid tumors. *PTPN11*/Shp2 activates the mitogen-activated protein kinase (MAPK) pathway, upstream of KRAS and MEK. Accordingly, *PTPN11* mutations were shown to sensitize leukemia cells to MEK inhibitors. **Methods:** We applied mass-spectrometry based genotyping (Sequenom Inc., Germany) to DNA extracted from tumor and matched normal tissue of 299 NSCLC patients (98 adenocarcinomas and 201 squamous cell (SCC)). *PTPN11* constructs with mutations (E76A, A72D) were generated and stably expressed in IL-3 dependent BaF3 cells and NSCLC cell lines (H1703, H157). The acquisition of MAPK pathway activation was evaluated using western blotting and reverse phase protein array (RPPA). *PTPN11*/Shp2 phosphatase activity was measured in whole cell protein lysates using Shp2 assay kit (R&D Systems). **Results:** Somatic *PTPN11* hotspot mutations occurred in 3 (3.1%) and 9 (4.5%) of adenocarcinomas and SCCs, respectively. Mutant *PTPN11*, compared to *PTPN11* wild type, promoted ten-fold IL-3 independent BaF3 cell survival. BaF3, H1703, and H157 cells expressing mutant *PTPN11* exhibited increased *PTPN11*/Shp2 phosphatase activity and phospho-ERK1/2 levels. shRNA was used to silence *PTPN11*/Shp2 in the NSCLC cell line H661, which has an activating *PTPN11* mutation (N58S). Silencing of *PTPN11*/Shp2 led to reduced cell proliferation and decreased phospho-ERK1/2 levels, suggesting that *PTPN11* mutation is crucial for cell tumorigenicity and MAPK pathway activation in H661 cells. Parental H661 (*PTPN11*-mutated, *KRAS*-wild type) and H1703 (*PTPN11/KRAS*-wild type) cells were treated with the novel MEK inhibitor BAY86-9766. IC50 values were 2.88 $\pm$ 0.6 μM in H661 cells and $<$ 50% growth inhibition at 10 μM in H1703 cells. **Conclusions:** *PTPN11*/Shp2 demonstrates the *in vitro* features of a driver oncogene, and potentially represents a new target in NSCLC.

11078 Poster Session (Board #292), Sun, 8:00 AM-11:30 AM

Identifying driver mutations in squamous cell lung cancer (SCC): The Lung Cancer Genomics Ireland (LCGI) study. *First Author: Shereen Rafee, St. James's Hospital, Dublin, Ireland*

Background: Targeting oncogenic drivers has transformed the care of lung adenocarcinoma. However, there is no approved targeted therapy for lung SCC. LCGI aims to identify potential targets in lung SCC. **Methods:** The LCGI study is being carried out in patients with surgically resected lung SCC. We used the platform of Sequenom's MassArray to perform genotyping for 548 somatic hotspot mutations in 49 genes including genes in the MAPK and PI3K pathways. We also evaluated *FGFR1* amplification by fluorescence in situ hybridization (FISH) and MET protein expression by immunohistochemistry (IHC). **Results:** Lung SCCs from 201 patients have been tested by Sequenom MassArray to date. Lung SCCs from 150 patients have been evaluated for MET protein expression and 89 for *FGFR1* amplification. 134 (66.7%) patients were male. The median age of the cohort was 68. The majority of patients were either current (32.8%) or former (64.2%) smokers at the time of diagnosis. 104 (57.1%) were stage I, 68 (33.8%) were stage II, 29 (14.5%) were stage III SCCs. At least one aberrant, potentially targetable oncogene was identified in the SCC of 81 (40.3%) patients (see Table). The presence of *PIK3CA* or *KRAS* mutations, or *FGFR1* amplification did not have a statistically significant impact on median overall survival or recurrence-free survival. However, the presence of two or more aberrations in driver oncogenes in a tumor (patients, n = 19) was associated with a worse median overall survival compared to patients with either a single driver aberration ($p = 0.04$) or no aberrations ($p < .001$). **Conclusions:** 40.3% of lung SCC patients have an aberrant, potentially targetable driver oncogene in their tumor. The presence of two or more aberrant oncogenes is a poor prognostic factor. These findings can be used to guide clinical trials in lung SCC.

Frequency of driver mutations in LCGI compared to The Cancer Genome Atlas (TCGA) study.

Mutation	LCGI (n = 201)	TCGA (n = 178)
FGFR1 amp (n = 89)	12.4%	16.8%
PIK3CA	12.4%	10.1%
KRAS	6.5%	0.6%
PTPN11	4%	1.7%
STK11	1.9%	1.7%
MYC	1.9%	0.0%
NRAS	1.5%	0.0%
BRAF	1.5%	3.9%
HRAS	1.5%	1.7%
CTNNB1	1.5%	1.7%
FBXW7	1.5%	3.4%
MET Overexpression (n = 150)	1.3%	NA
EGFR	0.9%	2.8%
AKT1	0.5%	0.6%
CDK4	0.5%	0.0%
GNA11	0.5%	0.6%
MAP2K1	0.5%	0.6%
DDR2	0%	1.1%

11079 Poster Session (Board #293), Sun, 8:00 AM-11:30 AM

The anti-proliferative effects of RF EMF amplitude-modulated at tumor specific frequencies and mediation by calcium. *First Author: Hugo Jimenez, Wake Forest University Baptist Health, Winston-Salem, NC*

Background: Experimental and clinical evidence shows that whole body administration of low-level radiofrequency electromagnetic fields, amplitude-modulated (AM RF EMF) at specific frequencies ranging from 400 Hz to 21 kHz has efficacy in advanced hepatocellular carcinoma (HCC) (Costa, de Oliveira et al, 2011). In vitro studies demonstrate that AM RF EMF treatment inhibits cancer cell growth in a tumor-specific manner (Zimmerman, Pennison et al, 2012). RNA-seq analysis of HepG2 cells treated with AM RF EMF revealed altered expression of several mRNAs belonging to the IP3/DAG signaling pathway. Given the central modulatory effect of calcium in this pathway, we hypothesized that calcium modulates the growth inhibitory effect of RF EMF. **Methods:** HCC and ovarian cancer cell lines as well as NOD SCID mice, carrying subcutaneous HCC xenografts, were exposed to 27.12 MHz RF EMF modulated at cancer-specific frequencies or random chose frequencies using exposure systems designed to replicate human exposure levels. Huh-7 cells were cultured in the presence or absence of BAPTA, a Ca^{2+} chelator, for three hours daily, seven days in a row. Mice carrying Huh-7 xenografts received treatment three hours daily for six weeks. The specific absorption rate (SAR) of AM RF EMF was 0.4 W/kg, which is identical to the highest SAR measured in patients receiving treatment with this therapy. mRNA expression of key mediators of the IP3/DAG signaling pathway was analyzed. **Results:** Ca^{2+} chelation fully abrogated AM RF EMF inhibition of HCC cell growth. ARHGDIB and S100B mRNA was down regulated in Huh-7 cells treated with cancer-specific AM RF EMF. In vivo Huh-7 was significantly inhibited in mice exposed to AM RF EMF. **Conclusions:** Ca^{2+} is a necessary mediator of AM RF EMF anti-proliferative effects in HCC, which modulate the IP3/DAG signaling pathway (Costa, F. P., et al, 2011. "Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields." *Br J Canc* **105**(5): 640-648; Zimmerman, J. W., et al, 2012. "Cancer cell proliferation is inhibited by specific modulation frequencies." *Br J Canc* **106**(2): 307-313).

11080 Poster Session (Board #294), Sun, 8:00 AM-11:30 AM

TBCRC-010: Phase I/II study of dasatinib in combination with zoledronic acid (ZA) for the treatment of breast cancer bone metastasis (MBC-bone). *First Author: Zahi Ibrahim Mitri, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Osteoclast activation and subsequent bone resorption release growth factors that promote tumor growth. These events are blocked by the Src/PDGF inhibitor dasatinib. The tyrosine kinase Src phosphorylates and activates the ER in ligand-independent manner. Dasatinib, by inhibiting Src, may facilitate the antitumor effect of endocrine therapy. **Methods:** A phase I/II study was completed by the TBCRC at three institutions: MD Anderson Cancer Center, Duke University, and University of Chicago. Pts with HER2-negative, MBC-bone received standard dose ZA IV on day 1 and Dasatinib 100 mg QD, days 1-28 of each 28 day cycle. Prior therapy with bone-modifying agents was allowed. Response was assessed by RECIST (non-bone disease) and MDACC criteria for bone. Pts progressing on endocrine therapy continued this therapy to determine dasatinib's effect. Change in urine n-terminal telopeptide levels (NTX) was correlated with response. **Results:** 25 pts were enrolled, 7 in phase I and 18 in phase II. An initial pt developed pleural and pericardial effusions in cycle 1 on dasatinib 70 mg BID, prompting change to 100mg/day for the MTD/RP2D (recommended phase 2 dose) 6 pt run-in cohort (0/6 developed DLT). Most adverse events (AEs) were grade 1-2: rash (32%), fatigue (28%), and nausea (20%). Grade 3 AEs: anemia (4%) and pain (4%). In pts treated at RP2D (n = 24, Table 1), RR (CR, PR) in bone was 5/24 (21%), all PRs. Clinical benefit rate (CR, PR, SD > 6months) in bone was 8/24 (33%). Median TTF was 2.69 months (1.77 - 5.45), 3.61 months (1.84 - 5.71) in ER+ disease and 0.67 months (0.26 – 1.73) in ER- disease. Response was associated with low grade, ER+ disease, and high baseline NTX levels. In ER+ disease pts who had progressed on, but continued their previous endocrine therapy (n = 14), 29% had PR in bone. In pts with metastatic sites outside the bone (n = 12), RR was 3/12 (25%) and CBR 4/12 (33%) for non-bone metastasis. **Conclusions:** Dasatinib and ZA were well tolerated, and may have benefit in a subset of pts. Clinical trial information: NCT00566618.

Characteristics of patients treated at RP2D.

