ONCOLOGY

Sixth Edition

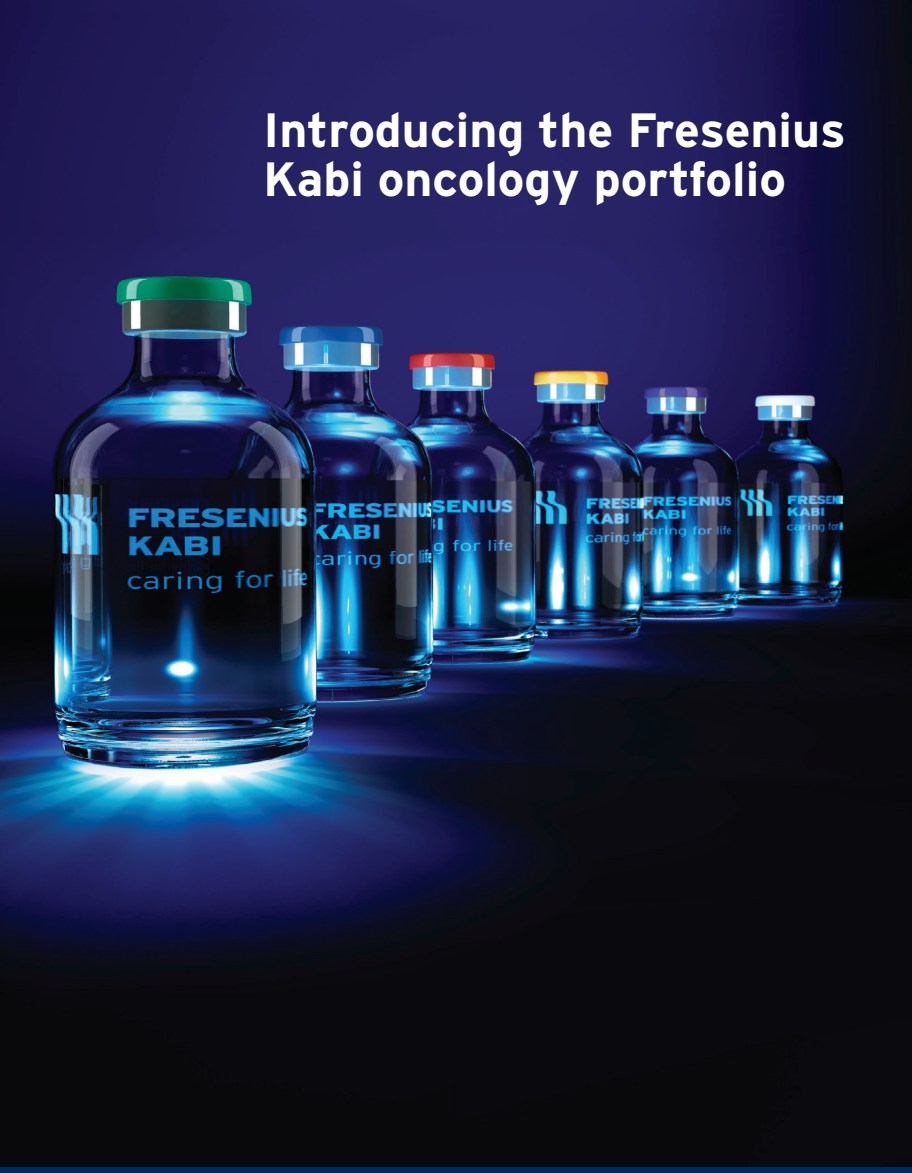
Handbook Of Cancer Chemotherapy

Department of Medical Affairs and Clinical Research,

Fresenius Kabi India Pvt Ltd.

FRESENIUS KABI
caring for life

Introducing the Fresenius Kabi oncology portfolio



Trusted Generics: Total Care

Fresenius Kabi is bringing its heritage in caring for the chronically and critically ill to the oncology market. Our range of generic oncology products is backed by a state of the art cleaning process and an established colour safety concept, providing reassurance to the pharmacy team.

We offer well priced products supported by manufacturing and supply chain expertise.

Fresenius Kabi Oncology

FRESENIUS
KABI
caring for life

PREFACE TO 6TH EDITION

During the past decade, innumerable developments has occurred in the chemotherapy of malignant tumors and are still going on. The encouraging impact on survival of traditional chemotherapeutic agents has renewed interest in developing newer cytotoxic agents and orally active compounds with improved therapeutic indices. In addition, new insights into the pathways of human tumorigenesis have led to novel approaches aimed at specific mechanism-based targets.

Since the "Handbook of Cancer Chemotherapy" was updated the last time, various new chemotherapy drugs and regimens have emerged on the scene. While some of the obsolete chemotherapy regimens from the prevous edition have been omitted, various new regimens have been added.

This edition of "Handbook of Cancer Chemotherapy" has been divided into two parts, Part I (Solid Tumors) & Part II (Hematological Malignancies). The indications in Parts I and II are presented in alphabetical order for the convenience of the reader and to simplify the tracing of information. Latest AJCC TNM staging (2010) and National Cancer Institute (NCI) epidemiology data (2012) and newly approved indications of previously approved drugs have also been included in this edition, making this handbook the most complete chemotherapy handbook available.

Lastly, we would like to stress that such a compilation of data should not replace the study of the original publications, usual text books and product information of manufacturers' brochure which contain exhaustive details regarding the dose modifications, co-medication, and supportive measures etc.

While every effort has been made to check the authenticity of the contents of this handbook, the reader is advised to cross check the primary references of the protocols as well as the prescribing information of individual agents. Comments and suggestions on further improving this handbook will be appreciated.

Department of Medical Affairs & Clinical Research
Fresenius Kabi India Pvt Ltd.

DISCLAIMER

The compilation of various chemotherapy schedules for various cancers in no way should replace the consultation of original publications, text books, product information, compendia or manufactures brochures and information.

These sources should be consulted in addition to above mentioned sources, in particular with respect to dosage & its modifications, side effects, contraindications, interactions etc.

Fresenius Kabi disclaims any representations or warranties of any kind, express or implied, concerning the quality, accuracy, completeness or legality of any information contained in this chemotherapy schedules compilation and accept no responsibility or liability for any acts or omissions resulting from reliance on this information.

This handbook contains information about products which may or may not be available in any particular country, and if applicable, may have received approval or market clearance by a government regulatory body for different indications and restrictions in different countries. Each country has specific laws, regulations and medical practices governing the communication of medical or other information about medical products. Nothing herein should be construed as a solicitation or promotion for any product or for an indication for any product which is not authorized by laws and regulations of country where the reader resides.

TABLE OF CONTENTS

PART - I
Solid Tumor

Anal Cancer

ANAL CANCER

Anal cancer is an uncommon malignancy, accounting for only a small percentage (4%) of all cancers of the lower alimentary tract. It is usually curable. The three major prognostic factors are site (anal canal vs. perianal skin), size (primary tumors <2 cm in size have better prognosis), and nodal status. As per the NCI data 6,230 new cases and 780 deaths in the United States are estimated in 2012.

Overall, the risk of anal cancer is rising, in people engaging in certain sexual practices, such as receptive anal intercourse, or persons with a high lifetime number of sexual partners are at increased risk of anal cancer. These practices may have led to an increase in number of individuals at risk of infection with human papillomavirus (HPV), which is strongly associated with anal cancer development.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Martenson JA et al. Cancer 76(10):1731-6, (1995).
Fuchshuber PR et al. J Am Coll Surg 185(5):494-505, (1997).
Johnson LG et al. Cancer 101(2):281-8, (2004).
Daling JR et al. N Engl J Med 317(16):973-7, (1987).
Palefsky JM et al. Cancer Res 51(3):1014-9, (1991).
Ryan DP et al. N Engl J Med 342(11):792-800, (2000).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Bowen's disease, High-grade Squamous Intraepithelial Lesion (HSIL), Anal Intraepithelial Neoplasia II–III (AIN II–III)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder*

**Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Concurrent chemoradiation for localized cancer
- Chemotherapy for metastatic cancer

CONCURRENT CHEMORADIATION FOR LOCALIZED CANCER

5-FU + Mitomycin + RT

Regimen 1		
5-FU	1000 mg/m^2/d civi	d1–4 and 29–32
Mitomycin	10 mg/m^2 iv bolus	d1 and 29
Concurrent radiotherapy	1.8 Gy/d x 5/w	for 5 weeks to 45 Gy
4–6 weeks later, perform full thickness biopsy.		
If biopsy positive for residual tumor, start salvage treatment:		
5-FU	1000 mg/m^2/d civi	d1–4
Cisplatin	100 mg/m^2 iv over 4–6 hrs	d2
Concurrent radiotherapy	1.8 Gy/d x 5 to 9 Gy	
6 weeks later, perform another full thickness biopsy.		
If still positive, do abdominoperineal resection		

Reference:
Ajani JA et al. JAMA 2008;299:1914. (Phase III trial)
Flam, M et al. J Clin Oncol 1996;14:2527. (Phase III trial)

Regimen 2		
5-FU	200 mg/m^2/d civi	d1–26
Mitomycin	10 mg/m^2 iv	d1
Concurrent radiotherapy	to 36 Gy over 4 wks	
2 wks later		
5-FU	200 mg/m^2/d civi	d1–17
Mitomycin	10 mg/m^2 iv	d1
Concurrent radiotherapy	to 23.4 Gy over 17 days	

Reference:
Bosset, JF et al. Eur J Cancer 2003;39:45. (Phase II trial)

CHEMOTHERAPY FOR METASTATIC CANCER

5-FU + Cisplatin

5-FU	1000 mg/m^2/d civi	d1–5
Cisplatin	100 mg/m^2 iv	d2
Q4w		

Reference: Faivre, C et al. Bull Cancer 1999;86:861.

PART - I
Solid Tumor

Biliary Tract Cancer

BILIARY TRACT CANCER

Cancer arising in the extrahepatic bile duct is an uncommon disease, curable by surgery in fewer than 10% of all cases. Prognosis depends in part on the tumor's anatomic location, which affects its resectability. Total resection is possible in 25% to 30% of lesions that originate in the distal bile duct, a resectability rate that is clearly better than for lesions that occur in more proximal sites.

Bile duct cancer may occur more frequently in patients with a history of primary sclerosing cholangitis, chronic ulcerative colitis, choledochal cysts, or infections with the fluke, Clonorchis sinensis. The most common symptoms caused by bile duct cancer are jaundice, pain, fever, and pruritus.

In most patients, the tumor cannot be completely removed by surgery and is incurable. Palliative resections or other palliative measures such as radiation therapy (e.g., brachytherapy or external-beam radiation therapy) or stenting procedures may maintain adequate biliary drainage and allow for improved survival. Many bile duct cancers are multifocal. Perineural invasion has a negative impact on survival.

Reference:
Henson DE et al. Cancer 70(6):1498-501, (1992).
Stain SC et al. Surg Gynecol Obstet 175(6):579-88, (1992).
de Groen PC et al. N Engl J Med 341(18):1368-78, (1999).
Bhuiya MR et al. Ann Surg 215(4):344-9, (1992).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct histologically
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery
T4	Tumor involves the celiac axis, or the superior mesenteric artery

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Gemcitabine + Cisplatin

Regimen 1		
Cisplatin	25 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1, 8
Q3w		

Regimen 2		
Gemcitabine	1250 mg/m^2 IV	d1, 8
Cisplatin	75 mg/m^2 IV	d1
Q3w		

Reference:
Valle J, et al. N Engl J Med 2010;362:1273-1281. (Phase III trial)
Thongprasert S et al. Ann Oncol 2005;16:279.

Gemcitabine

Gemcitabine	1000 mg/m^2 IV	d1, 8
Q3w		

Reference: Park, JS et al. Jpn J Clin Oncol 2005;35:68.

Docetaxel

Docetaxel	100 mg/m^{2}IV	
Q3w		

Reference: Papakostas, P et al. Eur J Cancer 2001;37:1833.

Gemcitabine + Capecitabine

Gemcitabine	1000 mg/m^2 IV	d1, 8
Capecitabine	650 mg/m^2 P.O.	b.i.d d1–14
Q3w		

Reference:
Koeberle D et al. J Clin Oncol 2008;26:3702.
Knox, JJ et al. J Clin Oncol 2005;23:2332.

Gemcitabine + Oxaliplatin

Regimen 1		
Gemcitabine	1000 mg/m^2 IV	d1
Oxaliplatin	100 mg/m^2 IV	d2
Q2w		

Regimen 2		
Gemcitabine	900 mg/m^2 IV	d1, 8
Oxaliplatin	80 mg/m^2 IV	d1, 8
Q3w		

Reference:
Andre, T et al. Ann Oncol 2004;15:1339.
Dwary AD et al. J Clin Oncol 2009;27 (Suppl): Abstr 4521.

Capecitabine + Oxaliplatin

Capecitabine	1000 mg/m^2 P.O. b.i.d	d1–14
Oxaliplatin	130 mg/m^2 IV	d1
Q3w		

Reference: Nehls O et al Br J Cancer. 2008 Jan 29;98(2):309-15. Epub 2008 Jan 8.

Capecitabine + Cisplatin

Capecitabine	1000 mg/m^2 P.O. b.i.d	d1–14
Cisplatin	130 mg/m^2 IV	d1
Q3w		

Reference:
Nehls O et al Br J Cancer. 2008 Jan 29;98(2):309-15. Epub 2008 Jan 8.

5-FU + Cisplatin

5-FU	1000 mg/m^2/d civi	d1–5
Cisplatin	100 mg/m^2 IV	d2
Q3w		

Reference: Ducreux, M et al. Ann Oncol 1998;9:653.

LV5FU-P

Leucovorin	200 mg/m^2 IV over 2 hrs	d1
5-FU	400 mg/m^2 IV bolus, followed by 600 mg/m^2 IV over 22 hrs,	d1 and 2
Cisplatin	50 mg/m^2 IV	d2
Q2w		

Reference: Taieb, J et al. Ann Oncol 2002;13:1192.

Erlotinib

Erlotinib	150 mg P.O.	qd

Reference: Philip PA et al. J Clin Oncol 2006;24:3069.

PART - I

Solid Tumor

Bladder Cancer

BLADDER CANCER

As per the NCI data, 73,510 new cases and 14,880 deaths from bladder cancer are estimated in the United States in year 2012. Approximately 70% to 80% of patients with newly diagnosed bladder cancer generally present with superficial tumors (i.e., stage Ta, Tis, or T1). Superficial, Noninvasive bladder cancer can often be cured, and those with deeply invasive disease can sometimes be cured by surgery, radiation therapy, or a combination of modalities that include chemotherapy.

The major prognostic factor includes the depth of invasion into bladder wall and degree of differentiation of the tumor. Most superficial tumors are well differentiated. Patients in whom superficial tumors are less differentiated, large, multiple, or associated with carcinomas in situ (Tis) in other areas of the bladder mucosa are at greatest risk for recurrence and the development of invasive cancer. Such patients may be considered to have the entire urothelial surface at risk for the development of cancer. Tis may exist for variable durations. Adverse prognostic features associated with a greater risk of disease progression include the presence of multiple aneuploid cell lines, nuclear p53 over expression, and expression of the Lewis-x blood group antigen. Expression of the tumor suppressor gene p53 also has been associated with an adverse prognosis for patients with invasive bladder cancer.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Hudson MA et al. J Urol 153(3 Pt 1):564-72, (1995).
Torti FM et al. J Clin Oncol 2(5):505-31, (1984).
Lacombe L et al. J Clin Oncol 14(10):2646-52, (1996).
Stein JP et al. J Urol 160(3 Pt 1):645-59, (1998).
Witjes JA et al. J Urol 160(5):1668-71; discussion 1671-2, (1998).
Quek ML et al. J Urol 174(1):103-6, (2005).
Thrasher JB et al. J Urol 149(5):957-72, (1993).
Esrig D et al. N Engl J Med 331(19):1259-64, (1994).
Lipponen PK: Int J Cancer 53(3):365-70, (1993).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria

pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	microscopically
pT3b	macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

REGIONAL LYMPH NODES (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0a	Ta	N0	M0
0is	Tis	N0	M0
I	T1	N0	M0
II	T2a	N0	M0
	T2b	N0	M0
III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
IV	T4b	N0	M0
	Any T	N1–3	M0
	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Neoadjuvant chemotherapy for stage II, III and non-metastatic stage IV cancer
- Concurrent chemoradiation for stage II, III and non-metastatic stage IV cancer
- Chemotherapy for metastatic cancer
- Single agent – Intravesicular instillation
- Miscellaneous

NEOADJUVANT CHEMOTHERAPY FOR STAGE II, III AND NON-METASTATIC STAGE IV CANCER

MVAC

Methotrexate	30 mg/m^2 IV	d1, 15 and 22
Vinblastine	3 mg/m^2 IV	d2, 15 and 22
Doxorubicin	30 mg/m^2 IV	d2
Cisplatin	70 mg/m^2 IV	d2
Q4w x 3 cycles		

Reference: Grossman HB et al. N Eng J Med 2003;349:859.

CMV regimen (Advanced or metastatic transitional cell carcinoma)

Methotrexate	30 mg/m^2 IV	d1, 8
Vinblastine	4 mg/m^2 IV	d1, 8
Cisplatin	100 mg/m^2 IV	d2
Q3w x 4 cycles		

Reference: Griffiths G et al. J Clin Oncol 2011;29:2171(Phase III trial).

CONCURRENT CHEMORADIATION FOR STAGE II, III AND NON-METASTATIC STAGE IV CANCER

Cisplatin + RT

Cisplatin	100 mg/m^2 IV	d1 and 22
Concurrent radiotherapy 39.6 Gy		
If in CR, one additional cycle of cisplatin 100 mg/m^2 IV and additional concurrent radiotherapy 25.2 Gy to a total of 64.8 Gy		
If no in CR, cystectomy		

Reference: Shipley, WU et al. J Clin Oncol 1998;16:3576.

CHEMOTHERAPY FOR METASTATIC CANCER

MVAC (Advanced or metastatic transitional cell carcinoma)

Methotrexate	30 mg/m^2 IV	d1, 15 and 22
Vinblastine	3 mg/m^2 IV	d2, 15 and 22
Doxorubicin	30 mg/m^2 IV	d2
Cisplatin	70 mg/m^2 IV	d2
Q4w x 6 cycles		

Reference:
Han KS et al. Br J Cancer 2008;98:86.
LoehrerPJ et al. J Clin Oncol 1992;10:1066.
Logothetis CJ et al. J Clin Oncol 1990;8:1050.

High-dose MVAC
MVAC delivered as 2-week cycles plus G-CSF support

Reference:
Sternberg CN et al. J Clin Oncol 2001;19:2638 (Phase III trial).
Sternberg CN et al. Eur J Cancer 2006;42:50

GC (Gemcitabine + Cisplatin)
(Advanced or metastatic transitional cell carcinoma)

Gemcitabine	1000 mg/m^2 IV over 30 - 60 min	d1, 8 and 15
Cisplatin	70 mg/m^2 IV	d2
Q4w x 6 cycles		

Reference:
von der Maase H et al. J Clin Oncol 2000;18:3068. (Phase III study)
Lorusso V et al. J Urol 2000;164(1):53.

GC (Gemcitabine + Carboplatin)

Gemcitabine	1000 mg/m^2 IV over 30 - 60 min	d1, 8 and 15
Carboplatin	AUC 4.5	
Q4w x 6 cycles		

Reference: von der Maase H et al. J Clin Oncol 2000;18:3068. (Phase III study)

M-CAVI (Methotrexate-Carboplatin-Vinblastine) (In surgically incurable advanced bladder carcinoma)

Methotrexate	30 mg/m^2 IV	day 1, 15 & 22
Carboplatin	AUC 4.5	day 1
Vinblastine	3 mg/m^2 IV	day 1, 15 & 22
Q4 weeks.		

Note: For patients who can not tolerate cisplatin based regimens.
Reference: De SantisM et al. Cancer. 2009 Nov 20;27(33):5634

Carboplatin + Paclitaxel

Carboplatin	AUC 6 IV	d1
Paclitaxel	225 mg/m^2 IV over 3 hrs	d1
Q3w x 6 cycles		

Reference: Vaughn DJ et al. Cancer 2002;95:1022.

Paclitaxel-Carboplatin (Metastatic transitional cell cancer of the urinary tract)

Paclitaxel	175 mg/m^2 IV	day 1
Carboplatin	AUC-5 IV	day 1
To be repeated every 3 weeks.		

Reference: Pycha et al. Urology 53:510-515, (1999).

Gemcitabine + Paclitaxel

Gemcitabine	1000 mg/m^2 IV	d1, 8 and 15
Paclitaxel	200 mg/m^2 IV over 3 hrs	d1
Q3w x 6 cycles		

Reference: Meluch AA et al. J Clin Oncol 2001;19:3018.

Gemcitabine + Cisplatin + Paclitaxel

Gemcitabine	1000 mg/m^2 IV over 30 – 60 min	d1, 8
Cisplatin	70 mg/m^2 IV	d1
Paclitaxel	80 mg/m^2 IV	d1, 8
Q3w x 6 cycles		

Reference: Bellmunt J et al. 2007 ASCO annual meeting. Abstract LBA5030.

Pemetrexed

Pemetrexed	500 mg/m^2 IV over 10 min q3w untill disease progression
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350 – 1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.	
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed	

Reference:
Sweeney CJ et al. J Clin Oncol 2006;24:3451
Galasky MD et al. Invest New Drugs 2007;25:265

Paclitaxel-Cisplatin-Methotrexate (metastatic refractory urothelial malignancy)

Paclitaxel	200 mg/m^2 IV	day 1
Cisplatin	70 mg/m^2 IV	day 1
Methtrexate	30 mg/m^2 IV	day 1
Q3W		

Reference: Tu SM et al. J Urology 154:1719-1722, (1995).

Paclitaxel-Carboplatin-Gemcitabine (Metastatic or locally unresectable Transitional cell carcinoma)

Paclitaxel	200 mg/m^2 IV	day 1
Carboplatin	AUC-5 IV	day 1
Gemcitabine	1000 mg/m^2 IV	day 1, 8
Q3W		

Reference: Hainsworth JD et al. Cancer. 2005 Jun 1;103(11):2298-303

Cisplatin-Epirubicin-Docetaxel (Locally advanced or metastatic urothelial TCC)

Docetaxel	75 mg/m^2 IV	day 1
Cisplatin	75 mg/m^2 IV	day 1
Epirubicin	40 mg/m^2 IV	day 1
Q3W		

Pectasides et al. EuJ Cancer 36:74-79, (2000).

Docetaxel-Gemcitabine (Second-line in advanced carcinoma)

Docetaxel	40 mg/m^2 IV	day 1, 8
Gemcitabine	800 mg/m^2 IV	day 1, 8
Q3W x 6 cycles		

Reference: Dreicer R et al. Cancer 2003;97:2743-2747

Paclitaxel-Ifosfamide (Locally unresectable or metastatic transitional cell carcinoma)

Paclitaxel	135 mg/m^2 IV (24 hr infusion)	day 4
Ifosfamide	1000 mg/m^2 IV	day 1–4
To be repeated every 3 weeks.		

Reference: Sweeney CJ et al. Cancer 1999;86:514-518

ITP (Metastatic or unresectable TCC)

Ifosfamide	1,500 mg/m^2 IV	day 1–3
(with mesna)		
Paclitaxel	200 mg/m^2 IV, 3 hr infusion	day 1
Cisplatin	70 mg/m^2 IV	day 1
Q4W (with G-CSF) (max. 6 cycles)		

Reference: Bajorin et al. J Clin Oncol16:2722-2727, (1998).

SINGLE AGENT - INTRAVESICULAR INSTILLATION

i) BCG	120 mg weekly for 6-8 weeks	
ii) Thiotepa	30-60 mg weekly for 4-6 weeks	
iii) Mitomycin	20-40 mg weekly for 6-8 weeks	
iv) Doxorubicin	50-60 mg weekly for 6-8weeks	

Reference:
Lum and Torti, J Narl Cancer Inst 83:682-694, (1991).
Boccardo et al. J Clin Oncol12:7-13, (1994).
Melekos et al. Cancer 72:1749-1753, (1993).
Witjes et al. Eur J Cancer 29A:1672-1676, (1993).

v) Gemcitabine	1250 mg/m^2	day 1, 8
To be repeated every 3 weeks.		

Reference:
Albers et al. Proc Am Cancer Soc Clin Oncol19:346a, abstr 1360, (2000).

vi) Paclitaxel	80 mg/m^2 IV 1 hour infusion	weekly x 4 weeks

Reference: Vaughn DJ et al. J Clin Oncol 20:937-940. 2002

vii) Docetaxel	100 mg/m^2	day 1
To be repeated every 3 weeks.		

Reference: De Wit et al. Br J Cancer 78:1342-1345, (1998).

MISCELLANEOUS

(CMV) Cisplatin-Methotrexate-Vinblastin (Adjuvant to transurethral resection for muscle invasive carcinoma)

Cisplatin	100 mg/m^2 IV	day 1
Methotrexate	30 mg/m^2 IV	day 1, 8
Vinblastine	4 mg/m^2 IV	day 1, 8
Cycle to be repeated every 3 weeks as tolerated.		

Reference: De La Rosa F et al. J Urol. 2002 Jun;167(6):2413-8

M-CAVI (Methotrexate-Carboplatin-Vinblastine) (In surgically incurable advanced bladder carcinoma)

Methotrexate	30 mg/m^2 IV	day 1, 15 & 22
Carboplatin	300 mg/m^2 IV	day 2
Vinblastine	3 mg/m^2 IV	day 2, 15 & 22
Repeat the cycle every 4 weeks.		

Note: For patients who can not tolerate cisplatin based regimens.
Reference: Bellmunt J et al. Cancer. 1997 Nov 15;80(10):1966-72

M-TEC (Methotrexate-Paclitaxel-Epirubicin-Carboplatin) (Advanced bladder cancer)

Paclitaxel	180 mg/m^2 IV	day 1
Carboplatin	AUC 5 IV	day 1
Epirubicin	40 mg/m^2	day 1 & 14
Methotrexate	30 mg/m^2 IV	day 14

Reference: Tsavaris N et al. J Chemother. 2005 Aug;17(4):441-8

PART - I
Solid Tumor

Brain Tumor

BRAIN TUMORS

Brain tumors are classified according to histology, but tumor location and extent of spread are important factors. The mortality is high in males than in females.

ADULT BRAIN TUMOR

Brain tumors account for 85% to 90% of all primary central nervous system (CNS) tumors. Worldwide, approximately 238,000 new cases of brain and other CNS tumors were diagnosed in the year 2008, with an estimated mortality of 175,000. In general, the incidence of primary brain tumors is higher in whites than in blacks, and mortality is higher in males than in females. As per the NCI data, estimated 22, 910 new cases and 13,700 deaths from brain and other nervous system tumors in the US are reported in year 2012. Anaplastic astrocytoma and glioblastoma accounts for approximately 38% of primary brain tumors; meningiomas and other mesenchymal tumors account for approx 27%.

General signs and symptoms include headaches; gastrointestinal symptoms such as nausea, loss of appetite, and vomiting; and changes in personality, mood, mental capacity, and concentration, focal cerebral syndromes such as seizures.

Brain metastases occur in 20% to 40% of cancer patients. 80% of brain metastases occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem. Metastases are multiple in more than 70% of cases, but solitary metastases can also occur. Primary cancers metastasizing to the brain are lung cancer (50%), breast cancer (15% – 20%), unknown primary cancer (10% – 15%), melanoma (10%), and colon cancer (5%).

Reference:
American Cancer Society: Cancer Facts and Figures 2012.
Parkin DM et al. Int J Cancer 94(2):153-6, (2001).
Hutter A et al. Neuroimaging Clin N Am 13(2):237-50, x-xi, (2003).
Patchell RA: Cancer Treat Rev 29(6):533-40, (2003).

CHILDHOOD BRAIN TUMOR

Primary brain tumors are a diverse group of diseases that together constitute the most common solid tumor of childhood. Between 2,500 and 3,500 children are diagnosed in the United States each year. Brain tumors are classified according to histology, but tumor location and extent of spread are important factors that affect treatment and prognosis. Approximately 50% of brain tumors in children are infratentorial, with three fourths located in the cerebellum or

fourth ventricle. Sellar/suprasellar tumors comprise of 20% of childhood brain tumors.

Primary central nervous system or spinal cord tumors comprise approximately 1% to 2% of all childhood nervous system tumors. 70% of all intramedullary spinal cord tumors are low-grade astrocytomas and/or gangliogliomas. Symptoms and signs are highly dependent on the location of the tumor and its extent. Some low-grade spinal cord tumors are associated with large cysts that extend rostrally and caudally.

Reference:
Constantini S et al. J Neurosurg 93 (2 Suppl):183-93, (2000).
Bouffet E et al. Cancer 83(11):2391-9, (1998).
Hardison HH et al. Childs Nerv Syst 3(2):89-92, (1987).

T-PRIMARY TUMOUR

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

SUPRATENTORIAL TUMOURS

T1 Tumour 5 cm or less in greatest dimension, limited to one side

T2 Tumour more than 5 cm in greatest dimension, limited to one side

T3 Tumour invades or encroaches upon the ventricular system

T4 Tumour crosses the midline of the brain, invades the opposite hemisphere, or invades infratentorially

INFRATENTORIAL TUMOURS

T1 Tumour 3 cm or less in greatest dimension, limited to one side

T2 Tumour more than 3 cm in greatest dimension, limited to one side

T3 Tumour invades or encroaches upon the ventricular system

T4 Tumour crosses the midline of the brain, invades the opposite hemisphere, or invades supratentorially

LYMPH NODE (N)

This category does not apply to this site.