Patients (N)	24
Median Age, (Range)	45, (36-74)
Hormone receptor	
Positive	21
Negative	3
NTX at baseline	
Low	16
Moderate	3
High	4
Reason for discontinuation	
PD	22
AE	2

11081 Poster Session (Board #295), Sun, 8:00 AM-11:30 AM

Prognostic significance of β2 adrenergic receptor expression in the patients with non-small cell lung cancer. *First Author: Tomohiro Yazawa, Department of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan*

Background: β2 adrenergic receptor (β2-AR) is highlty expressed in cancer cells and has a relationship with tumor cell progression and metastases. However, it remains unclear about the prognostic role of β2-AR expression in non-small cell lung cancer (NSCLC). The aim of this study is to clarify the clinicopathological importance of β2-AR expression in patients with NSCLC. **Methods:** Three hundreds and twenty eight patients with surgically resected NSCLC were investigated retrospectively. Tumor sections were stained by immunohistochemistry for β2-AR, Ki-67, and microvessel density (MVD) determined by CD34. **Results:** β2-AR was positively expressed in 27% of all patients, 29% of adenocarcinoma (AC) patients, and 24% of non-AC patients, respectively. The β2-AR expression was significantly correlated with lymphatic permeation ($r = 0.240$, $p < 0.001$) and vascular invasion ($r = 0.239$, $p < 0.001$), and Ki-67 ($r = 0.175$, $p = 0.009$) in AC patients, but not non-AC. A positive β2-AR expression indicated poor prognosis of AC patients (overall survival, OS: $p = 0.045$; progression-free survival, PFS: $p = 0.001$), especially stage I (OS, $p = 0.017$; PFS, $p = 0.003$). Multivaritate analysis confirmed that β2-AR expression was an independent factor for predicting poor progression-free survival in stage I AC patients (hazard ratio: 2.220; 95% confidence interval: 1.077-4.573; $p = 0.031$). **Conclusions:** β2-AR expression was identified as an independent prognostic factor for early stage AC patients. β2-AR could be a promising marker for predicting outcome after surgery in lung cancer.

11082 Poster Session (Board #296), Sun, 8:00 AM-11:30 AM

Mutant HRAS as novel target for MEK and mTOR inhibitors. *First Author: Michael Kiessling, University Hospital Zurich, Zurich, Switzerland*

Background: HRAS (Harvey-RAS) is a frequently mutated oncogene in cancer. HRAS is mutated in head and neck cancer (3.9%), bladder cancer (5.1%), vulvar squamous cell carcinoma (9.3%), cutaneous squamous cell carcinoma and lung cancer (3.8%). However, mutant HRAS as a drug target has not been investigated so far. **Methods:** Cell Proliferation and Viability Assays: Cell proliferation was measured with the Cell-Titer-Glo Reagent (Promega) according to manufacturer's instructions. Cells were plated in clear-bottomed 96-well plates at a density of 500 - 2500 cells per well. The next day, drugs were added at indicatend concentrations and cell proliferation was measured 4 days later. Apoptosis assays:Cell lines were treated with indicated concentrations of inhibitors and apoptosis was measured after 48h and 72h. Apoptosis was assessed by AnnexinV–APC (Enzo Lifescience) and propidium iodide (PI) (Sigma-Aldrich) by FACS. **Results:** Here, we show that mutant HRAS activates the RAS and the mTOR pathway in various cancer cell lines including lung, bladder and esophagus cancer. HRAS mutation sensitized toward growth inhibition by the MEK inhibitors AZD6244, MEK162 and PD0325901. Further, we found that MEK inhibitors induce apoptosis in mutant HRAS cell lines but not in cell lines lacking RAS mutations. In addition, knockdown of HRAS by siRNA blocked cell growth in mutant HRAS cell lines. Inhibition of the PI3K pathway alone or in combination with MEK inhibitors did not alter signaling nor had an impact on viability. However, combined inhibition of MEK and mTOR reduced cell growth in a synergistic manner. **Conclusions:** Our results show that HRAS mutations in cancer activate the RAS and mTOR pathways which might serve as a therapeutic option for mutated lung cancer patients.

11083 Poster Session (Board #297), Sun, 8:00 AM-11:30 AM

Stereotactic ablative radiotherapy (SABR) as re-irradiation for an isolated infield lymph node recurrence. *First Author: Neal Bhatt, University of Louisville, Louisville, KY*

Background: Oligometastatic disease presents a unique opportunity for local therapy to provide cure. The aims of this study were to evaluate the safety and efficacy of stereotactic ablative radiotherapy (SABR) as a local treatment for isolated lymph node recurrence in a previously irradiated field. **Methods:** Between January of 2010 and September of 2014, 33 patients were reviewed from a prospectively collected database. Eighteen of 33 patients had biopsy proven recurrence and all patients were shown to have isolated metastases by positron emission tomography (PET)–CT. All patients had previously received full dose radiation treatment with radical intent, with a median total dose of 56 Gy (range, 46-74) delivered with standard fractionation. The median duration from initial radiotherapy to lymph node recurrence was 11.2 months. The overall survival (OS), local control (LC) rate, and disease progression–free survival (DPFS) rate were calculated according to the Kaplan-Meier method. Comparison between prognosis groups and toxicities was performed using log-rank analysis. **Results:** All patients completed the prescribed treatment. The median tumor dose and fractions administered was 40 Gy (range, 24-50) in 5 fractions. The median follow-up was 10 months (range, 1-33). Three grade 3 toxicities were observed including radiation pneumonitis, displaced fracture, and pelvic pain. No Grade 4 toxicities were recorded. Results at last follow up demonstrated a local control of 90.9%, Regional control (adjacent nodal station) of 66.7%, and distant failure of 27.3%. The median time to any failure was 4.5 months with a 1 year OS of 45.5%, and DPFS 62.3%. **Conclusions:** SABR salvage to macroscopic nodal recurrences provides local control and long-term disease-free survival in carefully selected patients with a low incidence of toxicities. Further investigation is warranted to identify those patients who benefit most from this treatment modality.

11084 Poster Session (Board #298), Sun, 8:00 AM-11:30 AM

Germline variants in cancer risk genes detected by NGS-based comprehensive tumor genomic profiling (CGP). *First Author: Michael J. Hall, Fox Chase Cancer Ctr, Philadelphia, PA*

Background: NGS-based CGP is increasingly used in oncology to assess patient eligibility for targeted therapies. Previous work has demonstrated that variant germline/somatic status may be accurately predicted for research use from data generated by CGP (AACR 2014 #1893). The prevalence of germline variants in hereditary cancer risks genes and their potential clinical implications have not been previously reported in patients referred for CGP. **Methods:** Germline variants were predicted in data from 15060 tumor samples analyzed by Foundation Medicine. Variant analyses focused on 20 penetrant hereditary cancer risk genes identified by the ACMG as high priority for disclosure to patients if discovered during genomic testing. Pathogenicity of each variant and association with tumor histology (known vs unexpected) was assessed through expert review of clinical evidence from public variant annotation databases (dbSNP/ClinVar, BIC, HGMD), and other resources (PubMed, Internet). **Results:** Of tumors tested, 30.8% (4633/15060) had >1 germline variant in a cancer risk gene, with 521 unique variants identified overall. A likely pathogenic variant (PV) was found in 3.1% tumors ($n = 466/15060$), and an additional 3.9% (587/15060) had a suspicious variant but conflicting pathogenicity data. PV prevalence appeared higher than in the general population (CGP PV prevalence; estimated population prevalence): *MUTYH* (1.3%; 0.02%), *RET* (0.7%; 0.02%), *BRCA1* (0.6%; 0.001%), *BRCA2* (0.5%; 0.001%); *MLH1* (0.02%; 0.002%), *PMS2* (0.02%; 0.001%) and *TP53* (0.02%; 0.0002%). Early-onset cancer was most strongly associated with PV in *BRCA1*($p < 0.001$). Bladder cancer (4.1%, 10/243 tumors tested), squamous cell lung cancer (4.4%, 13/293) and kidney cancer (3.4%, 5/148) had the most unexpected PV. Data were insufficient to determine clinical pathogenicity for the majority of the missense variants identified. **Conclusions:** Germline PV in cancer risk genes are found in 3-7% of patients tested by CGP. There is a pressing need for further research to determine the association of these variants to disease risk. Additional clinical resources are needed to guide oncologists in the interpretation and management of potential PV uncovered by CGP.

11085 Poster Session (Board #299), Sun, 8:00 AM-11:30 AM

Higher CD3 cell counts in apheresis collection in relation to superior survival in patients with multiple myeloma. *First Author: Sharon Kim, Mayo Clinic, Rochester, MN*

Background: High dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) remain a standard of care for patients with multiple myeloma (MM). While the impact of transplant is primarily thought to be related to dose intensity, immunological reconstitution also plays a major role. We examined the impact of CD3 content of apheresis product on outcomes. **Methods:** Patients (pts, $n = 1187$) diagnosed with MM between 2006 and 2014 who had a stem cell collection were included. Overall survival (OS) outcomes were correlated with total CD3 collected, CD3/CD34 ratio in the collection, and CD3 infused. **Results:** Among all 1187 pts included (median age 61 years, 57% male), the median CD3 and CD34 content was 4.6×10^8/kg and 8.3×10^6/kg, respectively. Overall, 886 (75%) had undergone HDT. Since the total CD3 count depends on the total goal, we examined the impact of CD3/CD34 ratio on outcomes. The median OS from ASCT was 90 months for those with a ratio of $> 5 \times 10^3$, compared with 68 months for the rest ($p < 0.01$). Specifically looking at the first day CD3 counts, median OS was not reached for those patients with $> 2.3 \times 10^8$/kg compared with 68 months for the rest ($p < 0.01$). In addition, CD3 dose infused was also prognostic for OS. In a multivariable analysis, the prognostic value was independent of the disease status for HDT, timing of HDT, and for the number of prior therapies. Given that the CD3 collection can be a surrogate marker for the immune system, we examined the impact of CD3 content on patients who collected without receiving HDT, estimating the OS from collection date. Among the 301 pts not treated with HDT, the OS from the collection date was not affected by the total CD3 dose or CD3/CD34 ratio, but remained strongly prognostic for those who had HDT. **Conclusions:** The results suggest that we should not only collect enough CD34 for hematopoietic recovery, but also enough CD3 for immunologic recovery with direct impact in clinical outcomes in MM patients undergoing ASCT.