DISTANT METASTASIS (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

HISTOPATHOLOGIC GRADE (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately well differentiated
G3	Poorly differentiated
G4	Undifferentiated

HISTOPATHOLOGIC TYPE

Tumors that are included in the analysis and evaluation are as follows:

- Astrocytomas
- Oligodendrogliomas
- Ependymal and choroid plexus tumors
- Glioblastomas
- Medulloblastomas
- Meningiomas, malignant
- Neurilemmomas (neurinomas, schwannomas), malignant
- Hemangioblastomas
- Neurosarcomas
- Sarcomas

STAGE GROUPING

IA	G1	T1	MO
IB	G1	T2	MO
	G1	T3	MO
IIA	G2	T1	MO
IIB	G2	T2	MO
	G2	T3	MO
IIIA	G3	T1	MO
IIIB	G3	T2	MO
	G3	T3	MO
IV	G1	T4	MO
	G2	T4	MO
	G3	T4	MO
	G4	Any T	MO
	Any G	Any T	M1

CHEMOTHERAPY REGIMENS

- Anaplastic astrocytoma and glioblastoma
  - Adjuvant chemoradiation
  - Adjuvant chemotherapy
  - Chemotherapy for recurrent and progressive cancer
- Anaplastic oligodendroglioma
  - Chemotherapy for recurrent and progressive cancer
- Miscellaneous
  - Single agent chemotherapy
  - Combination chemotherapy

ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA ADJUVANT CHEMORADIATION

Temozolomide + RT

Radiotherapy to 60 Gy		
Concurrent		
temozolomide	75 mg/m^2 P.O.	qd
Post RT temozolomide	150–200 mg/m^2 5/28 schedule	
4 weeks after radiation, continue		
temozolomide	150–200 mg/m^2 P.O.	qd x 5 days every month.

Reference: Stupp, R et al. N Engl J Med 2005;352:987.

ADJUVANT CHEMOTHERAPY

Temozolomide

Temozolomide	200 mg/m^2/d P.O.	d1–5
Q4w x 8 cycles		
Temozolomide	75 mg/m^2/d P.O. qD (d1–42 during RT), plus	
150–200 mg/m^2 daily x 5 days every 28 days; OR		
150–200 mg/m^2 daily x 5 days every 28 days; OR		
150 mg/m^2 daily x 1 week on, 1 week off; OR		
75 mg/m^2 daily x 21 days every 28 days; OR		
40 mg/m^2 daily, continuousc		

Reference:
Wick Wolfgang W et al. 2008 ASCO annual meeting LBA 2007.
Wick W et al. J Clin Oncol 2009 Dec 10;27(35):5874.

Carmustine (BCNU)

Carmustine	150–200 mg/m^2 IV	d1
Q6w		

Shapiro WR et al. J Neurosurg 1989;71:1.

PCV

Regimen 1		
Procarbazine	100 mg/m^2 P.O. qd	d1–10
Lomustine	100 mg/m^2 P.O.	d1
Vincristine	1.5 mg/m^2 (maximum 2 mg) IV	d8, 29
Q6w x 12 cycles		

Reference: J Clin Oncol 2001;19:509.

Regimen 2		
Procarbazine	60 mg/m^2 P.O. qd	d8–21
Lomustine	110 mg/m^2 P.O.	d1
Vincristine	1.4 mg/m^2 (maximum 2 mg) IV	d8, 29
Q6–8w x 6 cycles		

Reference: Levin, VA et al. Int J Radiat Oncol Biol Phys 1990;18:321.

CHEMOTHERAPY FOR RECURRENT AND PROGRESSIVE CANCER

Temozolomide

Temozolomide	150–200 mg/m^2/d P.O.	d1–5
or	150 mg/m^2/d P.O.	d1–7 and 15–21
Q4w		

Reference:
Wick A et al. J Clin Oncol 2007;25:3357.
Nicholson HS et al. Cancer 2007;110:1542.
Stupp, R et al. N Engl J Med 2005;352:987.
Yung, WK et al. Br J Cancer 2000;83:588.
Yung, WK et al. J Clin Oncol 1999;17:2762.

Temozolomide	150–200 mg/m^2/d P.O.	d1–5
Q4w followed by		
Temozolomide	50 mg/m^2/d for upto 1 year	

Reference:
Perry JR et al. J Clin Oncol 2010;28:2051.
Perry JR et al. Cancer 2008;113:2152.

Enzastaurin

Enzastaurin	500 mg/d P.O. (1125 mg loading dose, d1)	d1
Q6w		

Reference: Wick,W et al. J Clin Oncol 2010;29:1168

Carmustine (BCNU)

Carmustine	80 mg/m^2 IV	d1–3
Q8w x 6 cycles		

Reference: Brandes, AA et al. Neurology 2004;63:1281

Procarbazine

Procarbazine	125–150 mg/m^2, P.O.	d1–28
Repeat every 56 days		

Reference: WK et al. Br J Cancer 2000;83:588.

Bevacizumab

Bevacizumab	10 mg/kg IV over 30–90 min
Q2w	

Reference:
Norden AD et al. Neurology 2008;70:779
Chamberlain MC et al. Cancer 2009;63:1281(Anaplastic oligodendrioglioma)
Chamberlain MC et al. J Neurooncol 2009;91:359(Anaplastic astrocytoma)

Irinotecan

Irinotecan	125 mg/m^2 IV	qw for 4 weeks
Q6w		

Reference:
Friedman, HS et al. J Clin Oncol 1999;17:1516.
Chamberlain MC et al. Cancer 2008;17:1516.

Irinotecan	600 mg/m^2 IV (for patients on EIAED)	Q3w
Irinotecan	325 mg/m^2 IV (for patients on non EIAED)	Q3w

Irinotecan + Bevacizumab

Irinotecan	125 mg/m^2 (non EIAED) or 340 mg/m^2 (EIAED) IV over 90 min
Bevacizumab	10 mg/kg IV over 30–90 min
Q2w	

Reference:
Taillibert S et al. Neurology 2009;72:1601.
Friedman HS et al. J Clin Oncol 2009;25:4722.
Kreisl TN et al. J Clin Oncol 2009;27:740.
Cloughesy T et al. J Clin Oncol 2008;26(15):2010b
Vredenburgh JJ et al. J Clin Oncol 2007;25:4722.
Chen W et al. J Clin Oncol 2007;25:4714.
Goli KJ et al. 2007 ASCO annual meeting. Abstract 2003.

PCV

Procarbazine	60 mg/m^2 P.O. qd	d8–21
Lomustine	110 mg/m^2 P.O.	d1
Vincristine	1.4 mg/m^2 (maximum 2 mg) IV	d8, 29
Q6w		

Reference: Kappelle, AC et al. Neurology 2001;56:118.

Cyclophosphamide

Cyclophosphamide	750 mg/m^2 IV	qd for 2 consecutive days
Q4w		

Reference: Chamberlain MC et al. Cancer 2004;100:1213.

Carboplatin-Etoposide (Recurrent high-grade glioma (GBM, AA))

Carboplatin	100 mg/m^2 IV	days 1–3.
Etoposide	120 mg/m^2 IV	days 1–3
To be repeated every 4 weeks		

Reference: Franceschi E, et al. Br J Cancer. 2004 Sep 13;91(6):1038-44

Irinotecan-Celecoxib (Recurrent malignant glioma)

Irinotecan	350 mg/m^2 IV infusion over 90 mins	Weeks 1, 2, 4 & 5.
Celecoxib	400 mg twice daily	days 1–42
Repeat every 6 weeks		

Note: Irinotecan to be given at a dose of 350 mg/m^2 for patients receiving enzyme-inducing antiepileptic drugs (EIAEDs) and at a dose of 125 mg/m^2 for those patients not receiving EIAEDs
Reference: Reardon DA, et al. Cancer. 2005 Jan 15;103(2):329-38

Imatinib-Hydroxyurea (Recurrent glioblastoma multiforme)

Imatinib	500 mg twice a day	day 1–28

Note: Imatinib mesylate dose was 500 mg twice a day for patients on enzyme inducing antiepileptic drugs (EIAEDs) and 400 mg once a day for those not on EIAEDs

Hydroxyurea	500 mg twice-daily	day 1–28

Reference: Reardon DA, et al. J Clin Oncol. 2005 Dec 20;23(36):9359-68

ANAPLASTIC OLIGODENDROGLIOMA CHEMOTHERAPY FOR RECURRENT AND PROGRESSIVE CANCER

PCV

Procarbazine	60 mg/m^2 P.O. qd	d8–21
Lomustine	110 mg/m^2 P.O.	d1
Vincristine	1.4 mg/m^2 (maximum 2 mg) IV	d8, 29
Q6w		

Reference: Brandes, AA et al. Cancer 2004;101:2079.

Temozolomide

Temozolomide	150–200 mg/m^2 P.O.	d1–5
Q4w		

Reference: Chinot, JL et al. J Clin Oncol 2001;19:2449.

MISCELLANEOUS SINGLE AGENT CHEMOTHERAPY

Temozolomide (GBM at first relapse)

Temozolomide	150–200 mg/m^2/day P.O.	days 1–5
To be repeated every 4 weeks		

Reference: Yung WK et al. Br J Cancer 2000;83:588-593).

Temozolomide-XRT-Temozolomide (Malignant Astrocytoma)

Temozolomide	75 mg/m^2/day P.O.	days 1–42
To be given along with XRT		
Temozolomide	150–200 mg/m^2/day P.O.	days 1–5
To be repeated every 4 weeks		

Reference: David A et al. J Clin Oncol 24:1253-1265, (2006).

Irinotecan (Glioblastoma multiforme)

Irinotecan	100–125 mg/m^2/wk x 4 weeks or 250–300 mg/m^2 IV (90 min infusion)
To be repeated every 21 days.	

Reference: Buckner J C et al. Cancer 2003:97 (9 Suppl):2352-2358.

Geftinib (Glioblastoma multiforme)

Geftinib	500 mg/day P.O.	Once daily

Note: Dose escalation to 750 mg then 1,000 mg may be required, if a patient receives enzyme-inducing antiepileptic drugs or dexamethasone.
Reference: Rich JN et al. J Clin Oncol. 2004 Jan 1;22(1):133-42

COMBINATION CHEMOTHERAPY

ICE (salvage therapy for recurrent malignant gliomas)

Ifosfamide	750–1,200 mg/m^2 IV	days 1–3*
(with mesna uroprotection)		
Carboplatin	75 mg/m^2 IV	days 1–3
Etoposide	75 mg/m^2 IV	days 1–3
To be repeated every 4 weeks.		
*according to haematological tolerance		

Reference: Sanson et al. Eur J Cancer, 32A (1996):2229-2235.

8-Drugs-in-One-Day-Regimen (*8 in 1*)

	Regimen A (mg/m^2)	Regimen B (mg/m^2)
Methylprednisolone	300	300
Vincristine	1.5 - 2.0	1.5 - 2.0
CCNU	75	75
Procarbazine	75	75
Hydroxyurea	1500	3000
Cisplatin	60	90
Cytarabine	300	300
Cyclophosphamide	300	-
Dacarbazine	-	150
Cyclophosphamide	300	-
Dacarbazine	-	150

Regimen A: medulloblastoma, PNET, ependymoma

Regimen B: glioblastoma

Reference: Pendergrass et al. J. Clin Oncol. 5:1221-1231, (1987).

Carmustine-Temozolomide (Before and after radiotherapy in inoperable newly diagnosed GBM)

Carmustine	150 mg/m^2	day 1
Temozolomide	110 mg/m^2	days 1 - 5
Repeat every 6 weeks		

Reference: Barrie M, et al. Ann. Oncol 2005;16:1177-1184

PART - I
Solid Tumor

Breast Cancer

BREAST CANCER

As per NCI data 226,870 new cases and 39,510 deaths in women and 2,190 new cases and 410 deaths in men are estimated in US in year 2012. Its risk factors include family history, nulliparity, early menarche, advanced age, and a personal history of breast cancer (in situ or invasive). Of all women with breast cancer, 5% to 10% may have a germ-line mutation of the genes BRCA1 and BRCA2. The estimated lifetime risk of developing breast cancer for women with BRCA1 and BRCA2 mutations is 40% to 85%. Carriers with a history of breast cancer have an increased risk of contralateral disease that may be as great as 5% per year. Male carriers of BRCA2 mutations are also at increased risk for breast cancer.

Prognosis and selection of therapy may be influenced by the age and menopausal status of the patient, stage of the disease, histologic and nuclear grade of the primary tumor, estrogen-receptor (ER) and progesterone-receptor (PR) status, measures of proliferative capacity, and HER2/neu gene amplification.

Pathologically, breast cancer can be a multicentric and bilateral disease. Bilateral disease is more common in patients with infiltrating lobular carcinoma. The risk in the contralateral breast is approximately 1% per year. Its development is associated with an increased risk of distant recurrence.

Patient age younger than 55 years at the time of diagnosis or lobular tumor histology appear to increase this risk to 1.5%. Carriers with a history of breast cancer have an increased risk of contralateral disease that may be as great as 5% per year.

BREAST CANCER & PREGNANCY

Breast cancer is the most common cancer in pregnant and postpartum women, occurring in about 1 in 3,000 pregnant women. The average patient is between 32 to 38 years of age and, with many women choosing to delay childbearing, it is likely that the incidence of breast cancer during pregnancy will increase. Overall survival of pregnant women with breast cancer may be worse than in nonpregnant women at all stages.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Blackwood MA, Weber BL: J Clin Oncol 16(5):1969-77, (1998).
Frank TS et al. J Clin Oncol 16(7):2417-25, (1998).
Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 91(15):1310-6, (1999).
Simpson JF et al. J Clin Oncol 18(10):2059-69, (2000).
Lehman CD et al. N Engl J Med 356(13):1295-303, (2007).
Solin LJ et al. J Clin Oncol 26(3):386-91, (2008).

Morrow J Clin Oncol 26(3):352-3, (2008).
Rosen PP et al. J Clin Oncol 11(11):2090-100, (1993).
Gustafsson A et al. J Am Coll Surg 178(2):111-6, (1994).
Broët P et al. J Clin Oncol 13(7):1578-83, (1995).
Healey EA et al. J Clin Oncol 11(8):1545-52, (1993).
Heron DE et al. Cancer 88(12):2739-50, (2000).
Yang WT et al. Radiology 239(1):52-60, (2006).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple is NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)*
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b

T4d Inflammatory carcinoma**

**Note: Invasion of the dermis alone does not qualify as T4.*
***Note: Inflammatory carcinoma is restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.*

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)

N0 No regional lymph node metastases

pN0 No regional lymph node metastasis identified histologically

pN0(I^-) No regional lymph node metastases histologically, negative IHC

pN0(I^+) Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)

pN0(mol^-) No regional lymph node metastases histologically, negative molecular findings (RT-PCR)

pN0(mol^+) Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC

N1 Metastases to movable ipsilateral level I, II axillary lymph node(s)

pN1 Micrometastases; or metastases in 1 to 3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected**

pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)

pN1a Metastases in 1 to 3 axillary lymph nodes, at least one metastasis greater than 2.0 mm

pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**

pN1c Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**

N2 Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases

pN2 Metastases in 4 to 9 axillary lymph nodes; or in clinically detected*** internal mammary lymph nodes in the absence of axillary lymph node metastases

N2a Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

pN2a Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)

N2b Metastases only in clinically detected*** ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastases

pN2b Metastases in clinically detected*** internal mammary lymph nodes in the absence of axillary lymph node metastases

N3 Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

pN3 Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected*** ipsilateral internal mammary lymph nodes in the presence of 1 or more positive level I, II axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**; or in ipsilateral supraclavicular lymph nodes

N3a Metastases in ipsilateral infraclavicular lymph node(s)

pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes

N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

pN3b Metastases in clinically detected*** ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**

N3c Metastases in ipsilateral supraclavicular lymph node(s)

pN3c Metastases in ipsilateral supraclavicular lymph nodes

**Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).*

***Note: Not clinically detected is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.*

****Note: Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in sitespecific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.*

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

DISTANT METASTASIS (M)

M0 No clinical or radiographic evidence of distant metastases (no pathologic M0; use clinical M to complete stage group)

cM0(i+) No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases

M1 Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
IA	T1*	N0	M0
IB	T0	N1mi	M0
	T1*	N1mi	M0
IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

**T1 includes T1mi*
***T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Adjuvant therapy
  - Hormonal therapy
  - Chemotherapy
  - Targeted therapy
- Metastatic breast cancer
  - Hormonal therapy
  - Chemotherapy
  - Targeted therapy
- Bone metastases/osteolysis/tumour induced hypercalcaemia
  - Bisphosphonates
- Miscellaneous

ADJUVANT THERAPY HORMONAL THERAPY

Tamoxifen

Tamoxifen	20 mg P.O.	qd x 5 years

Reference:
Lancet 2005;365:1687.
Albain KS et al. Lancet 2009;375:2055.

Tamoxifen + Goserelin

Tamoxifen	20 mg P.O.	qd
Goserelin	3.6 mg S.C.	qm
for 3–5 years		

Reference:
Gnant M et al. 2008 ASCO annual meeting. Abstract LBA4.
Lancet 2007;369:1711.

Tamoxifen + Goserelin + Zoledronic acid

Tamoxifen	20 mg P.O.	qd
Goserelin	3.6 mg S.C.	qm
Zoledronic acid	4 mg IV	q6m
for 3 years		

Reference: Gnant M et al. 2008 ASCO annual meeting. Abstract LBA4.

Anastrozole

Anastrozole	1 mg P.O.	qd x 5 years or qd x 2–3 years after 3–2 years of tamoxifen

Reference:
Lancet Oncol 2008;9:45.
Kaufmann M et al. J Clin Oncol 2007;25:2664.
Howell A et al. Lancet 2005;365:60.

Anastrozole + Goserelin

Anastrozole	1 mg P.O.	qd
Goserelin	3.6 mg S.C.	qm
for 3 years		

Reference: Gnant M et al. 2008 ASCO annual meeting. Abstract LBA4.

Anastrozole + Goserelin + Zoledronic acid

Anastrozole	1 mg P.O.	qd
Goserelin	3.6 mg S.C.	qm
Zoledronic acid	4 mg IV	q6m
for 3 years		

Reference: Gnant M et al. 2008 ASCO annual meeting. Abstract LBA4.

Letrozole

Letrozole	2.5 mg P.O.	qd x 5 years upfront or following 5 years of tamoxifen

Reference:
Crivellari D et al. J Clin Oncol 2008;26:1972.
Goss PE et al. J Clin Oncol 2008;26:1948.
Hyman B et al. J Clin Oncol 2008;26:1956.
Rasmussen BB et al. Lancet Oncol 2008;9:23.
Coates AS et al. J Clin Oncol 2007;25:486.
Goss PE et al. N Eng J Med 2003;349:1793.

Exemestane

Exemestane	25 mg P.O.	qd x 2–3 years after 3–2 years of tamoxifen or 5 years after 5 years of tamoxifen

Reference:
Mamounas EP et al. J Clin Oncol 2008;26:1965.
Coombes RC et al. Lancet 2007;369:559.
Coombes RC et al. N Eng J Med 2004;350:1081.

Goserelin (Adjuvant Therapy in premenopausal node positive breast cancer)

Goserelin	3.6 mg depot S.C.	every 4 weeks for 2 years.

Reference: Jonat W et al. J Clin OncoI 20(24):4628-35, (2002).

CHEMOTHERAPY

TAC

Docetaxel	75 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Cyclophosphamide	500 mg/m^2 IV	d1
Q3w x 6 cycles		
Filgrastim support		

Reference: Martin M et al. N Eng J Med 2005;352:2302.

Dose-dense AC-T

Doxorubicin	60 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q2w x 4 cycles		
Followed by		
Paclitaxel	175 mg/m^2 IV	d1
Q2w x 4 cycles		
Filgrastim or pegfilgrastim support		

Reference:
Roche H et al. J Clin Oncol 2006;24:5664.
Burstein HJ et al. J Clin Oncol 2005;23:8340.
Citron, ML et al. J Clin Oncol 2003;21:1431.

AC-Paclitaxel Q3w

Doxorubicin	60 mg/m^2 IV push over 5-15 min	d1
Cyclophosphamide	600 mg/m^2 IV over 30-60 min	d1
Q3w x 4 cycles		
Followed by		
Paclitaxel	175 mg/m^2 IV over 3 hours	
Q3w x 4 cycles		

Reference:
Sparano JA et al. N Eng J Med 2008;358:1663.
Mamounas EP. J Clin Oncol 2005;23:3686.
Henderson, IC et al. J Clin Oncol 2003;21:976.

AC-Paclitaxel Qw

Doxorubicin	60 mg/m^2 IV push over 5-15 min	d1
Cyclophosphamide	600 mg/m^2 IV over 30-60 min	d1
Q3w x 4 cycles		
Followed by		
Paclitaxel	80 mg/m^2 IV over 1 hour	
Qw x 12 cycles		

Reference: Sparano JA et al. N Eng J Med 2008;358:1663.

TC

Docetaxel	75 mg/m^2 IV over 30-60 min	d1
Cyclophosphamide	600 mg/m^2 IV over 30-60 min	d1
Q3w x 4 cycles		

Reference: Jones SE et al. J Clin Oncol 2006;24:5381.

AC

Doxorubicin	60 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q3w x 4 cycles		

Reference:
Muss HB et al. 2008 ASCO annual meeting. Abstract 507.
Fisher, B et al. J Natl Cancer Inst 2004;96:1823.

FAC

Regimen 1 P.O.		
5-FU	500 mg/m^2 IV	d1, 8 or d1, 4
Doxorubicin	50 mg/m^2 IV	d1
(or by 72 hrs continuous infusion)		
Cyclophosphamide	600 mg/m^2/d P.O.	d1
Q3w x 6 cycles		

Reference: Buzdar AU et al. Am J Clin Oncol 1989;12:123.

CAF

Regimen 1 P.O.		
Cyclophosphamide	100 mg/m^2/d P.O.	d1-14
Doxorubicin	30 mg/m^2 IV	d1, 8
5-FU	500 mg/m^2 IV	d1, 8
Q4w x 6 cycles		

Reference: Hutchins LF et al. J Clin Oncol 2005;23:8313.

Regimen 2 IV		
Cyclophosphamide	500 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
5-FU	500 mg/m^2 IV	d1
Q3w x 6 cycles		

Reference: Martin M et al. Ann Oncol 2003;14:833.

CEF

Cyclophosphamide	75 mg/m^2 P.O. qd	d1–14
Epirubicin	60 mg/m^2 IV	d1 and 8
5-FU	500 mg/m^2 IV	d1 and 8
With cotrimoxazole support		
Q4w x 6 cycles		

Reference:
Levine MN et al. J Clin Oncol 2005;23:5166.
Levine MN et al. J Clin Oncol 1998;16:2651.

CMF P.O.

Cyclophosphamide	100 mg/m^2/d P.O.	d1–14
Methotrexate	40 mg/m^2 IV	d1 and 8
5-FU	600 mg/m^2 IV	d1 and 8
Q4w x 6 cycles		

Reference:
Muss HB et al. 2008 ASCO annual meeting. Abstract 507.
Poole CJ et al. N Eng J Med 2006;355:1851.
Hutchins LF et al. J Clin Oncol 2005;23:8313.
Goldhirsch A et al. Ann Oncol 1998;9:489.
Bonadonna G et al. N Eng J Med 1976;294:405.
Colleoni M et al. Eur J Cancer 34(11):1693-700, (1998).

CMF IV

Cyclophosphamide	600 mg/m^2 IV	d1
Methotrexate	40 mg/m^2 IV	d1
5-FU	600 mg/m^2 IV	d1
Q3w x 6 cycles		

Reference: Weiss RB et al. Am J Med 1987;83:455.

AC-Docetaxel Q3w

Doxorubicin	60 mg/m^2 IV push over 5-15 min	d1
Cyclophosphamide	600 mg/m^2 IV over 30-60 min	d1
Q3w x 4 cycles		
Followed by		
Docetaxel (Taxotere) 100 mg/m^2 IV over 1 hour		
Q3w x 4 cycles		

Reference: Sparano JA et al. N Eng J Med 2008;358:1663.

Epirubicin-Cyclophosphamide

Epirubicin	100 mg/m^2 IV	d1
Cyclophosphamide	830 mg/m^2/d P.O.	d1
Q3w x 8 cycles		

Reference: Piccart MJ et al. J Clin Oncol 2001;19:3103.

Dose-dense ATC

Doxorubicin	60 mg/m^2 IV	d1
Paclitaxel	175 mg/m^2 IV	d1
Q2w x 4 cycles		
Followed by		
Cyclophosphamide	600 mg/m^2 IV	d1
Q2w x 4 cycles		
Filgrastim or pegfilgrastim support		

Reference: Roche H et al. J Clin Oncol 2006;24:5664.

FEC-T

5-FU	500 mg/m^2 IV	d1
Epirubicin	100 mg/m^2 IV	d1
Cyclophosphamide	500 mg/m^2 IV	d1
Q3w x 3 cycles		
Followed by		
Docetaxel	100 mg/m^2 IV	
Q3w x 3 cycles		

Reference: Roche H et al. J Clin Oncol 2006;24:5664.

FEC-weekly Paclitaxel

5-FU	600 mg/m^2 IV	d1
Epirubicin	90 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q3w x 3 cycles		
Followed by		
3 weeks of no treatment		
Followed by		
Paclitaxel	100 mg/m^2 IV	
Qw x 8 cycles		

Reference: Martin M et al. J Nat Cancer Inst 2008;100:805.

Nanoparticle Paclitaxel

Nanoparticle paclitaxel	220 mg/m^2 by 1 h IV infusion	day 1
Cycled every 3 wks		
Sequentially to doxorubicin-containing combination chemotherapy		

Reference:
Nanoxel Prescribing Information
Data on file (Phase I and II reports)

Epirubicin-CMF

Epirubicin	100 mg/m^2 IV	q3w x 4 cycles
Followed by		
CMF x 4 cycles		

Reference: Poole CJ et al. N Eng J Med 2006;355:1851.

AT-T

Doxorubicin	50 mg/m^2 IV	d1
Paclitaxel	200 mg/m^2 IV	d1
Q3w x 4 cycles		
Followed by		
Paclitaxel	80 mg/m^2 IV over 1 h qw x 12 weeks	

Reference: Loesch DM et al. 2007 ASCO annual meeting. Abstract 517.

Dose-dense EC-T

Epirubicin	120 mg/m^2 IV	d1
Cyclophosphamide	830 mg/m^2 IV	d1
Q2w x 6 cycles		
Paclitaxel	175 mg/m^2 IV	
Q3w x 4 cycles		
Filgrastim	5 mcg/kg S.C.	d2–13
Epoetin alfa	40,000 units S.C.	qw

Reference:
Burnell M et al. 2006 San Antonio Breast Cancer Symposium. Abstract 53.

Dose-dense Epirubicin-Paclitaxel-Cyclophosphamide

Epirubicin	150 mg/m^2	
Q2w x 3 cycles		
Paclitaxel	225 mg/m^2	
Q2w x 3 cycles		
Cyclophosphamide	2500 mg/m^2	
Q2w x 3 cycles		
Filgrastim	5 mcg/kg S.C.	d3–10

Reference: Moebus et al. 2006 San Antonio Breast Cancer Symposium. Abstract 43.

MFL

Methotrexate	100 mg/m^2 IV	d1, 8
5-FU	600 mg/m^2 IV	d1, 8
Leucovorin	15 mg/m^2 P.O. q6h x 6 doses beginning 24 hrs after methotrexate	
Q4w x 6 cycles		

Reference: Fisher B et al. J Natl Cancer Inst 1997;89:1673.

CMF-Tamoxifen

Tamoxifen	20 mg P.O./day	
Cyclophosphamide	100 mg/m^2 P.O.	days 1–14
Methotrexate	40 mg/m^2 IV	days 1 & 8
5-FU	600 mg/m^2 IV	days 1 & 8

Reference: Crivellari D et al. J Clin Oncol 18:1412-1422. 2000

TARGETED THERAPY

AC-TH

Doxorubicin	60 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q3w x 4 cycles		
Followed by		
Paclitaxel	175 mg/m^2 IV	q3w x 4 cycles, or 80 mg/m^2 IV qw x 12 weeks
Trastuzumab	4 mg/kg loading dose beginning with paclitaxel, then 2 mg/kg IV qw x 1 year	

Note: Approved by FDA on 11/16/06.
Reference:
Dang C et al. J Clin Oncol 2008;26:1216.
Romond EH et al. N Eng J Med 2005;353:1673.

Dose-dense AC-TH

Doxorubicin	60 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q2w x 4 cycles		
Followed by		
Paclitaxel	175 mg/m^2 IV	q2w x 4 cycles, and
Trastuzumab	4 mg/kg loading dose beginning with the first cycle of paclitaxel, then 2 mg/kg IV qw during paclitaxel treatment, followed by 6 mg/kg IV q3w, for a total of 1 year	
Pegfilgrastim	6 mg S.C.	d2

Reference: Dang C et al. J Clin Oncol 2008;26:1216.

TCH

Docetaxel	75 mg/m^2 IV	d1 q3w x 6 cycles
Carboplatin	AUC 6 IV	d1 q3w x 6 cycles
Trastuzumab	4 mg/kg loading dose followed by 2 mg/kg IV qw during chemotherapy; then 6 mg/kg IV q3w, for a total of 1 year	

Reference:
Slamon D et al. 2006 San Antonio Breast Cancer Symposium; Abstract 52.
Robert NJ et al. J Clin Oncol 2007;25:18S (Jun 20 Suppl) Abstract 19647.

Chemo-H

Trastuzumab can be given after completion of chemotherapy as well, loading dose 8 mg/kg, followed by 6 mg/kg, IV q3w for a total of 1 year.

Reference:
Smith I et al. Lancet 2007;369:29.
Piccart-Gebhart MJ et al. N Eng J Med 2005;353:1659.

DH-FEC

Docetaxel	100 mg/m^2 IV over 1 h	d1 q3w x 3 cycles
Trastuzumab	4 mg/kg IV over 90 min	d1
and then	2 mg/kg IV over 30 min	qw x 8
(total of 9 treatments)		
Followed by		
5-FU	600 mg/m^2 IV	d1
Epirubicin	60 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q3w x 3 cycles		

Reference: Joensuu H et al. N Eng J Med 2006;354:809.