11086 Poster Session (Board #300), Sun, 8:00 AM-11:30 AM

CTEP #8850: A phase I trial of riluzole and sorafenib in patients with advanced solid tumors. *First Author: Kristen Renee Spencer, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

Background: Metabotropic glutamate receptor 1 (GRM1) activates MAPK and PI3K/AKT signaling and is implicated in multiple cancers including breast, prostate and melanoma. GRM1 overexpression stimulates tumor angiogenesis via enhanced microvesicle secretion to facilitate endothelial cell growth. Riluzole (R) is a clinically available inhibitor of GRM1 signaling. Sorafenib (S), a kinase inhibitor that inhibits MAPK and PI3K/AKT signaling through C-RAF and B-RAF inhibition with antiangiogenic effects, was identified in preclinical screens to have synergistic antitumor activity when combined with R. This phase I trial identified the maximum tolerated dose (MTD) of R combined with S in patients (pts) with advanced cancer. **Methods:** Pts with refractory solid tumors were enrolled utilizing a standard 3+3 dose-escalation design. R was given in 28 day cycles at the highest dose used in clinical practice (100 mg BID) in combination with S, beginning at 200 mg daily and escalating in 200 mg increments per cohort. Restaging evaluations were performed every 2 cycles using RECIST criteria. **Results:** 29 pts enrolled, median age 59 (22-85), 13F, 16M, PS 0 (48%), 1 (35%) or 2 (17%). The most common toxicities were nausea (31%), fatigue (62%) and diarrhea (41%), anorexia (31%), rash (27% PPE, 31% other), and hypophosphatemia (34%). Grade 3-4 toxicities included hypophosphatemia (10%), elevated lipase (10%), LFT abnormalities (10%), rash/PPE (14%), and fatigue (13%). The most frequent dose limiting toxicity (DLT) was rash, observed in 3 pts at the MTD, dose level (DL) 4 (R 200 mg bid/S 400 mg bid). Best responses were SD in 9 pts (31%), lasting $>$ 3 months in 1 pt each with sarcoma, lung, colon, ovarian, and melanoma; and 1 GIST (9+ cycles with modest tumor reduction). **Conclusions:** R combined with S is safe with DLT of rash. While rash is a known side effect of sorafenib, its incidence and severity appeared increased in this study. An expansion cohort in pts with melanoma and sarcoma at DL3 (R 200 mg bid/S 400mg qam/200 mg qpm) is ongoing. Planned correlative assessments include circulating microvesicle quantification and immunohistochemical and western blotting to assess changes in activated signaling targets in pre and post treatment tumors. Clinical trial information: NCT01303341.

11087 Poster Session (Board #301), Sun, 8:00 AM-11:30 AM

Identification and functional characterization of a long non-coding RNA driving hormone-independent prostate cancer progression. *First Author: Francesco Crea, BC Cancer Agency, Vancouver, BC, Canada*

Background: Despite recent therapeutic advancements, castration-resistant prostate cancer (CRPC) remains an incurable disease. Most CRPCs display an aberrantly activated androgen receptor (AR) pathway, but the mechanisms underlying this phenomenon are not entirely elucidated. Long non-coding RNAs (lncRNAs) are non-translated transcripts, encoded by more than 50,000 *loci* of the human genome. Some lncRNAs are emerging as crucial mediators of neoplastic progression. We hypothesize that lncRNAs are functionally relevant in CRPC, and therefore they can be exploited as novel therapeutic targets. **Methods:** We developed isogenic pairs of patient-derived, prostate cancer xenografts (PCXs), showing opposite sensitivity to castration. We then profiled the transcriptome of sensitive *vs.* resistant PCXs and set out functional characterization of the most differentially expressed lncRNA. **Results:** Transcriptomic analysis revealed more than 100 lncRNAs specifically up-regulated ($>$ 2 fold) in the castration-resistant models. These uncharacterized genes have been named *HORAS*: *Hormone Resistance Associated Sequences*. The most highly up-regulated lncRNA was *HORAS1*, a gene mapping on chromosome 21. Using qPCR, we have confirmed dramatic *HORAS1* up-regulation in three isogenic castration-resistant/sensitive PCX pairs (5- to 113-fold change). *HORAS1* was highly expressed in AR-positive PCa cell lines and was prevalently localized in the cytoplasm. We then tested the function of *HORAS1* in two PCa cell lines grown in media containing castrate testosterone levels. *HORAS1* silencing induced a dramatic growth arrest and activation of caspase 3/7, 8 and 9 (two distinct small-interfering RNAs vs. negative control; $p < 0.01$, ANOVA and Tukey post-test for all the above mentioned experiments). *HORAS1* silencing also induced down-regulation of AR target genes. RNA Seq. analysis on 208 primary prostate cancer samples revealed that higher *HORAS1* expression predicts shorter disease-free free survival ($p < 0.01$, log-rank test). **Conclusions:** *HORAS1* is a previously uncharacterized regulator of the AR pathway. This lncRNA is required for hormone-independent prostate cancer proliferation.

11088 Poster Session (Board #302), Sun, 8:00 AM-11:30 AM

Characterization of LASEP3 as a serological and prognostic biomarker and a therapeutic target for lung cancer. *First Author: Atsushi Takano, Center for antibody and vaccine, The University of Tokyo, Tokyo, Japan*

Background: Characterization of cancer-specific oncoproteins could lead to the development of novel diagnostic/prognostic biomarkers or therapeutic targets. **Methods:** To develop new cancer biomarkers and therapies targeting oncoproteins, we used the strategies as follows: i) Identification of up-regulated genes in non-small cell lung cancers (NSCLCs) by means of cDNA microarray, ii) Validation of clinicopathological significance of their protein expression by tissue microarray, iv) Examination of the growth/invasive effect on cancer cells by siRNA assay, and v) Measurement of their serum protein levels by ELISA. **Results:** We identified a secreted protein, LASEP3 (lung cancer-associated serum protein 3) as a candidate. Immunohistochemical staining of LASEP3 showed that strong LASEP3 positivity was observed in 198 (54.8%) of 361 earlier stage NSCLCs that had undergone curative surgery. High level of LASEP3 expression was associated with poor prognosis for NSCLC patients. ($P = 0.0183$ by log-rank test). Serum LASEP3 levels were higher in NSCLC patients than in healthy volunteers. The proportion of serum LASEP3-positive cases was 160 (61.8%) of 259 NSCLCs (49.4% for stage I-II, 67.4% for stage III-IV), while 6 (5.5%) of 109 healthy volunteers were falsely diagnosed. Moreover serum LASEP3 levels were significantly higher in breast and colon cancer patients than in healthy volunteers. Furthermore, reduction of LASEP3 by siRNAs suppressed lung cancer cell proliferation and invasion. Flow cytometric analysis of these tumor cells transfected with siRNAs for LASEP3 revealed a significant increase of the cells at the sub G1 phase and induced the apoptosis of the cancer cells. Furthermore, subsequent *microarray* analysis of these cancer cells transfected with siRNAs identified several candidate downstream genes of LASEP3 that relate to cell growth/invasion signals. **Conclusions:** LASEP3 is a possible diagnostic and prognostic biomarker and a therapeutic target for lung and various types of solid cancer.

11089 Poster Session (Board #303), Sun, 8:00 AM-11:30 AM

A prospective validation of plasma ddPCR for rapid *EGFR* and *KRAS* genotyping of advanced NSCLC patients (pts). *First Author: Adrian G. Sacher, Dana-Farber Cancer Inst, Cambridge, MA*

Background: Plasma genotyping of cell-free DNA (cfDNA) has the potential to allow for noninvasive genotyping while avoiding the inherent shortcomings of tissue genotyping and repeat biopsies. We have developed a quantitative droplet digital PCR (ddPCR)-based plasma genotyping assay capable of detecting common *EGFR* and *KRAS* mutations (Oxnard *et al.*, CCR 2014). This is the first prospective study designed to validate the test characteristics of plasma ddPCR in advanced NSCLC. **Methods:** Pts with newly diagnosed or progressive advanced NSCLC were eligible. All pts were required to have a biopsy available or planned for tissue genotyping which was used for gold standard comparison; rebiopsy was required for pts with acquired resistance to EGFR TKI. Pts underwent an initial blood draw and immediate plasma ddPCR for *EGFR* exon 19 del, L858R, T790M and/or *KRAS* G12X. Test turnaround time (TAT) was measured in business days from date of blood draw until test reporting. Test characteristics were studied only in pts completing both plasma ddPCR and tissue genotyping for a given mutation. **Results:** 170 pts have been enrolled: 95 newly diagnosed, 43 with acquired resistance to EGFR TKIs and 32 others with progressive disease. Tumor genotype: 68 *EGFR* exon 19/L858R mutants, 27 *KRAS* G12X mutants, 75 others. Median TAT for plasma ddPCR was 3 days (range 1-5). Specificity of plasma ddPCR was 98% for 19 del/L858R (55/56) and 100% for *KRAS* (57/57), but lower for T790M at resistance (84%, 21/25; $p = 0.03$). Sensitivity of plasma ddPCR was 74% for 19 del/L858R (50/68) and 76% for T790M (19/25) but lower for *KRAS* (48%, 13/27; $p = 0.03$). Sensitivity for *EGFR* or *KRAS* was 78% in pts with extra-pulmonary disease (58/74) but 30% in pts with lung only disease (7/23; $p < 0.01$). **Conclusions:** Plasma ddPCR for driver mutations in *EGFR* and *KRAS* has a rapid TAT and high specificity suggesting it could be used to avoid biopsies for genotyping in some pts with advanced NSCLC. The false positive rate for T790M is likely related to tumor heterogeneity in resistant disease. This assay is currently being transitioned into the pathology laboratory for clinical use. Funding: US Department of Defense, Conquer Cancer Foundation of ASCO, Stading-Younger Cancer Research Foundation

11090 Poster Session (Board #304), Sun, 8:00 AM-11:30 AM

Ocular toxicity with MEK inhibitors in phase I trials: A single centre experience across six clinical trials. *First Author: Vasiliki Michalarea, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: MEK is a crucial signalling protein downstream of multiple receptor and non-receptor protein kinases that drive cancer. A range of allosteric MEK inhibitors have been developed and one has been licensed for use in malignant melanoma. We have assessed ocular toxicity in detail across a range of MEK inhibitors. **Methods:** Patients enrolled in phase I trials of MEK inhibitors between February 2009 and November 2014 were considered eligible for this study. Patients underwent testing of visual acuity by Snellen's chart, ocular pressure assessment and ocular tomography (OCT) at baseline and at various points in each trial. **Results:** 94 (M:F, 42:52) patients were assessed in 6 trials. The most common tumour types included colorectal, lung, ovarian cancer and melanoma. Significant retinal changes on OCT were detected in 30/94 (31%) patients. 15 (50%) of these patients were symptomatic due to peripheral epithelial detachment (PED), central serous detachment (CSR) and a combination (PED+CSR) in 9/15, 3/15 and 3/15 cases. In 15 asymptomatic patients, significant retinal changes on OCT included PED in 13/15 and PED+CSR in 2/15. National Cancer Institute Common Toxicity Criteria (NCI-CTC) Grade 0, 1, 2 and 3 numbered 60, 30, 4 and 2 events respectively. In patients where OCT was performed, there was a statistically significant difference in average thickness and central thickness of the macula ($p = 0.0009$ and $p = < 0.0001$, respectively), but not in total macular volume ($p = 0.67$), between patients who reported any Grade 0-3 ocular toxicities on ANOVA. There were no episodes of toxicity related drug discontinuations or irreversible ocular toxicity. **Conclusions:** Reversible retinal changes occur across a diverse number of MEK inhibitors indicating this to be a class effect. Approximately half of patients were symptomatic; however, with careful monitoring by OCT, appropriate dose delays and dose reductions, it is possible to continue treatment in most instances.