H-FECH (Neoadjuvant regimen)

Trastuzumab	4 mg/kg IV for 1 dose beginning just prior to 1st dose of paclitaxel	
Followed by		
Trastuzumab	2 mg/kg IV	qw x 23 weeks
Paclitaxel	225 mg/m^2 IV over 24 h	q3w x 4 cycles
(OR Paclitaxel	80 mg/m^2 IV over 1 h	q1w x 12 cycles
Followed by		
5-FU	500 mg/m^2 IV	d1, 4
Epirubicin	75 mg/m^2 IV	d1
Cyclophosphamide	500 mg/m^2 IV	d1
Q3w x 4 cycles		

Reference: Buzdar A et al. J Clin Oncol 2005;23:3676.

METASTATIC BREAST CANCER HORMONAL THERAPY

Tamoxifen

Tamoxifen	20 mg P.O.	qd

Reference: Ingle, JN et al. N Engl J Med 1981;304:16.

Anastrozole

Anastrozole	1 mg P.O.	qd

Reference: Osborne, CK et al. J Clin Oncol 2002;20:3386.

Anastrozole + Goserelin

Goserelin	3.6 mg S.C. d1	qm
Anastrozole	1 mg P.O.	qd, beginning on d22

Reference: Carlon RW et al. 2007 ASCO annual meeting. Abstract 1030.

Letrozole

Letrozole	2.5 mg P.O.	qd

Reference: Mouridsen, H et al. J Clin Oncol 2003;21:2101.

Exemestane

Exemestane	25 mg P.O.	qd

Reference:
Chia S et al. J Clin Oncol 2008;26:1664.
Kaufmann, M et al. J Clin Oncol 2000;18:1399.

Fulvestrant

Fulvestrant	250 mg I.M. or	qm
	500 mg loading dose I.M.	d1
	followed by	
	250 mg I.M.	d14, 28 and qm thereafter

Reference:
Chia S et al. J Clin Oncol 2008;26:1664.
Perey L et al. Ann Oncol 2007;18:64.
Howell, A et al. J Clin Oncol 2002;20:3396.

Idoxifene

Postmenopausal patients with hormone receptor positive or unknown metastatic breast cancer

Idoxifene	60 mg/day P.O. loading dose	for first 21 days
Followed by	40 mg/day maintenance dose	

Reference: Arpino G et al. Ann Oncol 14:233-241, (2003).

CHEMOTHERAPY

CAF

Cyclophosphamide	100 mg/m^2 P.O.	d1–14
Doxorubicin	30 mg/m^2 IV	d1 & 8
5-Fluorouracil	500 mg/m^2 IV	d1 & 8
Q4w		

Reference: Bull JM et al. Cancer 1978;41:1649.

FAC

5-Fluorouracil	500 mg/m^2 IV	d1 & 8 or d1 & 4
Doxorubicin	50 mg/m^2 IV	d1
Cyclophosphamide	500 mg/m^2 P.O.	d1
Q3w		

Reference: Hortobagyi GN et al. Cancer 1979;43:1225.

FEC

Cyclophosphamide	400 mg/m^2 P.O.	d1 & 8
Epirubicin	50 mg/m^2 IV	d1 & 8
5-Fluorouracil	500 mg/m^2 IV	d1 & 8
Q4w		

Reference: Ackland SP et al. J Clin Oncol 2001;19:943.

AC

Doxorubicin	60 mg/m^2 IV	
Cyclophosphamide	600 mg/m^2 IV	
Q3w		

Reference: Brown AM et al. J Clin Oncol 1990;8:1483.

EC

Epirubicin	75 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q3w		

Reference: Langley RE et al. J Clin Oncol 2005;23:8322.

Doxorubicin-Paclitaxel (AT)

Regimen 1		
Doxorubicin	50 mg/m^2 IV	d1
Paclitaxel	200 mg/m^2 IV over 3 hours	d2
Q3w x 6–8 cycles		

Reference: Gennari A et al. J Clin Oncol 2006;24:3912.

Regimen 2

Doxorubicin	50 mg/m^2 IV	day 1
Paclitaxel	150 mg/m^2 IV	day 1

Note: To be repeated every 3 weeks (with G-CSF support).
Reference:
Hortobagyi et al. Semin Oncol24(17):65-68, (1997).
Sledge et al. J Clin OncoI 21(4):588-92, (2003).

Regimen 3

Doxorubicin	60 mg/m^2 IV	day 1
Paclitaxel	175 mg/m^2 IV over 3 hours	day 1

Note: To be repeated every 3 weeks for a maximum of 6 cycles.
Reference: Laura Biganwli et al. Cancer 97, 1:40-45, (2003).

Regimen 4

Doxorubicin	60 mg/m^2 IV	day 1
Paclitaxel	125 - 200 mg/m^2 IV	day 1

Note: To be repeated every 3 weeks.
Reference: Gianni L et al. J Clin Oncol 1995, 13:2668, (2003).

Regimen 5

Doxorubicin	50 mg/m^2 IV	d1
Docetaxel	75 mg/m^2 IV	d1
Q3w		

Reference: Nabholtz JM et al. J Clin Oncol 2003;21:968.

EP

Epirubicin	75 mg/m^2 IV	d1
Paclitaxel	200 mg/m^2 IV over 3 hours	d1
Q3w		

Reference: Langley RE et al. J Clin Oncol 2005;23:8322.

CMF P.O.

Cyclophosphamide	600 mg/m^2 IV	d1
Methotrexate	40 mg/m^2 IV	d1
5-FU	600 mg/m^2 IV	d1
Q3w x 6 cycles		

Reference: Weiss RB et al. Am J Med 1987;83:455.

Docetaxel + Capecitabine

Docetaxel	75 mg/m^2 IV	d1
Capecitabine	1000 mg/m^2 P.O.	b.i.d x 14 days
Q3w		

Reference: O'Shaughnessy, J et al. J Clin Oncol 2002;20:2812.

Paclitaxel + Gemcitabine (GT)

Paclitaxel	175 mg/m^2 IV	d1
Gemcitabine	1250 mg/m^2 IV	d1 and 8
Q3w		

Reference: Albain, KS et al. J Clin Oncol 2004:22;14S:510.

Paclitaxel	175 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1 and 8
Q3w		

Reference: Albain, KS et al. 2004 ASCO annual meeting; Abstract 510.

Ixabepilone + Capecitabine

Regimen 1		
Ixabepilone	40 mg/m^2 IV	d1
Capecitabine	2000 mg/m^2 P.O.	d1–14
Q3w		

Reference: Thomas ES et al. J Clin Oncol 2007;25:5210.

Regimen 2		
Ixabepilone	40 mg/m^2 IV over 3 hours	d1
Capecitabine	1000 mg/m^2 P.O.	b.i.d d1–14
Q3w until progression		

Note: Approved by FDA on 10/16/07.
Reference: Thomas ES et al. J Clin Oncol 2007;25:5210.

PREFERRED SINGLE AGENTS
ANTHRACYCLINES

Doxorubicin

Regimen 1		
Doxorubicin	60–75 mg/m^2 IV d1	q3w
(q3w)		

Reference: Chan S et al. J Clin Oncol 1999;17:2341.

Regimen 2		
Doxorubicin	20 mg/m^2 IV weekly	

Reference: Gundersen S et al. Eur J Cancer Clin Oncol 1986;22:1431.

Epirubicin

Epirubicin	60–90 mg/m^2 IV d1	q3w

Reference: Basholt L et al. J Clin Oncol 1996;14:1146.

Pegylated liposomal encapsulated doxorubicin

	50 mg/m^2 IV d1	q4w

Reference: O' Brien et al. Annals Oncol 2004;15(3):440.

TAXANES

Paclitaxel

Regimen 1 (q3w)		
Paclitaxel	175 mg/m^2 IV over 3 hours	q3w
until progression or limiting toxicity		

Reference:
Sledge GW et al. J Clin OncoI21(4):588-92, (2003).
Bishop, JF et al. J Clin Oncol 1999;17:2355.
Seidman A et al. J Clin OncoI 1995;13:2575.

Regimen 2 (qw) (preferred)		
Paclitaxel	80 mg/m^2 IV over 1 hour	qw
until progression or limiting toxicity		

Reference:
Perez, EA et al. J Clin Oncol 2001;19:4216.
Seidman AD et al. J Clin Oncol 2008;26:1642.
Verrill MW et al. 2007 ASCO annual meeting. Abstract LBA1005.

Docetaxel

Regimen 1 (q3w) (preferred)		
Docetaxel	60–100 mg/m^2 IV	q3w

Reference:
Harvey V et al. J Clin Oncol 2006;24:4963.
Alexandre, J et al. J Clin Oncol 2000;18:562.
BurrisHAR et al. Seminars Oncol 1997;26:1-6.
Valero V et al. Seminars Oncol 1997;24(S13):S11-18.

Regimen 1 (q1w)		
Docetaxel	40 mg/m^2 IV	
qw x 6w followed by a 2 week rest, then repeat		

Reference: Burstein HJ et al. J Clin Oncol 2000;18:1212.

Albumin bound paclitaxel

Regimen 1		
Albumin bound paclitaxel	100 mg/m^2 or 150 mg/m^2 IV	d1, 8 and 15
q4 w		

Reference:
Gradishar WJ et al. J Clin Oncol 2005;23:7794
Gradishar WJ et al. 2007 25(Jun 20 S); Abstract 1032

Regimen 2 (q3w)		
Albumin bound paclitaxel	260 mg/m^2 IV	q3w

Reference: Gradishar WJ et al. J Clin Oncol 2005;23:7794

Nanoparticle Paclitaxel

After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

Nanoparticle paclitaxel	220 mg/m^2 by 1 h IV infusion	day 1
Cycled every 3 wks		

Reference:
Nanoxel Prescribing Information
Data on file (Phase I and II reports)

ANTI-METABOLITES

Capecitabine

Capecitabine	1000–1250 mg/m^2 P.O.	b.i.d d1–14 days x q3w

Reference:
Bajetta E et al. J Clin Oncol 2005;23:2155.
Fumoleau, P et al. Eur J Cancer 2004;40:536.

Gemcitabine

Regimen 1		
Gemcitabine	725 mg/m^2 IV	qw x 3 wks evey 4 wks

Reference: Carmichael, J et al. J Clin Oncol 1995;13:2731.

Regimen 2		
Gemcitabine	800–1200 mg/m^2 IV	d1, 8, 15 evey 4 wks

Reference:
Seidman AD. Oncology Williston Park 2001;15(S3):11.
Blackstein M. et al. Oncology 62(1):2-8, (2002).

OTHER MICROTUBULE INHIBITORS

Vinorelbine

Vinorelbine	25 mg/m^2 IV over 1 hour	qw,

Reference: Zelek L et al. Cancer 2001;92:2267.

Vinorelbine	20 mg/m^2 IV over 1 hour	qw,
increase to 25 mg/m^2 qw if the first 4 courses are well tolerated		

Reference: Gasparini, G et al. J Clin Oncol 1994;12:2094.

Vinorelbine (Palliative regimen after failure with anthracyclines and taxanes in metastatic disease)

Vinorelbine	30 mg/m^2 IV infusion over 30 min	every week

Note: Dose modification based on observed toxicities
Reference: Zelek L et al. Cancer 92(9):2267-72, (2001).

Eribulin	1.4 mg/m^2 IV d1, 8	q3w,

Ixabepilone

Premedication		
Diphenhydramine	50 mg P.O.	1 hour before ixabepilone
Ranitidine	150 mg P.O.	1 hour before ixabepilone
If allergic reaction, add		
dexamethasone	20 mg P.O. or 20 mg IV	1 hour before ixabepilone 30 min before ixabepilone
Regimen 1		
Ixabepilone	40 mg/m^2 IV over 3 hours	q3w

Note: Approved by FDA on 10/16/07.
Reference:
Perez EA et al. J Clin Oncol 2007;25:3407.
Thomas E et al. J Clin Oncol 2007;25:3399.
Roche H et al. J Clin Oncol 2007;25:3415.

Regimen 2		
Ixabepilone	6 mg/m^2/d IV	d1–5 q3w

Reference:
Denduluri N et al. J Clin Oncol 2007;25:3421.
Low JA et al. J Clin Oncol 2005;23:2726.

NFL

Mitoxantrone	12 mg/m^2 IV	day 1
5-FU	350 mg/m^2	day 1–3
Leuvocorin	300 mg IV	day 1–3
(immediately preceding administration of 5-FU)		

Note: To be repeated every 3 weeks (at least 8 cycles for responding patients; as an initial palliative treatment option for elderly patients or patients who have exhibited poor tolerance to other chemotherapy regimens).
Reference: Hainsworth et al. Cancer 79(4):740-748, (1997).

FILM (metastatic, locally advanced or inoperable disease)

5-FU	750 mg/m^2 IV (max. 1500 mg)	day 1
Leucovorin	200 mg/m^2 IV (max. 350 mg)	day 1
Mitomycin	6 mg/m^2 IV	day 1
Ifosfamide	1,000 mg/m^2 IV	day 1
(with mesna)		

Note: To be repeated every 3 weeks (except for mitomycin which is given on alternate cycles).
Reference: Davidson et al. Breast (7):114-118, (1998).

Paclitaxel-Cisplatin (Locally advanced or metastatic breast cancer)

Paclitaxel	175 mg/m^2 IV, 3 hour infusion	day I
Cisplatin	50 mg/m^2 IV, 24 hour infusion	day I

Note: To be repeated every 3 weeks.
Reference: Hsu C et al. Cancer 95(10):2044-50, (2002).

Paclitaxel (Locally advanced or metastatic breast cancer)

Paclitaxel	250 mg/m^2 IV over 24 hour	q3w

Reference: Smith RE et al. J Clin Oncol:3403-3411, (1999).

Vinorelbine-Ifosfamide (In anthracycline resistant metastatic breast cancer)

Ifosfamide	2,000 mg/m^2 IV	day 1–3
(with mesna)		
Vinorelbine	25 mg/m^2 IV	day I, 8

Note: To be repeated every 3 weeks (as an alternative to taxanes for patients previously treated with anthracyclines).
Reference: Campisi C et al. Ann Oncol9(5):565-567, (1998).

Vinorelbine-5FU (Metastatic breast cancer after anthracycline therapy failure)

Vinorelbine	25 mg/m^2 IV	day 1, 5
5-FU	750 mg/m^2/day IV	day 1–5
(continuous infusion)		

Note: Repeat every 3 weeks.
Reference: Bonneterre] et al. Br J Cancer 87(11):1210-5, (2002).

Vinorelbine-Cisplatin

Vinorelbine	25 mg/m^2 IV	day I, 8
Cisplatin	80 mg/m^2 IV	day I

Note: Repeat every 3 weeks.
Reference: Mustacchi G et al. Ann OncoI13(11):1730-6, (2002).

Vinorelbine-Doxorubicin

Vinorelbine	25 mg/m^2 IV	day 1, 8
Doxorubicin	25 mg/m^2 IV	day 1, 8

Note: Repeat every 3 weeks.
Reference: Pawlicki M et al. Oncologist 7(3):205-9, (2002).

Gemcitabine-Cisplatin (Previously treated, relapsed breast cancer)

Cisplatin	30 mg/m^2 IV	day I, 8
Gemcitabine	1,000 mg/m^2 IV	day 1.8

Note: Repeat every 3 weeks.
Reference: Nagourney RA et al.] Clin OncoI18(11):2245-9, (2000).