11091 Poster Session (Board #305), Sun, 8:00 AM-11:30 AM

Investigation of non-V600 BRAF mutations commonly found in NSCLC for their sensitivity to dabrafenib or trametinib. *First Author: Amir Noeparast, Medical Oncology, Oncologisch Centrum, UZ Brussel, Brussels, Belgium*

Background: The most common BRAF mutations in non-small cell lung cancer (NSCLC) are non-V600 in contrast to melanoma. BRAF pathway inhibitors have not been systematically investigated in non-V600 mutations *in vitro* and in the clinic. We tested the effect of two clinically available BRAF pathway inhibitors (Trametinib and Dabrafenib) on a subset of clinically identified BRAF mutations in a cohort of lung cancers enriched for adenocarcinoma in patients with no or limited smoking history. **Methods:** NSCLC tumor samples (FFPE) were tested for the presence of EGFR, KRAS, NRAS, HRAS and BRAF mutations by DGGE or NGS-based methods. We generated 15 BRAF expression plasmids, harboring the mutations found in the given cohort and others described in the literature. BRAF mutants were subjected to an *in vitro* kinase assay. BRAF constructs were also expressed in HEK293T cells (with and without wt-CRAF) to study their impact on ERK signaling and determine the effect of inhibitors. **Results:** Among 229 NSCLC patients, 12 patients (5.2%) were found to harbor a BRAF mutation in their tumor: V600 (25%), G469A (16.7%), G469V (8.3%), D594N (25%), D594E (8.3%), G596C (8.3%) and G466V (8.3%). Mutations were characterized as activating or kinase-impaired (in-vitro kinase assay) . Kinase-impaired BRAF mutants could still activate the ERK pathway in a CRAF-dependent manner, more than wt-BRAF/wt-CRAF co-transfectant. A MEK inhibitor (*Trametinib)* and a selective BRAF-inhibitor (*Dabrafenib)* were tested at clinically relevant doses on HEK293T transfectants (either expressing BRAF mutant alone or together with CRAF). ERK signaling induced by activating mutations was reduced in response to both inhibitors separately. *Trametinib*inhibited the CRAF-dependent ERK signaling induced by impaired-kinase BRAF mutations. *Dabrafenib* activated the ERK pathway in cells expressing only CRAF as well as cells co-expressing a kinase-impaired BRAF mutation and CRAF. **Conclusions:** This study predicts sensitivity of activating non-V600 BRAF mutations in lung cancer to *Trametinib* or *Dabrafenib*. Targeting kinase impaired BRAF mutations which signal through CRAF using *Dabrafenib* will require the addition of *Trametinib.*

11092 Poster Session (Board #306), Sun, 8:00 AM-11:30 AM

A functional kinome screen to identify pathways of anthracycline resistance in patient-derived breast cancer cells. *First Author: Hannah Richards, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Despite 5 decades of generalized anthracycline use in breast cancer, rates of progression following exposure remain very high. In order to identify biologic mechanisms contributing to resistance, we performed high-throughput small interfering RNA (siRNA) screens on breast cancer cells from patients whose disease had progressed after anthracyclines. **Methods:** Cells were isolated directly from metastatic tumors and peritoneal or pleural effusions from patients with anthracycline-resistant breast cancer ($n = 26$, recruitment ongoing), expanded in culture, confirmed to be of epithelial origin by expression of keratin and stem cell markers (CD44+, CD24-), and could be grown as organoids. Low passage cells were transfected in triplicate with siRNAs targeting 713 kinases alone (IC0) or in the presence of doxorubicin (IC30, inhibitory concentration 30%) and viability measured at 72 hours. Candidate sensitizer genes were called using the Z-transformed mean normalized viability across all plates, robust Z-score within each plate ($-2 > Z > 2$), and T-test p-value ($p < 0.05$). Pathway enrichment was computed for hits using Gene Ontology, KEGG, and Reactome databases. **Results:** Unsupervised hierarchical clustering of knockdown hits revealed clear separation by doxorubicin exposure for the first 4 patients evaluated (2 luminal b, 2 triple negative cases). Knockdown of 111 kinases resulted in significantly decreased proliferation in the IC0 screen. Knockdown of 228 kinases from the IC30 screen resulted in anthracycline sensitization and the top pathway implicated was ceramide biosynthesis/metabolism. **Conclusions:** For the first time, we demonstrate the feasibility of an individualized systems medicine approach using high-throughput siRNA screening in specimens directly derived from patients. Our top pathway hit identified was the ceramide pathway, only previously observed in anthracycline resistant cell lines. Larger scale RNAi and targeted agent drugs screens are ongoing in additional patients to validate the ceramide pathway and to identify novel drug targets in patients with anthracycline resistant disease toward our goal of reducing the burden of recurrence.

11093 Poster Session (Board #307), Sun, 8:00 AM-11:30 AM

Genomics, transcriptomics, and proteomics in the clinical setting: Integrating whole genome and RNA sequencing with quantitative proteomics to better inform clinical treatment selection. *First Author: Shahrooz Rabizadeh, Nantworks, Culver City, CA*

Background: Genomic panels, limited to a few hundred target mutations, are the current standard to provide therapeutic insights; however, lack of confirmation of expression of mutated genes is a limitation of these targeted genomics approaches. We report the first comprehensive pan-omic approach, overcoming these issues by integrating analysis of whole genome DNA sequencing with RNA data, including pathway analysis to provide predictive and, subsequently, quantitative proteomics to better identify clinically actionable targets in a timely manner. **Methods:** Over 50 unique tumors from primary and metastatic disease were selected for pan-omic tumor profiling. A cloud-based DNA and RNA supercomputing platform was developed to produce copy-number estimates, somatic variants, rearrangements, and RNA-abundance estimates from FFPE biopsies. Machine-read pathway analysis integrated whole genome DNA sequencing and RNA data to infer proteomics and predict drug targets. Quantitative, multiplexed proteomic analysis by mass-spectrometry validated therapeutic targets at attomoles per μg of tissue. **Results:** Approximately 80% of tumors had somatic events in previously published "actionable" genes. Multiple cases showed confirmation between predicted actionable genes and quantitatively increased protein expression; however, many mutations showed little or no expression at the transcriptomic level. These findings were confirmed by quantitative proteomic measurements. Also observed were genomic mutations and protein expression for which approved drugs are available, independent of anatomical tumor type. **Conclusions:** This is the first report of a fully integrated DNA, RNA, and proteomic diagnostic assay to establish a more accurate view of therapeutic interventions for patients, especially in this era of immuno-oncology. We conclude that the molecular signature of a cancer patient is independent of the anatomical tumor type and, given that many gene mutations were not expressed, that an informed clinical treatment decision requires insight into downstream protein expression and not just DNA alterations alone.

11094 Poster Session (Board #308), Sun, 8:00 AM-11:30 AM

Measurement of soluble Programmed Death-Ligand 1 (soluble PD-L1) to predict survival in biliary tract cancer patients treated with chemotherapy. *First Author: Hyerim Ha, Department of Internal medicine, Seoul National University Hospital, Seoul, South Korea*

Background: Programmed death-ligand 1 (PD-L1) expression in cancer cells or tumor microenvironment is under investigation as a candidate biomarker in the new drug development of immuno-oncology field. Preparation of tumor tissues for PD-L1 expression has some challenges. The soluble form of PD-L1 (sPDL1) is suggested as retaining immunosuppressive activity. In this study, we measure the levels of sPDL1 in serum and evaluate its role in prediction of overall survival (OS) in biliary tract cancer (BTC) patients. **Methods:** Seventy seven BTC patients' serum was collected before initiation of standard palliative chemotherapy. sPDL1 was measured using an enzyme-linked immunosorbent assay. Clinical data including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII, neutrophil X platelet/lymphocyte) were collected. Cut-off of each variable for OS prediction was determined by ROC curve. **Results:** The primary site of BTCs were;30IHCC, 28 GB ca, 8 EHBTC, 11 AoV ca. OS of all patients was 10.7 months (95% CI; 8.53-14.93) and 1-year overall survival rate was 46.8%. Median sPDL1 level was 1.20 ng/ml (range 0.02-7.3, mean 1.48, SD 1.19). Median values of NLR, PLR, SII were 2.34, 8.81 and 514.8 respectively. High level of sPDL-1 ($>$ 1.10 ng/ml) conferred poor prognosis (OS 7.7 m vs 17.7 m, p = 0.001). High levels of NLR ($>$ 2.10), PLR ($>$ 9.5), SII ($>$ 650) were also significant factors for poor OS (P = 0.029, P = 0.015, P = 0.002). However, in multivariate analysis, only sPDL1 predicts worse survival (HR 2.16, p = 0.008). Patients with high sPDL1 showed decreased albumin level, high NLR, PLR, SII. Among 77 patients, 19 outliers with longer survival (OS $>$ 20m) had lower levels of sPDL1 (P = 0.007). **Conclusions:** The soluble form of PD-L1 (sPDL1) can be measured in the serum of BTC patients, and it has significant impact on the prognosis of BTC patients treated with standard chemotherapy.

11095 Poster Session (Board #309), Sun, 8:00 AM-11:30 AM

Correlation of cancer-associated macrophage-like cells with systemic therapy and pathological stage in numerous malignancies. *First Author: Daniel L Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Recently we published preliminary data on the presence of Cancer Associated Macrophage-Like cells (CAMLs) in a variety of malignancies and their clinical use in tracking cancer progression (Adams et al., PNAS 2014). This report is a follow-up in identifying and tracking CAMLs, with an emphasis on correlating clinical and pathological stage from baseline samples. **Methods:** This multi-institutional prospective pilot study consisted of 105 patient (pt) samples: Stage I-IV; breast (n = 34), prostate (n = 25), pancreatic (n = 39) and lung (n = 7). Evaluators were blinded to the source and stage of the pts. Additionally, 30 non-blinded healthy controls with no known malignant disease were analyzed. 7.5 mL of whole blood was collected; filtered by the CellSieve microfiltration assay; and stained with DAPI, CK 8/18/19, EpCAM and CD45. CAMLs were enumerated and identified as large multinucleated circulating myeloid cells (e.g. CD14+). We report CAML number at clinical stage in relation to healthy controls and compare with patient's pathological stage. **Results:** CAMLs were identified in 98/105 samples (93%), ranging from 0-105 CAMLs per peripheral blood sample at baseline, while 0 were found in 30 healthy controls; Sensitivity = 93.3% (CI95% 87-97%) and Specificity = 100% (CI95% 88-100%). Pts with breast, prostate and pancreatic cancer underwent surgical procedures and pathologically staged (n = 98). The number of CAMLs at baseline had a weak association with clinical stage; stage I (8.7 per sample), Stage II (6.8), Stage III (16), Stage IV (26.1); R^2= 0.82. However, the number of CAMLs at baseline highly correlated with final pathological staging; stage I (4.3), Stage II (6.3), Stage III (14), Stage IV (24.6); R^2= 0.94. **Conclusions:** Our data suggests that 1) CAMLs are circulating immune cells specific to malignant disease and 2) the number of CAMLs is weakly associated with clinical stage but highly correlative with pathological stage in a variety of malignancies. These findings indicate that CAMLS may be a valuable supplement to current screening and staging procedures.

11096 Poster Session (Board #310), Sun, 8:00 AM-11:30 AM

Effect of the timing of sunitinib administration on the predictive value of biomarkers in renal cell cancer (mRCC). *First Author: John Michael Louis Ebos, Roswell Park Cancer Institute, Buffalo, NY*

Background: Angiogenic cytokines influence tumor growth in mRCC patients (pts) and are modulated by diurnal fluctuations. The timing of antiangiogenic tyrosine kinase inhibitor (TKIs) administration may impact efficacy, toxicity and biomarker expression. **Methods:** 34 mRCC pts, randomized to receive sunitinib at 8 AM or 8 PM on a 28 days (d) on/14 d off schedule, had blood sampling before and during Rx on the first cycle for potential biomarkers including: sunitinib and metabolite blood levels, 18 circulating angiogenic factors (CAFs) and 4 circulating angiogenic cell types including circulating endothelial cells (CECs). **Results:** Spearman analysis of the 24 biomarkers obtained on d 14 showed significantly better correlations with OS and PFS in PM-treated pts. Three CAFs in PM-treated pts significantly correlated with both OS and PFS. These included Leptin (r = 0.7182, p = 0.0128 and r = 0.8364, p = 0.0022, respectively), IL-8 (r = -0.635, p = 0.0485 and r = -0.5735, p = 0.031, respectively) and PDGF-$\beta\beta$ (r = -0.8455, p = 0.001 and r = -0.6818, p = 0.0251, respectively). Circulating Leptin levels correlated with sunitinib-metabolite levels in both AM and PM-treated patients (r = 0.7832, p = 0.0038 and r = 0.6848, p = 0.0347, respectively). **Conclusions:** This is the first study to suggest that a consistent sunitinib dosing time may improve the predictive value of some biomarkers for OS and PFS in mRCC pts. A panel of predictive circulating cytokines (Leptin, IL-8, and PDGF-$\beta\beta$) was identified for pts receiving Rx at night. Furthermore, Leptin may have value as a biomarker of sunitinib-metabolite levels independent of dosing timing. The potential impact of Rx-time on the predictive value of some biomarkers may have hampered the discovery of consistently useful predictive biomarkers for sunitinib efficacy in mRCC patients to date. Clinical trial information: OCT125.

11097 Poster Session (Board #311), Sun, 8:00 AM-11:30 AM

Personalized therapy in diverse cancers: Meta-analysis of 32,149 patients in phase II clinical trials. *First Author: Maria Clemence Schwaederle, Center for Personalized Cancer Therapy and Division of Hematology and Oncology, University of California, San Diego, CA*

Background: The benefit of a personalized cancer treatment strategy (matching patients with drugs based on specific biomarkers) is still a matter of debate. We performed a systematic review and meta-analysis of recently published phase II studies in order to compare outcomes between arms that adopted a biomarker-based approach and those that did not. **Methods:** This analysis included 570 phase II studies (641 single-agent arm(s); 32,149 patients) (January 1st, 2010 to December 31st, 2012; Pubmed search). A weighted pooled analysis and a meta-analysis were performed. Response rate (RR), progression-free survival (PFS), overall survival (OS), and death rate were compared for treatment arms that used a personalized strategy versus those that did not. **Results:** Personalized arms (N = 112) accrued 8,078 patients compared to 24,071 patients for non-personalized arms (N = 529 arms). Multivariable analysis (both weighted multiple linear regression and random effect meta-regression) demonstrated that the personalized approach consistently and independently correlated with higher RR (31% vs 10.5%, P $<$ 0.0001), prolonged median PFS (5.9 vs 2.7 months, P $<$ 0.0001) and OS (13.7 vs 8.9 months, P = 0.0001). Non-personalized targeted arms (i.e., targeted agent without biomarker selection) had poorer outcomes compared to either personalized targeted therapy or cytotoxics (211/212 cytotoxic arms were non-personalized): RR 4, 30 and 11.9%, respectively; median PFS, 2.6, 6.9, and 3.3 months (all P $<$ 0.0001); and OS, 8.7, 15.9, and 9.4 months (all P $\leq$ 0.05), respectively. Personalized arms using a "genomic biomarker" had higher RR and longer PFS and OS (all P $<$ 0.05) than those using a "protein biomarker". A lower treatment-related death rate was observed in personalized arms (1.5% vs 2.3%, P = 0.0008). **Conclusions:** Comprehensive analysis of Phase II, single agent arms revealed that, across malignancies, a personalized strategy was an independent predictor of better outcomes and fewer toxic deaths. In addition, non-personalized targeted arms were associated with significantly poorer outcomes than cytotoxic agents, which in turn were worse than personalized targeted therapy.

11098 Poster Session (Board #312), Sun, 8:00 AM-11:30 AM

Identification of subtypes of triple negative breast cancer (TNBC) that are sensitive to CDK4/6 inhibition. *First Author: Uzma Asghar, Institute of Cancer Research, London, United Kingdom*

Background: CDK4/6 inhibitors in combination with hormone therapies have shown activity in estrogen receptor positive (ER+ve) breast cancers. We investigated whether CDK4/6 inhibitors have activity in subsets of Triple Negative Breast Cancer (TNBC), and assessed combination therapeutic approaches. **Methods:** We screened 18 TNBC cell lines for sensitivity to the CDK4/6 inhibitor palbocicilb in long-term clonogenic assays, with assessment of combination effect with Combination Index and Bliss Independence (BI). Cell lines were ascribed to Lehmann subtypes. BRDU proliferation assays, mRNA expression and western blots were conducted to investigate the mechanisms of sensitivity to CDK4/6 inhibition in specific subsets. In addition we interrogated datasets from the TCGA breast cancer cohort to compare gene expression, copy number alterations or cell cycle genes across the different TNBC subtypes. **Results:** TNBC cell lines of the luminal-androgen (LAR) and mesenchymal-stem like (MSL) subsets were sensitive to palbociclib in both in clonogenic and BRDU proliferation assays [$p = < 0.0001$ LAR vs basal-like subtypes]. Sensitivity was associated with expression of androgen receptor ($p = 0.0013$), and the absence/or low levels of cyclin E1 ($p = 0.01$). Resistant mesenchymal (M) and basal TNBC cell lines had elevated levels of cyclin E1 mRNA and protein. Analysis of TCGA data revealed that high-level amplification of cyclin E1 is more common in basal tumours compared to the luminal subgroups ($p = 0.0069$). Sensitivity of TNBC LAR/MSL cell lines to palbociclib was limited by low-level cell cycle entry despite CDK4/6 inhibition. Combination studies highlighted PI3K inhibition was synergistic with CDK4/6 inhibition in *PIK3CA*mutated TNBC cell lines (BI score: $<$ 1.0), with a greater effect in LAR/MSL subgroups compared to M/basal subgroups ($p = 0.015$). The combination induced sustained proliferative arrest compared to palbociclib alone in LAR sub group ($p = 0.0007$). **Conclusions:** We demonstrate that LAR cell lines represent a TNBC subgroup that may benefit from CDK4/6 inhibition. Interestingly, TNBC with *PIK3CA* mutations could also benefit by targeting both cell cycle and PI3K-mTOR signaling.

11099 Poster Session (Board #313), Sun, 8:00 AM-11:30 AM

Squamousness: Next-generation sequencing to reveal shared molecular features across squamous tumor types. *First Author: Maria Clemence Schwaederle, UC San Diego Moores Cancer Center, La Jolla, CA*

Background: In order to gain a better understanding of the underlying biology of squamous cell carcinoma (SCC), we tested the hypothesis that SCC originating from different organs may possess common molecular alterations. **Methods:** SCC samples ($N = 361$) were examined using clinical-grade targeted next-generation sequencing (NGS) (182 or 236 cancer-related genes). **Results:** The most frequent SCC tumor types were head and neck, lung, cutaneous, gastrointestinal and genitourinary. The most common gene alterations were *TP53* (64.5% of patients), *PIK3CA* (28.5%), *CDKN2A* (24.4%), *SOX2* (17.7%), and *CCND1* (15.8%). By comparing NGS results of our SCC cohort to a non-SCC cohort ($N = 277$), we found that *CDKN2A*, *SOX2*, *NOTCH1*, *TP53*, *PIK3CA*, *CCND1*, and *FBXW7* were significantly more frequently altered, unlike *KRAS,* which was less frequently altered in SCC specimens (all $P < 0.05$; multivariable analysis). Therefore, we identified "squamousness" gene signatures (*TP53, PIK3CA, CCND1, CDKN2A, SOX2, NOTCH 1,* and *FBXW7* aberrations, and absence of *KRAS* alterations) that were significantly more frequent in SCC versus non-SCC histologies. A multivariable co-alteration analysis established two SCC subgroups: (i) patients in whom *TP53* and cyclin pathway (*CDKN2A* and *CCND1)* alterations strongly correlated but in whom *PIK3CA* aberrations were less frequent; and (ii) patients with *PIK3CA* alterations in whom *TP53* mutations were less frequent (all $P \leq 0.001$, multivariable analysis). **Conclusions:** We identified a set of eight genes altered with significantly different frequencies when SCC and non-SCC were compared, suggesting the existence of patterns for "squamousness." Targeting the PI3K-AKT-mTOR and/or cyclin pathway components in SCC may be warranted.