Gemcitabine-Vinorelbine

Vinorelbine	30 mg/m^2 IV	day 1, 8
Gemcitabine	1,200 mg/m^2 IV	day 1, 8

Note: Repeat every 3 weeks,
Reference: Sanal SM et al. Breast] 8(3):171-6, (2002).

Epirubicin-Vinorelbine

Vinorelbine	25 mg/m^2 IV	30 min infusion	day 1, 5
Epirubicin	100 mg/m^2 (bolus) IV		day 1

Note: Repeat every 3 weeks with G-CSF on day 7 to 12 of every cycle.
Reference: Vici Pet ai. J Clin OncoI20(11):2689-94, (2002).

TARGETED THERAPY

Paclitaxel + Bevacizumab

Paclitaxel	90 mg/m^2 IV	d1, 8 and 15
Bevacizumab	10 mg/kg IV	d1 and 15
Q4w		

Note: Approved by FDA on 2/22/08.
Reference: Miller KD et al. N Eng J Med 2007;357:2666.

Docetaxel + Bevacizumab

Docetaxel	100 mg/m^2 IV	q3w x 9 cycles
Bevacizumab	7.5 mg/kg or 15 mg/kg IV	q3w
until progression or unacceptable toxicity		

Reference: Miles D et al. 2008 ASCO annual meeting. LBA1011.

Capecitabine + Bevacizumab

Capecitabine	1000-1250 mg/m^2 P.O.	b.i.d d1-14
Bevacizumab	15 mg/kg IV	d1
Q3w until disease progression		

Reference:
Sledge G et al. 2007 ASCO annual meeting. Abstract 1013.
Miller K et al. J Clin Oncol 2005;23:792.

PREFERRED 1ST LINE AGENTS WITH TRASTUZUMAB FOR HER-2 POSITIVE DISEASE

TRASTUZUMAB COMPONENT

Trastuzumab	4 mg/kg IV over 90 min	d1 first wk
followed by		
	2 mg/kg IV over 30 min	d1 qw

Reference:
Slamon DJ et al. NEJM 2001;344:783.
Cobleigh MA et al. J Clin Oncol 1999;17:2639.

OR

Trastuzumab	4 mg/kg IV over 90 min	d1 first wk
followed by		
	2 mg/kg IV over 30 min	d1 qw

Reference: Leyland-Jones et al. J Clin Oncol 2003;21:3965.

COMBINATIONS

TCP

Trastuzumab	4 mg/kg IV over 90 min	d1 first wk
followed by		
	2 mg/kg IV over 30 min	d1 qw
Paclitaxel	175 mg/m^2 IV	d2 q3w
Carboplatin	AUC 6 IV	d2 q3w

Reference: Robert N et al. J Clin Oncol 2006;24:2786.

Weekly TCP

Paclitaxel	80 mg/m^2 IV	d1, 8, 15
Carboplatin	AUC 2 IV	d1, 8, 15
Q4w		

Reference: Perez E et al. The Oncologist 2004;9:518.

TCH

Docetaxel	75 mg/m^2 IV over 1 h	d1 q3w x 6 - 8 cycles
Carboplatin	AUC 6 IV over 1 h	d1 q3w x 6 - 8 cycles
Trastuzumab	4 mg/kg IV over 90 min	first week
followed by		
	2 mg/kg IV over 30 min	qw
	(may change to 6 mg/kg q3w after chemotherapy) until disease progression	

Reference:
Pegram M et al. 2007 ASCO annual meeting. Abstract LBA1008.
Pegram M et al. J Natl Cancer Inst 2004. 96:759.

Trastuzumab

Trastuzumab	4 mg/kg IV over 90 min	first wk
followed by		
	2 mg/kg IV over 30 min	qw

Reference:
Cobleigh, MA et al. J Clin Oncol 1999;17:2639.
Vogel CL et al. J Clin OncoI20(3):719-26, (2002).

Trastuzumab + Anastrozole (for postmenopausal women with Her2 and ER/PR + cancer)

Trastuzumab	4 mg/kg IV over 90 min	first wk
followed by		
	2 mg/kg IV over 30 min	qw
Anastrozole	1 mg P.O.	qd

Reference:
Mackey JR et al. 2006 San Antonio Breast Cancer Symposium; Abstract 2.
Kaufman B et al. 31st Congress of the European Society for Medical Oncology (ESMO) 2006; Late breaking abstract 2.

SINGLE AGENTS

Trastuzumab + Paclitaxel q3w

Trastuzumab	4 mg/kg IV over 90 min	first wk
followed by		
	2 mg/kg IV over 30 min	qw
Paclitaxel	175 mg/m^2 IV	q3w

Reference:
Robert N et al. J Clin Oncol 2006;24:2786.
Slamon, DJ et al. N Engl J Med 2001;344:783.

Trastuzumab + Paclitaxel qw

Trastuzumab	4 mg/kg IV over 90 min	first wk
followed by		
	2 mg/kg IV over 30 min	qw
Paclitaxel	80–90 mg/m^2 IV	qw

Reference:
Seidman, AD et al. J Clin Oncol 2008;26:1642.
Seidman, AD et al. J Clin Oncol 2001;19:2587.

Trastuzumab + Docetaxel (TH) q3w

Trastuzumab	4 mg/kg IV over 90 min	first wk
followed by		
	2 mg/kg IV over 30 min	qw
	(may change to 6 mg/kg q3w after chemotherapy) until disease progression	
Docetaxel	80–100 mg/m^2 IV	q3w x 6–8 cycles

Reference:
Pegram M et al. 2007 ASCO annual meeting. Abstract LBA1008.
Marty M et al. J Clin Oncol 2005;23:4265.

Trastuzumab + Docetaxel qw

Trastuzumab	4 mg/kg IV over 90 min	first wk
followed by		
	2 mg/kg IV over 30 min	qw
Docetaxel	35 mg/m^2 IV	qw

Reference:
Tedesco, KL et al. J Clin Oncol 2004;22:1071.
Esteva FJ et al. J Clin Oncol 2002;20:1800.

Trastuzumab-Docetaxel

Trastuzumab	4 mg/kg IV over 90 min	first wk
followed by		
	2 mg/kg IV over 30 min	qw
Start docetaxel upon disease progression on trastuzumab		
Docetaxel	100 mg/m^2 IV	q3w

Reference: Bontenbal M et al. 2008 ASCO annual meeting. Abstract 1014.

Trastuzumab-Vinorelbine

Vinorelbine	25–30 mg/m^2/week IV	day 1
Trastuzumab	4 mg/kg IV (as loading dose)	day 1
	Followed by	
	2 mg/kg/week starting on day 8	

Reference:
Chan A et al. Br J Cancer. 2006 Oct 9;95(7):788-93. Epub 2006 Sep 12.
Burstein HJ et al. Cancer. 2007;110:965.

Trastuzumab + Capecitabine

Regimen 1

Trastuzumab	4 mg/kg IV over 90 min	first week
	followed by	
	2 mg/kg IV over 30 min	qw
Capecitabine	1250 mg/m^2 P.O.	b.i.d d1–14 q3w

Reference: Schaller G et al. J Clin Oncol 2007;25:3246.

Regimen 2		
Trastuzumab	8 mg/kg IV loading dose	
followed by		
	6 mg/kg IV	q3w
Capecitabine	1250 mg/m^2 P.O.	b.i.d d1–14 q3w

Reference:
Von Minchwitz G et al. 2008 ASCO annual meeting. Abstract 1025.
Bartsch R et al. J Clin Oncol 2007;25:3853.

Trastuzumab + Docetaxel + Capecitabine

Trastuzumab	8 mg/kg IV loading	
followed by		
	6 mg/kg IV d1	q3w
Docetaxel	75 mg/m^2 IV	d1 q3w
Capecitabine	940 mg/m^2 P.O.	b.i.d. d1–14 q3w

Reference: Wardley A et al. Oncology (ESMO) 2006; Late breaking abstract 6.

PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER-2 POSITIVE DISEASE

Trastuzumab	4 mg/kg IV over 90 min	d1 first wk
followed by		
	2 mg/kg IV over 30 min	d1 qw

Reference:
Slamon DJ et al. NEJM 2001;344:783.
Cobleigh MA et al. J Clin Oncol 1999;17:2639.

OR		
Trastuzumab	4 mg/kg IV over 90 min	d1 first wk
followed by		
	2 mg/kg IV over 30 min	d1 qw

Reference: Leyland-Jones et al. J Clin Oncol 2003;21:3965.

Lapatinib + Capecitabine

Lapatinib	1250 mg P.O.	qd
Capecitabine	1000 mg/m^2 P.O. b.i.d.	d1–14 q3w

Note: Approved by FDA on 3/13/07
Reference: Geyer CE et al. N Eng J Med 2006;355:2733.

Lapatinib + Trastuzumab

Lapatinib	1000 mg P.O.	qd
Trastuzumab	4 mg/kg IV over 90 min	first week
followed by		
	2 mg/kg IV over 30 min qw	

Reference: O'Shaughnessy J et al. 2008 ASCO annual meeting. Abstract 1015.

Lapatinib + Paclitaxel

Lapatinib	1500 mg P.O.	qd
Paclitaxel	175 mg/m^2 IV	q3w

Reference: Di Leo A et al. 2007 ASCO annual meeting. Abstract 1011.

Lapatinib (for inflammatory breast cancer)

Lapatinib	1500 mg P.O.	qd

Reference: Johnston S et al. J Clin Oncol 2008;26:1066.

Lapatinib (for brain metastases)

Lapatinib	750 mg P.O.	b.i.d.

Reference: Lin NU et al. J Clin Oncol 2008;26:1993.

Lapatinib + Capecitabine (for brain metastases)

Lapatinib	1250 mg P.O.	qd
Capecitabine	1000 mg/m^2 P.O.	b.i.d. x 14 days q3w

Reference: Lin NU et al. 2007 San Antonio Breast Cancer Symposium. Abstract 6076.

BONE METASTASES/OSTEOLYSIS/TUMOUR INDUCED HYPERCALCAEMIA BISPHOSPHONATES

Clodronate-pamidronate

Clodronate	300–1,500 mg/day IV	1–10 days
Pamidronate	30 mg (calcium levels $<$12 mg/d/) to 90 mg (calcium levels $>$16 mg/d) IV	(4–24 hour infusion)

Note: To be Repeated every 3-4 weeks.
Reference: Body et al. Eur J Cancet 34(2):263-9, (1998).

Pamidronate

Pamidronate	90 mg IV	day 1

Note: Repeat every 3-4 weeks.
Reference: Allan Lipton, Cancer 97(53):848-853, (2003)

Zoledronic acid

Zoledronic acid	4 mg IV	(15 min infusion)

Note: Repeat every 3-4 weeks.
Reference: Lipton A et al. Cancer 97(53):848-853, (2003).

MISCELLANEOUS

Megestrol acetate (Second line hormonal therapy in advanced breast cancer)

Megestrol acetate	160 mg/day P.O.

Reference: Kaufmann M. et al. Oncology 54 (suppl2):2-5, (1997).

Medroxyprogesterone (Second line hormonal therapy in advanced breast cancer)

Medroxyprogesterone	400–1200 mg/day P.O.

Reference: Kaufmann M. et al. Oncology 54 (suppl2):2-5, (1997).

PART - I
Solid Tumor

Cancer of Unknown Primary

CANCER OF UNKNOWN PRIMARY

The site of origin of a histological carcinoma is not identified clinically in approximately 3% of patients; this situation is often referred to as carcinoma of unknown primary (CUP) origin or occult primary malignancy. They are usually adenocarcinomas or undifferentiated tumors and less common squamous cell carcinoma, melanoma, sarcoma, and neuroendocrine tumors can also present with a primary site of origin that cannot be determined. The prognosis is poor with a median survival of approximately 3 to 4 months with less than 25% and 10% of patients alive at 1 and 5 years respectively. It is represented by a heterogeneous group of diseases all of which have presented with metastasis as the primary manifestation.

It is a tumor that has a greater propensity for early dissemination than the primary tumor that is apparent with or without metastasis. Lung metastases are twice as common in primary usually found above the diaphragm or liver metastases below the diaphragm.

Reference:
Pavlidis N et al. Eur J Cancer 39(14):1990-2005, (2003).
McCredie M et al. Eur J Cancer 27(7):928-31, (1991).
Muir C, Weiland L: Cancer 75 (1 Suppl):147-53, (1995).
Parkin DM et al. eds.: Cancer Incidence in Five Continents. Volume VII. Lyon, France: International Agency for Research on Cancer, (1997).
Briasoulis E et al. Oncologist 2(3):142-152, (1997).
Hainsworth JD et al. N Engl J Med 329(4):257-63, (1993).
Neumann KH et al. Semin Oncol 9(4):427-34, (1982).
Moertel CG et al. Cancer 30(6):1469-72, (1972).
Altman E et al. Cancer 57(1):120-4, (1986).
Ringenberg QS: Med Pediatr Oncol 13(5):301-6, (1985).

STAGING

Opinions are divergent concerning the value and extent of evaluation that should be performed to determine the primary tumor in patients who present with carcinoma of unknown primary (CUP). Clinical and pathological investigations to detect tumors that are potentially responsive to treatment (e.g., lymphoma, germ cell tumor, breast, or ovarian tumor) may be undertaken. In the case of a primary of unknown origin, staging can only be based on clinical suspicion of the primary origin (e.g., T0 N1 M0).

Reference:
Carcinoma of Unknown Primary Treatment (PDQ®): National Cancer Institute; available at http://www.cancer.gov/cancertopics/pdq/treatment/unknownprimary/healthprofessional/allpages
Cancer staging atlas, AJCC, 2006

CHEMOTHERAPY REGIMENS
ADENOCARCINOMA

Paclitaxel-Carboplatin

Paclitaxel	200 mg/m^2 IV 3 hour infusion	day 1
Carboplatin	AUC-5 IV	day 1

Note: Repeat every 3 weeks.
Follow the usual paclitaxel desensitiztion regimen with dexamethasone. Hl- and H2- histamine receptor antagonists.
Reference:
El-Rayes BF et al. Am J Clin Oncol April;28(2):152-6, (2005).
BriasoulisE et al. J Clin Oncol 2000;18:3101.

Paclitaxel + Carboplatin + Etoposide

Paclitaxel	200 mg/m^2 IV	d1
Carboplatin	AUC 6 IV	d1
Etoposide	50 mg alternating with 100 mg P.O.	d1–10
Q3w		

Reference:
Hainsworth JD et al. J Clin Oncol 1997;15:2385.
Greco F et al. Cancer 2000;89:2655.
Hainsworth JD et al. Cancer J 2010;16:70.
Greco F et al. Oncologist 2004;9:644.

Docetaxel-Carboplatin

Docetaxel	65 mg/m^2 IV	day 1
Carboplatin	AUC 6 IV	day 1

Reference: Greco F et al. Ann Oncol 2000;11:211.

Docetaxel-Carboplatin

Docetaxel	65 mg/m^2 IV	day 1
Carboplatin	AUC 5 IV	day 1

Reference: El-Rayes BF et al. Am J Clin Oncol April;28(2):152-6, (2005).