11100 Poster Session (Board #314), Sun, 8:00 AM-11:30 AM

Association of paclitaxel-induced sensory peripheral neuropathy with the *ABCB1* genetic variant and age. *First Author: Chikako Shimizu, Natl Cancer Ctr Hosp, Tokyo, Japan*

Background: The development of paclitaxel-induced peripheral neuropathy (PIPN) is influenced by the age and genetic composition of patients. Paclitaxel is known to act as a substrate in *SLCO1B3*-mediated influx, *ABCB1*-mediated efflux from cancer cells, and *CYP2C8*-mediated metabolism. We conducted a prospective study to investigate whether age and these single nucleotide polymorphisms (SNPs) are correlated with PIPN. **Methods:** Breast cancer patients who received adjuvant weekly paclitaxel were genotyped for five SNPs in three genes, including rs4149117 in *SLCO1B3*; rs2032582, rs1045642, and rs1128503 in *ABCB1*; and rs10509681 in *CYP2C8*, using PCR quenching probe method. Clinical data, including the paclitaxel dose and onset and severity of neuropathy, were correlated with the genetic data. **Results:** We enrolled 127 Japanese patients with a median age of 50 years (range, 25–75 years). The mean total paclitaxel dose administered was 933 mg/m^2 (range, 560–960 mg/m^2), and 85% received the full dose intensity treatment (960 mg/m^2 over 12 weeks). The majority of patients (98.4%) developed all grade neuropathy, and 51.9% of patients exhibited grade 2 or higher severity. Severe neuropathy, defined as those requiring a dose delay, dose reduction, or early termination of chemotherapy, occurred in 15.0% of patients. Of the five SNPs evaluated, the *ABCB1* (rs1128503) TT genotype was associated with a grade 2 or higher neuropathy compared with the CC/CT genotype ($p = 0.05$). Of note, patients with the TT genotype aged $>$ 60 years had a higher incidence of grade 2 or higher severity ($p = 0.008$) than those with the CC/CT genotype. Patients without PIPN were all wild type for the five SNPs. Patients aged $>$ 60 years had a higher incidence of grade 2 or higher severity ($p = 0.006$) than younger patients, regardless of the SNPs. **Conclusions:** *ABCB1* rs1128503 SNP and advanced age are correlated with PIPN. This findings may help clinicians determine which patients should avoid paclitaxel. Clinical trial information: UMIN000005294.

11101 Poster Session (Board #315), Sun, 8:00 AM-11:30 AM

Exosomes isolation and characterization in non small cell lung carcinoma patients: Proof of concept study. *First Author: Christian D. Rolfo, Universitair Ziekenhuizen Antwerpen, Antwerp, Belgium*

Background: The liquid biopsy is a noninvasive tool that could change the vision of diagnostic, prognostic and predictive analysis in oncology. In the liquid biopsy potential blood-based biomarkers such as exosomes could be determinate. These biological nanovescicles (40-100 nm) are involved in regulation of tumor progression and it was demonstrated that they transport miRNAs. miRNAs are shown to be key regulators of many biological processes and promising disease biomarkers. The main aim of this study is to investigate whether exosomes isolation from clinical samples (fresh plasma from NSCLC pts) is feasible. Furthermore we have investigated selected exosome miRNAs known to be related with NSCLC. **Methods:** A total of 12 patients with NSCLC (adenocarcinoma) were included in this pilot project, after obtaining the informed consent. Exosomes were isolated from fresh plasma by means of both Density-Gradient centrifugation and commercial isolation kit and characterized through Western-Blot (WB), NanoSight and Trasmission Electron Microscopy (TEM) analysis. The expression of selected miRNAs was performed through Real-Time PCR; miR-1228 was used as endogenous control and the fold change was calculated according the formula $\mathbf{2^{-\Delta\Delta Cq}}$. **Results:** Exosomesof all samples are characterized through WB analysis for ALIX and TSG-101, known as exosome markers, and by NanoSight and TEM analysis where all samples contains particles of size between 40-100nm. Interestingly, miR-30b and -30c are up-regulated in all samples, except for one patient (adenosquamous carcinoma with a predominance of squamous cell carcinoma) in which miR-30c is down-regulated. This result might indicate that miR-30c could be related to squamous histology. In our series we have one EGFR-positive sample (exon19 deletion) that show the highest expression of miR30b, -30c, -103, -195, -221, -222. This is partially in concordance with the results from Garofalo et al., which mir-30b, -30c, -221 and -222 are regulated by EGFR and MET receptor. **Conclusions:** With this pilot study we have demonstrated that exosome analysis and exosomal miRNAs profiling is feasible in NSCLC this might be a noninvasive test for follow up, response and resistance to therapy.

11102 Poster Session (Board #316), Sun, 8:00 AM-11:30 AM

Impact of BMI on survival and toxicity in early breast cancer: An exploratory analysis of prospective randomized phase III study N-SAS BC02 and 03. *First Author: Yoichi Naito, National Cancer Center Hospital East, Chiba, Japan*

Background: Obesity is reported to be associated with worse prognosis in early breast cancer. As obesity is rare and low BMI is relatively common in Japanese population compared to Caucasians, the impact of BMI on survival and toxicity in Japanese cohort should be assessed. Here we report an exploratory analysis of the data included in randomized phase III trials for early breast cancer in Japan. **Methods:** Patients included in phase III trial N-SAS BC02 or BC03 were analyzed. N-SAS BC02 investigated four arms of adjuvant chemotherapy consisted of taxane alone or in combination with anthracycline-containing regimen (median follow up of 6.1 years). NSAS BC03 compared anastorozole with tamoxifen as adjuvant endocrine therapy (median follow up of 6.4 years). The correlations of BMI and overall survival or toxicity were retrospectively analyzed. **Results:** A total of 1726 patients were included in our study. Median age was 56 years, 71.2% of tumors were ER positive, and 9.7% were HER2 overexpressed, 76% had lymph node metastasis. Mean value of BMI was 23.3 and only 4.6% of patients had BMI over 30. 33.1% of patients had BMI under 22 and 4.8% had BMI under 18.5. In the Cox proportional hazards model adjusted randomized arms, lower BMI was significantly associated with worse prognosis (BMI $>=$ 27 vs $<$ 27, HR 0.55, $p = 0.025$). The same trend was observed in adjusted analysis for prognostic factors (HR 0.61, $p = 0.064$). Subgroup analysis of hormone receptor positive cohort showed that higher BMI was correlated with worse prognosis in premenopausal patients; on the other hand, in postmenopausal patients higher BMI was correlated with better prognosis. There was no significant correlation between BMI and toxicity. **Conclusions:** We confirmed that obesity was rare in Japanese patients with early breast cancer. In this non-obese population, lower BMI was correlated with worse prognosis without significant impact on toxicity. Subgroup analysis suggested interaction between menopausal status and BMI on survival. Detrimental effect of higher BMI on survival is limited to premenopausal hormone receptor positive patients.

11103 Poster Session (Board #317), Sun, 8:00 AM-11:30 AM

Precision oncology: the UC San Diego Moores Cancer Center PREDICT experience. *First Author: Barbara A. Parker, UC San Diego Moores Cancer Center, La Jolla, CA*

Background: By profiling their patients' tumors, oncologists now have the option to use molecular results to match patients with drug(s) based on specific biomarkers. **Methods:** In this observational study, clinical outcomes of 348 patients with solid advanced cancers who had next-generation sequencing (NGS, 182 or 236 genes) performed were analyzed under the PREDICT (Profile Related Evidence Determining Individualized Cancer Therapy) study protocol. Progression-free survival (PFS) and responses were recorded for patients that received a matched therapy. **Results:** Of 348 patients analyzed, 47 (13.5%) were treated with a matched therapy after NGS results. Two additional patients were matched but were lost to follow up. Thirty-four percent of patients (16/47) achieved stable disease (SD) $>$ 6months ($n = 7$)/complete response (CR, $n = 0$)/partial response (PR, $n = 9$). The median PFS for the matched patients was 4.0 months ($N = 47$, range, 0.5 to 22.3 months). The median PFS was 9.5 months (range, 3.4 to 22.3 months) for the 16 patients with SD $>$ 6 months/CR/PR. The median PFS (PFS2) of the patients given matched therapies was longer than the median PFS (PFS1) of the available prior therapies (PFS1; $N = 38$ available; $P = 0.038$). There was no difference between the median PFS when the matched drug targeted the alteration "directly" (agent impacts the molecular alteration or its immediate downstream effector) versus "indirectly" ($>$ 1 effector removed from the alteration) ($N = 32$ vs 15 patients; PFS = 3 vs 4 months; $P = 0.74$); if we defined direct matches as including only drugs targeting the alteration itself, and indirect matches when the alteration was $>$ 1 effector removed, the differences in PFS remained insignificant. **Conclusions:** Patients with advanced cancers treated with a biomarker-based approach (matched therapy) achieved a 34% rate of SD $>$ 6 months/CR/PR and had a significantly longer median PFS than that for the available last prior therapies. Although the numbers are small, there were no differences in PFS between patients who received therapy that was directly versus indirectly matched to their alteration(s).

11105 Poster Session (Board #319), Sun, 8:00 AM-11:30 AM

Pharmacodynamic (PD) assessment using FLT-PET/CT imaging in patients treated with an interrupted high-dose axitinib schedule. *First Author: Ludimila Cavalcante, University of Wisconsin, Madison, WI*

Background: Axitinib (AX) is a potent inhibitor of receptor tyrosine kinases (RTK) of VEGFR-1,2,3. We previously showed that exposure to AX resulted in a decrease in tumor proliferation and vascular parameters, and during acute AX withdrawal, a rebound flare (proliferative and vascular) was present during cycle 1 (C1). Here we evaluate the impact of AX dose on the rebound pharmacodynamics, as well as assess whether this flare persists in later cycles of therapy with AX using an intermittent therapy schedule. **Methods:** Pts with prostate cancer or other advanced solid malignancies were enrolled. In the safety cohort, AX was administered at 7 mg BID on a 2 week on, 1 week off schedule. In the PD cohort, static/dynamic FLT PET/CT scans were obtained at baseline, week 2 (on AX), and wk 3 (off AX) in C1, and repeated again in C3 (pre-day 1, wk 2, wk 3). Plasma VEGF and AX PK levels were obtained at each imaging timepoint. **Results:** 24 pts were enrolled (safety cohort $n = 8$, PD cohort $n = 16$). Pts in the safety cohort received AX starting at 7 mg BID. Three pts developed significant hypertension and thrombovascular events; hence it was not felt that this starting dose was appropriate. For the PD cohort, AX dose was administered at 5 mg BID. 14 pts had scans on C1, and 5 pts completed scans during C3. Similar changes in proliferation/vasculature parameters were seen in C1 as previously reported. Decreases in proliferation/vasculature parameters were also seen in C3 (on AX) with rebound flare present at wk 3. **Conclusions:** Although dose-escalation of AX (up to 10 mg BID) has been shown to be feasible in renal cell cancer, use of intermittent AX at a starting dose of 7 mg BID was not feasible in our non-RCC pt population. We confirm previous findings that AX exposure results in a decrease in proliferation/vasculature parameters and that acute AX withdrawal results in a tumor/vasculature flare. We show with ongoing intermittent AX therapy, a similar PD change was observed in pts during C3. This result supports a *sequential strategy* of using intermittent AX in combination with S-phase specific chemotherapy in order to exploit the tumor/vasculature rebound in order to improve the therapeutic index of the cytotoxic chemotherapy. Clinical trial information: NCT01540526.

11106 Poster Session (Board #320), Sun, 8:00 AM-11:30 AM

The long term outcome of clinical trial-based treatment comparing standard treatment for metastatic breast cancer. *First Author: Gun Min Kim, Yonsei University, Seoul, South Korea*

Background: All NCCN guidelines have black box recommendations as "NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged". However, we still don't know the level of evidence for this recommendation. We evaluated the clinical impact of clinical trial-based treatment on long term outcome for metastatic breast cancer. **Methods:** The Yonsei Cancer Center Metastatic Breast Cancer Database identified 762 patients with metastatic breast cancer who were diagnosed between 2006 and 2013. We analyzed retrospectively the information about demographics, clinical and pathologic characteristics, survival, and treatments. Descriptive analyses were conducted to investigate on the impact of clinical trial-based treatment comparing standard treatment on long term outcome of MBC. Clinical trial is defined as any clinical trials which were approved by IRB regardless of investigator-initiated or sponsor-initiated trial. **Results:** Of the 762 patients, 179 (23.5%) patients received first-line treatment as clinical trial-based. Baseline demographics showed 534 (70.1%) patients were recurrent MBC and 30% were de novo MBC. The proportion of patient who received clinical-trial based treatment was similar between recurrent MBC (24%) and de novo MBC (22.4%). Median follow-up was 31.8 months (range 0.1-108). Median OS was 47.6 months (95% CI 37.6-57.6) versus 31.5 months (95% CI 27.9-35.1) for patients with clinical trial-based treatment versus standard treatment, respectively. Patient with initial brain metastasis (34, 4.5%) or leptomeningeal metastasis (3, 0.4%) could not be enrolled into the clinical trial. Median OS of patients with CNS metastasis is extremely lower than patients without CNS metastasis (15.1 versus 35.4 months, $p < 0.0001$). Analysis after exclusion of patients with CNS metastasis still showed better outcome for patient who received clinical-trial based treatment as first line therapy (44.9 versus 33.2 months, $p < 0.011$). **Conclusions:** Patient who received clinical trial-based treatment as first-line therapy showed better long term outcome compared to patients who took a standard treatment.

11107 Poster Session (Board #321), Sun, 8:00 AM-11:30 AM

Theranostic biomarkers involved in immunomodulation and the PI3KCA signal transduction pathway in HPV-induced cervical, oropharyngeal, and anal carcinoma. *First Author: Nooshin Hashemi Sadraei, University of Cincinnati, Cincinnati, OH*

Background: Several distinct cancers are caused by human papillomavirus (HPV)- including squamous cell carcinomas of the cervix (CSCC), anal canal (ASCC), and oropharynx (OSCC). Importantly, platinum based chemoradiation protocols are similarly effective in these entities. We assessed CSCC, ASCC, and OSCC for additional evidence of shared characteristics which could be used to identify potential molecular targets across the spectrum of HPV induced cancers. **Methods:** 201 ASCC, 321 CSC and 358 OSCC tumors underwent molecular profiling with a multiplatform approach (Caris Life Sciences). TP53 wild type status was used as a surrogate for HPV. Testing included sequencing (NGS, Sanger), protein expression (IHC) and gene amplification (ISH). The 2-tail Fisher's exact test ($p \leq 0.05$), JMPv10.0 (SAS Institute Inc., Cary, NC) was utilized for statistical analysis. **Results:** Excluding TP53-mutated patients, 197 ASCC, 317 CSCC and 317 OSCC were included in the study. Multiplatform profiling reveals marked similarities among the HPV-induced cancers. None of the frequencies observed displayed statistically significant differences. Selected results appear below. **Conclusions:** Unlike the genomic instability observed in many solid tumors, HPV-induced carcinogenesis yields a more homogenous phenotype. These data support previous work identifying the PIK3CA-AKT-mTOR pathway as a potential target. Given the phenomenon of HPV E6 & E7-induced oncogene addiction following viral integration, the need to explore PD1/PDL1 inhibition in these cancers is implicit.

Frequency (positivity, underexpression#, amplified or mutated): Greyed boxes indicate Rx is NCCN-endorsed

	Rx Association	Anal	Cervical	Oropharyngeal
PGP IHC	Taxanes	9%	3%	3%
TLE3 IHC		32%	31%	37%
TUBB3# IHC		89%	75%	83%
ERCC1# IHC	Platinums	51%	60%	67%
BRCA1 NGS		10%	15%	7%
BRCA2 NGS		10%	30%	10%
EGFR IHC	Anti-EGFR	92%	70%	92%
EGFR_ISH		7%	17%	18%
HER2	Anti-HER2	0%	4%	2%
HER2_ISH		2%	6%	3%
PTEN# IHC	PAM pathway inhibitors	55%	47%	50%
PIK3CA NGS		29%	34%	18%
PTEN NGS		4%	2%	5%
AKT NGS		2%	2%	4%
PD1 IHC	Immuno-modulatory	50%	78%	81%
PDL1 IHC		0%	18%	9%
FBXW7 NGS	mTOR inhibitors	14%	6%	6%
KRAS NGS	MEK inhibitors	1%	3%	4%

11108 Poster Session (Board #322), Sun, 8:00 AM-11:30 AM

Drug efflux pump expression in 50,000 molecularly-profiled cancer patients. *First Author: Rebecca Feldman, Caris Life Sciences, Phoenix, AZ*

Background: The multidrug resistance (MDR) phenotype reduces the efficacy of various chemotherapies. MDR is linked to the overexpression of ATP-binding cassette (ABC) transporters in cancer cells, including P-glycoprotein (PGP/ABCB1), multidrug resistance protein (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2). We assessed protein expression patterns of the drug efflux pumps across all tumor types for insight on how to exploit MDR status to circumvent treatment dilemmas. **Methods:** 51,939 patients molecularly profiled with a commercial multiplatform approach (Caris Life Sciences) were evaluated. Protein expression by IHC was assessed. The Caris Registry was queried for patients in this analysis with available clinical outcomes. **Results:** Across all tumors profiled ($n = 51{,}939$), MRP1 positivity (pos.) was highest at 81% (19935/24682), BCRP at 66% (8849/13409) and PGP the lowest at 23% (11969/51313). GI cancers exhibited the most abundant expression of all three drug pumps (80%, 90%, 53%), with highest average combined expression observed in liver cancers (81%). In contrast, brain, thymic and head and neck cancers exhibited the lowest average combined expression of all 3 drug pumps (39%, 40% and 42%, respectively). 6,002 patients were evaluable for co-expression with 29% (1728/6002) exhibiting pos. for all 3 drug pumps (ABC+) (highest frequencies in colon, pancreas, ovary, breast and lung), 42% (2494/6002) pos. for 2/3 drug pumps and 21% (1263/6002) pos. for 1/3 drug pumps. Only 9% (517/6002) exhibited negative status for all 3 drug pumps (ABC-) (highest frequencies in breast, lung, ovary, skin and endometrial). To determine the prognostic role of the drug pumps on patient survival, we assessed the differences in median survival between a cohort of ABC+ ($n = 31$) and ABC – ($n = 27$) patients with breast ($n = 6, 2$), ovary ($n = 12, 6$) and lung cancers ($n = 13,19$). Median survival since specimen used for profiling was collected for ABC + was 596 days compared to 855 days for ABC – patients. **Conclusions:** Tumors show broad and overlapped expression patterns for drug efflux pumps. Further study is needed to determine how transporter expression may impact clinical outcomes (e.g. ABC - status is more favorable than ABC + status).

TPS11109 Poster Session (Board #324a), Sun, 8:00 AM-11:30 AM

The DETECT Study Program: Personalized treatment in advanced breast cancer based on circulating tumor cells (CTCs). *First Author: Amelie Schramm, Universitaetsfrauenklinik Ulm, Ulm, Germany*

Background: The prognostic value of circulating tumor cells (CTC) in metastatic breast cancer (MBC) has been repeatedly shown, but potential implications of CTC presence and CTC phenotypes for treatment decisions are still not well understood. The main aims of the DETECT study program are to evaluate efficacy of individualized breast cancer treatments based on presence and phenotype of CTCs, and to investigate the role of CTCs in predicting specific treatment responses. **Methods:** In the phase III study DETECT III women with HER2-negative MBC but HER2-positive CTCs are randomized to physician´s choice therapy (single-agent endocrine or single-agent chemotherapy) with or without HER2-targeted therapy with lapatinib. The phase II study DETECT IV offers two treatment options for women with HER2-negative MBC and only HER2-negative CTCs. Patients with hormone-receptor positive MBC receive endocrine therapy plus everolimus, and patients with triple-negative MBC or hormone-receptor positive MBC plus indication for chemotherapy receive cytostatic treatment with eribulin. In the phase IIIa study DETECT V, women with HER2-positive and hormone-receptor positive MBC are treated with either endocrine therapy or chemotherapy added to a dual HER2-targeted backbone treatment with trastuzumab and pertuzumab. Clinical efficacy will be estimated by CTC clearance and progression-free survival in DETECT III and DETECT IV. As the focus of DETECT V is on the comparison of safety and quality of life between the two treatment arms, primary and main secondary endpoints are rate of adverse events and quality-adjusted survival (Q-TWiST method). Translational research projects try to identify additional predictive markers of therapy response by molecular characterization of CTCs. Therefore, prevalence of CTCs using the FDA-cleared CellSearch System (Janssen Diagnostics, LLC) and their HER2 status is determined. As of January 2015, more than 1100 patients have been screened for CTCs, making the DETECT study program the worldwide largest trial for MBC. The results will provide crucial information regarding suitability of CTCs as liquid biopsy to guide more individualized therapy decisions. Clinical trial information: NCT01619111/NCT02035813/NCT02344472.