Gemcitabine + Cisplatin

Gemcitabine	1250 mg/m^2 IV	d1, 8
Cisplatin	100 mg/m^2 IV	d1
Q3w		

Reference: Culine S et al. J Clin Oncol 2003;21:3479.

Gemcitabine-Docetaxel

Gemcitabine	1000 mg/m^2 IV	d1, 8
Docetaxel	75 mg/m^2 IV	day 8
Q3w		

Reference: Pouessel D et al. Cancer 2004;100(6):1257.

SQUAMOUS CELL CARCINOMA

Paclitaxel + Cisplatin + 5-FU

Paclitaxel	175 mg/m^2 IV	d1
Cisplatin	100 mg/m^2 IV	d2
5-FU	500 mg/m^2/d continuous infusion over 120 hrs	
Q3w		

Reference: Hitt R et al. J Clin Oncol 2005;23:8636.

Docetaxel + Cisplatin + 5-FU

Docetaxel	75 mg/m^2 IV	day 1
Cisplatin	750 mg/m^2 IV	d2
5-FU	750 mg/m^2/d continuous infusion	d1–5
Q3w		

Reference: Pointreau Y et al. J Clin Oncol 2009;101(7):498.

Gemcitabine + Carboplatin + Paclitaxel-Paclitaxel

Gemcitabine	1000 mg/m^2 IV	d1, 8
Carboplatin	AUC 5 IV	d1
Paclitaxel	200 mg/m^2 IV	d1
Q3w x 4 cycles		
Followed by		
Paclitaxel	70 mg/m^2 IV	qw x 6 wks every 8 wks x 3 cycles

Reference: Greco FA et al. J Clin Oncol 2002;20:1651.

Cisplatin + Etoposide + Bleomycin

Cisplatin	20 mg/m^2/d IV	d1–5
Etoposide	100 mg/m^2/d IV	d1–5
Bleomycin	30 U IV	d1, 8 and 15
Q3w		

Reference: Hainsworth JD et al. J Clin Oncol 1992;10:912.

Bevacizumab + Erlotinib

Bevacizumab	10 mg/kg IV over 30–90 min	q2w
Erlotinib	150 mg P.O.	qd

Reference: Hainsworth JD et al. J Clin Oncol 2007;25:1747.

Paclitaxel + Carboplatin + Bevacizumab + Erlotinib

Paclitaxel	175 mg/m^2 IV 3 hour infusion	day 1
Carboplatin	AUC-6.0 IV	day 1
Bevacizumab	15 mg/kg IV	q2w
Erlotinib	150 mg P.O.	qd
Q3w		

Reference: Hainsworth JD et al. The Oncol 2009;14:1179.

Doxorubicin-Mitomycin

Doxorubicin	50 mg/m^2 IV	day 1, 22
Mitomycin	20 mg/m^2 IV	day 1
Repeat every 42 days.		

Note: Do not exceed a 540-mg/m^2 cumulative dose of doxorubicin.
Reference: Hainsworth J et al. N Engl J Med 329:257, (1993).

PART - I
Solid Tumor

Carcinoid Tumors

CARCINOID TUMORS

The majority of carcinoid tumors are slow-growing tumors that can be treated and often cured, especially in early stages. The occurrence of metastasis from carcinoid tumors relates directly to the size of the primary tumor. They are classified as neuroendocrine or amine precursor uptake and decarboxylation tumors. Carcinoid tumors may arise from various sites, most commonly the gastrointestinal tract and the lung. The appendix, small bowel, and rectum account for over 90% of surgical cases occurring in the gastrointestinal tract. Symptoms may be chronic, suggesting partial obstruction or intussusception. Primary carcinoids of the extrapelvic colon are uncommon, typically present with metastatic disease, and have a poor prognosis. Patients with carcinoid tumor are at increased risk for synchronous or metachronous second malignancies. The most common site for a second primary malignancy is the gastrointestinal tract.

Surgical resection is the standard curative modality. If the primary tumor is localized and resectable, 5-year survival rates are excellent (70%–90%). Even in patients with distant metastasis, the disease is usually very indolent, with median survivals of 2 years or more. Radiation therapy has a minor role in patients with regionally unresectable disease and may palliate the pain of bone metastasis. Patients with carcinoid syndrome can usually be effectively palliated by injections of somatostatin analogue two to three times a day. A long-acting somatostatin analogue that can be given as an injection once a month, with equivalent efficacy, is now available.

Reference:
Moertel CG: J Clin Oncol 5(10):1502-22, (1987).
Kulke MH, Mayer RJ: N Engl J Med 340(11):858-68, (1999).
Mani S et al. J Am Coll Surg 179(2):231-48, (1994).
Moertel CG et al. N Engl J Med 317(27):1699-701, (1987).
Martin JK et al. Arch Surg 118(5):537-42, (1983).
Moertel CG: J Clin Oncol 1(11):727-40, (1983).
Delcore R, Friesen SR: J Am Coll Surg 178(2):187-211, (1994).
Spread C et al. Dis Colon Rectum 37(5):482-91, (1994).
Modlin I.M., Sandor A: Cancer 79(4):813-29, (1997).
Gerstle JT, Kauffman GL Jr, Koltun WA: J Am Coll Surg 180(4):427-32, (1995).
Rubin J et al. J Clin Oncol 17(2):600-6, (1999).

PRIMARY TUMOR (T)

Stomach

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/dysplasia (tumor size <0.5 mm), confined to mucosa
T1	Tumor invades lamina propria or submucosa and ≤ 1 cm in size
T2	Tumor invades muscularis propria or >1 cm in size
T3	Tumor penetrates subserosa
T4	Tumor invades visceral peritoneum (serosa) or other organs or adjacent structures

For any T, add (m) for multiple tumors

Duodenum/Ampulla/Jejunum/Ileum

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size ≤ 1 cm* (small intestinal tumors); tumor ≤ 1 cm (ampullary tumors)
T2	Tumor invades muscularis propria or size >1 cm (small intestinal tumors); tumor >1 cm (ampullary tumors)
T3	Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into nonperitonealized tissues.
T4	Tumor invades visceral peritoneum (serosa) or invades other organs

For any T, add (m) for multiple tumors
**Tumor limited to ampulla of Vater for ampullary gangliocytic paraganglioma*

Colon or Rectum

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size ≤2 cm
T1a	Tumor size <1 cm in greatest dimension
T1b	Tumor size 1 to 2 cm in greatest dimension
T2	Tumor invades muscularis propria or size >2 cm with invasion of lamina propria or submucosa
T3	Tumor invades through the muscularis propria into the subserosa, or into non peritonealized pericolic or perirectal tissues
T4	Tumor invades peritoneum or other organs

For any T, add (m) for multiple tumors

REGIONAL LYMPH NODES (N)

Stomach

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Duodenum/Ampulla/Jejunum/Ileum

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Colon or Rectum

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

Stomach

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

Duodenum/Ampulla/Jejunum/Ileum

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

Colon or Rectum

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis*	N0	M0
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

**Note: Tis applies only to stomach.*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Octreotide

Octreotide	150–250 mcg S.C.	tid
or	depot 20 mg I.M.	q4w

Reference: Saltz L et al. Cancer 1993;72:244.

Octreotide LAR	30 mcg I.M.	q4w

Reference: Rinke A et al. J Clin Oncol 2009;27:4656.

Alpha-interferon + Octreotide/Lanreotide

Alpha-interferon	9–25 million units	qw
Octreotide	100–1500 mcg S.C.	qd
Lanreotide	6000 mcg S.C.	qd

Reference: Fjallskog ML et al. Med Oncol 2002;19(1):35.

Lanreotide + Alpha-interferon

Lanreotide	1 mg tid S.C.	qd
Alpha-interferon	5 x 106 U S.C.	3 times qw

Reference: Faiss S et al. J Clin Oncol 2003;21(41):2689.

Streptozocin + 5-FU

Streptozocin	500 mg/m^2/d IV	d1–5
5-FU	400 mg/m^2/d IV	d1–5
Q6w		

Reference: Moertel CG et al. N Eng J Med 1992;326:519.

Streptozocin + Doxorubicin

Streptozocin	500 mg/m^2/d IV	d1–5
Doxorubicin	50 mg/m^2 IV	d1, 22

Reference: Moertel CG et al. N Eng J Med 1992;326:519.

5-FU + Streptozocin + Doxorubicin

5-FU	400 mg/m^2/d IV	d1–5
Streptozocin	400 mg/m^2/d IV	d1–5
Doxorubicin	40 mg/2	d1
Q4w		

Reference: Kouvaraki MA et al. J Clin Oncol 2004;22:4762.

Etoposide + Cisplatin

Etoposide	130 mg/m^2/d civi	d1–3
Cisplatin	45 mg/m^2/d civi	d2–3
Q3w		

Reference: Moertel CG et al. Cancer 1991;68:227.

Sunitinib

Sunitinib	37.5 mg P.O.	qd

Reference: Raymond E et al. NEJM 2011;364:6.

Sunitinib	50 mg P.O.	qd for 4 weeks
Repeat after 2 weeks rest. May escalate to 62.5 mg and 75 mg.		
Continue treat until disease progression or unacceptable toxicity		

Reference: Kulke MH et al. J Clin Oncol 2008;26:3403.

Everolimus + Octreotide LAR

Everolimus	10 mg P.O. od
Octreotide LAR	30 mg od q4w

Reference: Pavel ME et al. Lancet 2011;378(9808):2005.

Everolimus	10 mg P.O. od

Reference: Yao JC et al. NEJM 2011;364(6):514.

Everolimus	5 or 10 mg P.O. od
Octreotide LAR	30 mg od q4w

Reference: Yao JC et al. J Clin Oncol 2008;26:4311.

Temozolomide

Temozolomide	200 mg/m^2/d P.O. x 5d	Q4w

Reference: Eklebad S et al. Clin Cancer Res 2007;13:2986.

Temozolomide + Thalidomide

Temozolomide	150 mg/m^2/d P.O. x 7d	every alternate week
Thalidomide	50 – 400 mg qd	

Reference: Kulke MH et al. J Clin Oncol 2006;24(3):401.

Temozolomide + Bevacizumab

Temozolomide	150 mg/m^2/d P.O. x 7d	every alternate week
Bevacizumab	5 mg/kg BW	every alternate week

Reference: Kulke MH et al. J Clin Oncol 2006;24(Jun 20 S):4044.

Capecitabine + Temozolomide

Capecitabine	750 mg/m^2 BD x d1–14
Temozolomide	200 mg/m^2 od P.O. x d10–14

Reference: Strosberg JR et al. Cancer 2011;117(2):268.

Etoposide + Doxorubicin + Cisplatin + Mitotane

Etoposide	100 mg/m^2/d civi	d5–7	
Doxorubicin	20 mg/2		d1 and 8
Cisplatin	40 mg/m^2/d civi	d1 & 9	
Q4w			
Mitotane	4 g/d P.O.		

Reference: Berruti A et al. Endocr related Cancer 2005;12(3):657.

PART - I
Solid Tumor

Cervical Cancer

CERVICAL CANCER

As per the NCI 12,170 new cases and 4,220 deaths from cervical (uterine cervix) cancer are estimated in the US in year 2012. The prognosis for patients with cervical cancer is markedly affected by the extent of disease at the time of diagnosis. A vast majority (>90%) of these cases can and should be detected early through the use of the Pap test and HPV testing. Among the major factors that influence prognosis are stage, volume and grade of tumor, histologic type, lymphatic spread, and vascular invasion.

More than 6 million women in the United States are estimated to have HPV infection, and proper interpretation of these data is important. Women with human immunodeficiency virus have more aggressive and advanced disease and a poorer prognosis. The major risk factor for development of preinvasive or invasive carcinoma of the cervix is HPV infection, which far outweighs other known risk factors such as high parity, increasing number of sexual partners, young age at first intercourse, low socioeconomic status, and positive smoking history.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
National Cancer Institute Workshop JAMA 262(7):931-4, (1989).
Schiffman MH et al. J Natl Cancer Inst 85(12):958-64, (1993).
Brisson J et al. Am J Epidemiol 140(8):700-10, (1994).

PRIMARY TUMOR (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	*	Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a**	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread

T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with ahorizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

**FIGO staging no longer includes Stage 0 (Tis)*
***All macroscopically visible lesions—even with superficial invasion—are T1b/IB.*

REGIONAL LYMPH NODES (N)

TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIB	Reginal lymph node metastasis

DISTANT METASTASIS (M)

TNM	FIGO	
M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular or mediastinal lymph nodes, lung, liver, or bone)

STAGE GROUPING

GROUP	T	N	M
Stage 0*	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1–3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

**FIGO no longer includes Stage 0 (Tis)*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Concurrent Chemoradiation
- Neoadjuvant Chemotherapy
- Chemotherapy for stage IVB (metastatic) cancer

CONCURRENT CHEMORADIATION

Cisplatin + RT

Cisplatin	40 mg/m^2 IV	qw
Concurrent radiotherapy	55–75 Gy	

Reference:
Rose PG et al. J Clin Oncol 2007;25:2804.
Lanciano R et al. J Clin Oncol 2005;23:8289.
Rose PG et al. N Eng J Med 1999;340:1144.
Keys HM et al. N Eng J Med 1999;340:1154.

Cisplatin + 5-FU + RT

Cisplatin	70 mg/m^2 IV	d1 q3w x 2 cycles
5-FU	1000 mg/m^2/d civi	d1–4 q3w x 2 cycles
Concurrent radiotherapy	49.3 Gy	
Followed by		
Cisplatin	70 mg/m^2 IV	d1 q3w x 2 more cycles
5-FU	1000 mg/m^2/d civi	d1–4 q3w x 2 more cycles

Reference:
Peters, WA III et al. J Clin Oncol 2000;18:1606.
Kim JS et al. Int J Rad Oncol Bio Phy 2003;55:1247.
Chung YL et al. Gynec Oncol 2005;97:126.

NEOADJUVANT CHEMOTHERAPY

Cisplatin + Paclitaxel

Cisplatin	60 mg/m^2 IV	d1
Paclitaxel	60 mg/m^2 IV	d1
Every 10 days x 3 cycles		

Reference: Park DC et al. Gynecol Oncol 2004;92:59.

Cisplatin-Ifosfamide

Cisplatin	20 mg/m^2 IV 1 hour infusion	day 1–5
Ifosfamide	1,200 mg/m^2 IV 30 min infusion	day 1–5

Note: To be repeated every 3 weeks (neoadjuvant 2 cycles).
Refirence: De Jonge et al. IntJ Gynecol Cancer 7:158-162, (1997).

CHEMOTHERAPY FOR STAGE IVB (METASTATIC) CANCER
FIRST-LINE COMBINATION THERAPY

Cisplatin + Paclitaxel

Cisplatin	50 mg/m^2 IV	d1
Paclitaxel	135 mg/m^2 IV	d1
Q3w		

Reference:
Monk BJ et al. J Clin Oncol 2009;27:4649.
Moore, DH et al. J Clin Oncol 2004;22:3113.