TPS11110 Poster Session (Board #324b), Sun, 8:00 AM-11:30 AM

The genomics of Young Lung Cancer Study. *First Author: Barbara J. Gitlitz, University of Southern California Keck School of Medicine, Los Angeles, CA*

Background: Primary lung cancer is increasingly understood as a heterogeneous disease made up of genomically defined subtypes requiring distinct treatment strategies. We hypothesize young age at diagnosis (< 40 years) is a clinical characteristic associated with an increased chance for a targetable genomic alteration. This ALCMI study will prospectively characterize the somatic and germline genomics of young lung cancer. Our goals are to identify a genomically enriched subtype of lung cancer, facilitate delivery of targeted therapy and lay groundwork for further studies of heritable and environmental lung cancer risk factors. **Methods:** Accrual opened 07/2014. Patients are eligible if they were diagnosed with bronchogenic lung cancer less than age 40. A study specific website allows for virtual consenting so patients can participate remotely from anywhere in the country or the world; and use social media to share our trial. We have an integrated data and biorepository (Open Medicine Institute) that allows for seamless communication and completion of study activities like remote consenting, storage and routing of blood and tumor specimens. We have defined 7 genomic alterations of interest based on the Lung Cancer Mutational Consortium (LCMC) (EGFR, KRAS, HER2, BRAF, ALK, ROS1, RET). On study subjects without a known genotype will undergo comprehensive genomic profiling with the FoundationOne test to ensure that all of these genes have been tested. Subjects with advanced adenocarcinoma who are wild-type for all 7 genes will receive additional genomic profiling using the FoundationOne Heme test with the goal of identifying novel oncogenic drivers. Additional investigational genomics will include blood for germline analysis. All on study genomic analysis is at no cost to the participant. We aim to demonstrate that the prevalence of targetable genomic alterations will be greater in our population compared to the LCMC and have powered our study to show an increase from 35% to 50%; and an improvement in use of targeted therapy from 22% to 40%. The trial is currently accruing (NCT02273336) https://www.openmednet.org/site/alcmi-goyl. (Supported by grants from The Bonnie J. Addario Lung Cancer Foundation, Peter Barker Foundation, Genentech and Schmidt Legacy Foundation.) Clinical trial information: NCT02273336.

TPS11111 Poster Session (Board #325a), Sun, 8:00 AM-11:30 AM

MyPathway: An open-label phase IIa study of trastuzumab/pertuzumab, erlotinib, vemurafenib, and vismodegib in patients who have advanced solid tumors with mutations or gene expression abnormalities targeted by these agents. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: While many targeted agents are approved for specific cancers, molecular profiling has increasingly led to the identification of genetic abnormalities in tumor types for which targeted agents are not currently approved. MyPathway explores the activity and safety of therapies that target HER2, EGFR, BRAF, and Hedgehog pathways in cancers for which these treatments are not FDA-approved. **Methods:** MyPathway (trial registration NCT02091141) is a multicenter, non-randomized, phase IIa study of patients with advanced solid tumors that have progressed following standard therapy or for which there is no approved treatment. Eligible patients have a tumor with a potentially actionable genetic alteration, as determined by a Clinical Laboratory Improvement Amendments-certified laboratory. Patients with >1 mutation are treated based on the mutation considered most critical by the investigator; they may later enroll based on a different mutation, if initial therapy fails. For each pathway, treatments are dosed based on the approved regimen. Patients are evaluated for response after 2 cycles of therapy; those with an objective response or stable disease may continue therapy until tumor progression or unacceptable toxicity. Safety is monitored in real time and reviewed every 3–6 mos. The primary outcome is response rate. Secondary outcomes are disease control rate, progression-free survival, and 1-year survival. Outcomes will be studied by tumor type and pathway (tumor-pathway cohorts). Sample sizes for tumor-pathway cohorts are based on Simon's 2-stage design procedure. Use of the master protocol will allow possible future exploration of additional pathways as new agents become available. Evidence of activity in this trial may be studied in larger dedicated trials. Clinical trial information: NCT02091141.

Pathway	Molecular alteration	Treatment(s)
HER2	Overexpression of HER2 or activating mutation	Trastuzumab and pertuzumab
EGFR	EGFR-activating mutation	Erlotinib
BRAF	BRAF-activating mutation (V600E and others)	Vemurafenib
Hedgehog	SMO-activating mutation, PTCH-1 loss-of-function mutation	Vismodegib

TPS11112 Poster Session (Board #325b), Sun, 8:00 AM-11:30 AM

NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) will reduce invasive cancer events in patients (pts) with positive axillary (Ax) nodes who are ypN0 after neoadjuvant chemotherapy (NC). *First Author: Eleftherios P. Mamounas, NRG Oncology/NSABP, and the MD Anderson Cancer Center Orlando, Pittsburgh, PA*

Background: This phase III post-NC trial will evaluate if CWRNRT post Mx or whole breast irradiation (WBI) with RNRT after BCS significantly reduces the invasive breast cancer recurrence-free interval (IBCR-FI) rate in pts presenting with positive Ax nodes that are negative after NC. Secondary aims are OS, LRR-FI, DRFI, DFS-DCIS, and second primary cancer as well as comparing RT effect on cosmesis in reconstructed Mx pts. Correlative science examines RT effect by tumor subtype, molecular outcome predictors for residual disease pts, and predictors for the degree of reduction in loco-regional recurrence. **Methods:** Clinical T1-3, N1 IBC pts with positive Ax nodes (FNA or core needle biopsy) complete ≥ 12 wks of NC (anthracycline and/or taxane). HER2-positive pts receive anti-HER2 therapy (tx). After NC BCS or Mx is performed with a sentinel node biopsy (≥ 3 nodes) and/or Ax dissection with histologically negative nodes. ER/PR and HER-2 neu status before NC is required. Pts receive required systemic tx. Radiation credentialing with a facility questionnaire and a case benchmark is required. Randomization for Mx pts is to no CWRNRT or CWRNRT and for BCS pts to WBI or WBI RNRT. **Statistics:** 1636 pts to be enrolled over 5 yrs with definitive analysis at 7.5 yrs. Study is powered at 80% to test that RT reduces the annual hazard rate of events for IBCR-FI by 35% for an absolute risk reduction in the 5-yr cumulative rate of 4.6%. Intent-to-treat analysis with 3 interim analyses at 43, 86, and 129 events, with a 4th/final analysis at 172 events will occur. Accrual as of 1/15/15 is 96. Pt-reported outcomes focusing on RT effect will be provided by 736 pts before randomization and at 3, 6, 12, and 24 mths. **Support:** U10 CA 12027, 69651, -37377, -69974; -2166; -180868, -180822; CA189867; Elekta Clinical trial information: NCT01872975.

11113 Poster Session (Board #323), Sun, 8:00 AM-11:30 AM

Randomized phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer: Results of the SHIVA trial. *First Author: Christophe Le Tourneau, Institut Curie, Department of Medical Oncology, Paris, France*

Background: Non-randomized studies suggested that selecting molecularly targeted agents (MTAs) based on the molecular profile of pts' tumors, independently of tumor location and histology, improves outcome. We evaluated this histology-agnostic approach in pts who have failed standard of care therapy. **Methods:** Eligible pts underwent a biopsy of a metastatic site in order to establish the molecular profile of their tumor. Pts for whom a molecular alteration was identified and matched a MTA according to a pre-specified treatment algorithm (Table), were stratified according to the molecular pathway and randomly allocated to matching MTA or treatment at physician's choice (TPC). MTAs were only allowed outside their licensed indication and if not previously given. The primary end point was PFS. **Results:** Among 741 included pts, 195 were randomized. 82, 89 and 24 pts were allocated to the HT, PI3K and RTK/MAPK subgroups. G3/4 AEs rates were 43% and 35% in the MTA and TPC arms. ORR was 4.1% in the MTA arm vs 3.4% in the TPC arm. Global PFS and according to the molecular pathway are presented in the Table. **Conclusions:** The SHIVA trial did not demonstrate that the administration of MTAs outside their indications according to the pre-specified treatment algorithm improves PFS as compared to TPC in heavily pretreated pts. This histology-agnostic approach warrants further investigation in the RTK/MAPK pathway. Clinical trial information: NCT01771458.

			Median PFS (months)			
Molecular pathways	Molecular alterations	MTAs	TPC arm (n = 96)	MTA arm (n = 99)	HR (95%CI)	p-value
All patients			2.0	2.3	0.88 [0.65-1.19]	0.41
Hormonal (HT)	AR protein expression > 10% ER/PR protein expression > 10%	Abiraterone Tamoxifen or Letrozole	2.0	2.1	1.12 [0.70-1.78]	0.64
PI3K/AKT/mTOR (PI3K)	PI3KCA/AKT1 mut/amplif AKT2,3/mTOR/RAPTOR/RICTOR amplif PTEN/STK11 mut/LOH	Everolimus	1.9	2.4	0.79 [0.51-1.24]	0.30
RTK/MAP kinase (RTK/MAPK)	PDGFRA or B/FLT3 mut/amplif KIT/ABL/RET mut/amplif HER-2 mut/amplif BRAF mut/amplif EGFR mut/amplif SRC mut/amplif EPHA2/LCK/YES amplif	Sorafenib Imatinib Lapatinib + Trastuzumab Vemurafenib Erlotinib Dasatinib	2.0	3.7	0.58 [0.24-1.37]	0.20

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B

C

D

E

F

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J

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