Carboplatin-Paclitaxel (Advanced or recurrent cervical carcinoma)

Carboplatin	AUC-5–6 IV 30 min infusion	day 1
Paclitaxel	155–175 mg/m^2 IV 3 hour infusion	day 1

Note: To be repeated every 4 weeks.
Reference:
Tinker AV et al. Gynecol Oncol. 2005 Jul;98(1):54-8
Moore KN et al. Gynecol Oncol. 2007;105:299
Pectasides D et al. Int J Gynecol Cancer 2009;19:777
Saito I et al. Jpn J Clin Oncol 2010;40:90

Cisplatin + Topotecan

Cisplatin	50 mg/m^2 IV	d1
Topotecan	0.75 mg/m^2/d IV	d1–3
Q3w x 6 cycles		

Note: Approved by FDA on 6/14/2006
Reference:
Monk BJ et al. J Clin Oncol 2009;27:4649.
Long HJ 3rd et al. J Clin Oncol 2005;23:4626.

Cisplatin + Gemcitabine

Regimen # 1

Cisplatin	50 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1, 8
Q3w x 6 cycles		

Reference:
Monk BJ et al. J Clin Oncol 2009;27:4649.
Duenas-Gonzalez A et al. J Clin Oncol 2009;27 (S); Abstract CRA5507

Regimen # 2

Cisplatin	30 mg/m^2 IV	day 1, 8
Gemcitabine	800 mg/m^2 IV	day 1, 8

Note: To be repeated every 4 weeks.
Reference: Brewer CA et al. Gynecol Oncol. 2006 Feb;100(2):385-8.

Cisplatin + Vinorelbine

Regimen # 1		
Cisplatin	50 mg/m^2 IV	d1
Vinorelbine	30 mg/m^2 IV	d1, 8
Q3w x 6 cycles		

Reference: Monk BJ et al. J Clin Oncol 2009;27:4649.

Regimen # 2		
Cisplatin	80 mg/m^2 IV	day 1
Vinorelbine	25 mg/m^2 IV	day 1, 8
To be repeated every 3 weeks.		

Reference: Sandro Pignata et al. J Clin OncoI 17(3):756-760, (1999).

Carboplatin + Docetaxel

Carboplatin	AUC 6 IV	d1
Docetaxel	60 mg/m^2 IV	d1
Q3w		

Reference: Nagao, S et al. Gynecol Oncol 2005;96:805.

Cisplatin-Ifosfamide

Cisplatin	50 mg/m^2 IV	day 1
Ifosfamide	5,000 mg/m^2 IV 24 hour infusion	day 1
(with mesna)		

Note: To be repeated every 3 weeks for 6 cycles.
Reference: Bloss JP et al. J Clin OncoI 20(7):1832-7, (2002).

Tirapazamine-Cisplatin (Advanced or recurrent cervical cancer)

Tirapazamine	330 mg/m^2 IV, 2 hour infusion	day 1
1 hr after Tirapazamine		
Cisplatin	75 mg/m^2 IV, 1 hour infusion	day 1

Note: To be repeated every 3 weeks for 8 cycles.
Reference: Maluf FC et al. Int J Gynecol Cancer. 2006 May-Jun;16(3):1165-71

Cisplatin-Fluorouracil-Hydroxyurea

Fluorouracil	4 g/m^2 IV, 96 hour infusion	day 1, 29
Cisplatin	50 mg/m^2 IV	day 1, 29
Hydoxyurea	2 g/m^2 P.O. twice weekly	6 Weeks

Reference: Rose PG et al. N Engl J Med. 1999 Apr 15;340(15):1144-53

Mitomycin-Ifosfamide-Cisplatin (Recurrent, persistent or disseminated cervical cancer)

Mitomycin	6 mg/m^2 IV	day 1
Cisplatin	50 mg/m^2 IV	day 1
Ifosfamide	3 g/m^2 IV	day 1
To be repeated every 3 weeks.		

Reference: Serkies K et al. Int J Gynecol Cancer. 2006 May-Jun;16(3):1152-6.

POSSIBLE 1ST LINE SINGLE AGENT THERAPY

Cisplatin

Cisplatin	50 mg/m^2 IV
Q3w	

Reference:
Moore, DH et al. J Clin Oncol 2004;22:3113.
Bonomi, P et al. J Clin Oncol 1985;3:1079.
Pectasides D et al. Cancer Treatment Rev 2008;34:603.

Carboplatin

Carboplatin	AUC 6 IV	d1
Q3w		

Reference: Weiss GR et al. Gynecol Oncol 1990;39:332.

Paclitaxel

Paclitaxel	110 – 200 mg/m^2 IV
Q3w	

Reference:
McGuire, WP et al. J Clin Oncol 1996;14:792.
Curtin, JP et al. J Clin Oncol 2001;19:1275.
Kudelka AP et al. Anticancer Drugs 1997;8:657.

SECOND-LINE THERAPY

Bevacizumab

Bevacizumab	15 mg/kg IV	Q3w

Reference: Monk BJ et al. J Clin Oncol 2009;27:1069.

Docetaxel

Docetaxel	60 mg/m^2 IV	d1
Q3w		

Reference: Garcia AA et al. Am J Clin Oncol 2007;30:428.

5-Fluorouracil

Leucovorin	200 mg/m^2 IV bolus
Fluorouracil	370 mg/m^2 IV bolus
for 5 days	Q4w for 1st 2 courses Subsequent courses Q5w

Reference: Look KY et al. Am J Clin Oncol 1996;19(5):439.

Gemcitabine
Vinorelbine

Vinorelbine	30 mg/m^2 IV
Qw	

Reference: Morris, M et al. J Clin Oncol 1998;16:1094.

Topotecan

Topotecan	1.5 mg/m^2/d IV	d1-5
Q3-4ws		

Reference:
Muderspach, LI et al. Gynecol Oncol 2001;81:213.
Bookman, MA et al. Gynecol Oncol 2000;77:446.

PART - I
Solid Tumor

Colorectal Cancer

COLORECTAL CANCER

Worldwide, colorectal cancer is the third most common form of cancer. In 2000, colorectal cancer accounted for 9.4% of the world's new cancers, with 945,000 cases diagnosed, and 7.9% of the world's cancer deaths, with 492,000 deaths. Colorectal cancer affects men and women almost equally. Among all racial groups in the United States, African Americans have the highest sporadic colorectal cancer incidence and mortality rates. As per the NCI data 103,170 new cases of colon and 40,290 of rectal with 51,690 deaths are estimated in US in year 2012. Adenocarcinomas account for the vast majority of rectal tumors in the United States. Rare tumors, including carcinoid tumors, lymphomas, and neuroendocrine tumors, account for less than 3% of colorectal tumors.

Cancer of the colon is a highly treatable and often curable disease when localized to the bowel. Surgery is the primary form of treatment and results in cure in approximately 50% of the patients. Recurrence following surgery is a major problem and is often the ultimate cause of death. The prognosis is clearly related to the degree of penetration of tumor through the bowel wall, the presence or absence of nodal involvement, and the presence or absence of distant metastases. These three characteristics form the basis for all staging systems developed for CRC. Bowel obstruction and perforation are the indicators of poor prognosis. Elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance. The American Joint Committee on Cancer and a National Cancer Institute-sponsored panel recommended at least 12 lymph nodes to be examined in patients to confirm the absence of nodal involvement by tumor.

Treatment decisions depend on factors such as physician and patient preferences and the stage of the disease rather than the age of the patient. Groups that have a high incidence include those with hereditary conditions, such as familial polyposis, HNPCC or Lynch syndrome variants I and II, and a personal history of ulcerative colitis or Crohn's colitis together thay account for 10–15% Of CRC. More common conditions with an increased risk include a personal history of colorectal cancer or adenomas; first-degree family history of colorectal cancer or adenomas and a personal history of ovarian, endometrial, or breast cancer. These high-risk groups account for only 23% of all colorectal cancers.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Parkin DM: Lancet Oncol 2(9):533-43, (2001).
Albano JD et al. J Natl Cancer Inst 99(18):1384-94, (2007).
Kauh J et al. Curr Probl Cancer 31(3):123-33, (2007 May-Jun).

Kang H et al. Int J Colorectal Dis 22(2):183-9, (2007).
Steinberg SM et al. Cancer 57(9):1866-70, (1986).
Filella X et al. Ann Surg 216(1):55-9, (1992).
AJCC Cancer Staging Manual. 6th ed. NY: Springer, 2002, pp. 113-124.
Compton CC, Greene FL: CA Cancer J Clin 54(6):295-308, (2004 Nov-Dec).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria*
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum**
T4b	Tumor directly invades or is adherent to other organs or structures^,**

**Note: Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.*

^Note: Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retro-peritoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix or vagina).

***Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2 – 3 regional lymph nodes

N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4 to 6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes

Note: A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2) or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, non-regional node).
M1b	Metastases in more than one organ/site or the peritoneum.

DUKES' STAGING

A	Confined to mucosa
B	Varies by system
C	Positive lymph nodes
D	Distant metastases (Turnbull system only)

GUIDELINES FOR DUKES' AND SUMMARY STAGINGS FOR COLON CANCER:

- Invasion of serosa. Serosa, or outside layer of the colon is only one cell thick, so involvement of serosa means that cancer is through the serosa and can spread.
- Serosa is also called the visceral layer of peritoneum, so serosal invasion is considered regional stage unless there is definite evidence of distant spread.
- Muscular layer is sometimes called the bowel wall, but in colon the subserosa and serosa lay beyond the muscular layer.

- Be mindful of words "extension through bowel wall" and "penetration of entire muscularis": both cases are still considered localized.
- Find out from your pathologist whether he means "muscularis" or "all layers of bowel" when he refers to "wall."
- It is important to find out which version of Dukes staging is being referred to, and to use that version consistently when doing studies.

STAGE GROUPING

GROUP	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

**Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.*
Reference:
AJCC, 2010, 7th edition
SEER Training Modules: National Cancer Institute. Available at: http://training.seer.cancer.gov/staging/systems/schemes/duke.html

CHEMOTHERAPY REGIMENS

- Colon Cancer
  - Adjuvant chemotherapy
  - Chemotherapy for stage IV (metastatic) cancer
- Rectal Cancer
  - Neoadjuvant chemoradiation
  - Adjuvant chemoradiation

COLON CANCER ADJUVANT CHEMOTHERAPY

Modified FOLFOX6

Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU d1	
5-FU	400 mg/m^2 IV bolus d1 followed by 1200 mg/m^2 IV over 46 hrs	
Oxaliplatin	85 mg/m^2 IV d1	
Q2w		

Reference: Cassidy J et al. J Clin Oncol 2008;26:2006

FLOX

5-FU	500 mg/m^2 IV bolus 1 hr after start of leucovorin qw x 6 weeks	
	every 8 weeks for 3 cycles	
Leucovorin	500 mg/m^2 IV over 2 hrs qw x 6 weeks every 8 weeks for 3 cycles	
Oxaliplatin	85 mg/m^2 IV over 2 hrs before 5-FU and Leucovorin week 1, 3, 5	
	of each 8-week cycle for 3 cycles	

Reference:
Wolmark N et al. 2008 ASCO annual meeting. LBA4005.
Kuebler JP et al. J Clin Oncol 2007;25:2198.

Capecitabine

Capecitabine	1250 mg/m^2 P.O.	b.i.d. x 14 days
Q3w x 8 cycles		

Reference: Twelves C et al. N Engl J Med 2005;352:2696.

XELOX

Capecitabine	1000 mg/m^2 P.O.	b.i.d. x 14 days
Oxaliplatin	130 mg/m^2 IV over 2 hrs	d1
Q3w x 8 cycles		

Reference: Schmoll H et al. J Clin Oncol 2007;25:102.

5-FU + LV (Roswell park regimen)

5-FU	500 mg/m^2 IV bolus 1 h after the start of leucovorin
Leucovorin	500 mg/m^2 IV over 2 hrs
Qw x 6 wks every 8 wks for 3 - 4 cycles	

Reference:
Lembersky BC et al. J Clin Oncol 2006;24:2059.
Haller, DG et al. J Clin Oncol 2005;23:8671.

5-FU + LV (Mayo clinic regimen)

5-FU	370 - 425 mg/m^2/d IV bolus	d1 - 5
Leucovorin	20 - 25 mg/m^2/d IV bolus	d1 - 5
Q4w x 6 cycles		

Reference:
QUASAR Collaborative Group. Lancet 2007;370:2020.
Haller, DG et al. J Clin Oncol 2005;23:8671.
O'Connell, MJ et al. J Clin Oncol 1997;15:246.

Uracil-Tegafur + Leucovorin

Uracil-Tegafur	100 mg/m^2 P.O. every 8 hours x 4 weeks
Leucovorin	30 mg P.O. every 8 hours x 4 weeks
Avoid food 1 hour before and 1 hour after each dose	
Q5w x 5 cycles	

Reference: Lembersky BC et al. J Clin Oncol 2006;24:2059.

FOLFOX4

Leucovorin	200 mg/m^2 IV over 2 hrs before 5-FU, d1 and 2
5-FU	400 mg/m^2 IV bolus and then 600 mg/m^2 IV over 22 hrs, d1 and d2
Oxaliplatin	85 mg/m^2 IV d1
Q2w x 12 cycles	

Reference:
de Gramont A et al. 2007 ASCO annual meeting. Abstract 4007.
Goldberg RM et al. J Clin Oncol 2006;24:4085.
Andre, T et al. N Engl J Med 2004;350:2343.

FOLFOX6

Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU d1
5-FU	400 mg/m^2 IV bolus d1 followed by 2400 mg/m^2 IV over 46 hrs
Oxaliplatin	100 mg/m^2 in 500 ml dextrose 5% IV over 2 hours d1
Q2w x 12 cycles	

Reference:
Tournigand, C et al. J Clin Oncol 2004;22:229.
Chemotherapy for stage IV (metastatic) cancer

Modified FOLFOX6

Oxaliplatin	85 mg/m^2 IV d1	
Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU, d1	
5-FU	400 mg/m^2 IV bolus d1 followed by 2400 mg/m^2 IV over 46–48 hrs IV continuous infusion	
Q2w until progression or unacceptable toxicity		

Reference:
Cassidy J et al. J Clin Oncol 2008;26:2006.
Cheeseman SL et al. Br J Cancer 2002;87:393.

Modified FOLFOX6 + Bevacizumab

Oxaliplatin	85 mg/m^2 IV d1
Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU, d1
5-FU	400 mg/m^2 IV bolus d1 followed by 2400 mg/m^2 IV over 46–48 hrs
Bevacizumab	5 mg/kg IV d1
Q2w until progression or unacceptable toxicity	

Reference:
Cheeseman SL et al. Br J Cancer 2002;87:393.
Emmanoulides C et al. BMC Cancer 2007;7:91.
Hochster, HS et al. J Clin Oncol 2008;26:3523.

Modified FOLFOX6 + Panitumumab

Oxaliplatin	85 mg/m^2 IV d1
Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU, d1
5-FU	400 mg/m^2 IV bolus d1 followed by 2400 mg/m^2 IV over 46–48 hrs
Panitumumab	6 mg/kg IV over 60 min d1
Q2w	

Reference:
Cheeseman SL et al. Br J Cancer 2002;87:393.
Douillard JY et al. J Clin Oncol 2010;28:4697.

Capecitabine

Capecitabine	850–1250 mg/m^2 P.O.	b.i.d. x 14 days
Q3w		

Reference: VanCutsem E et al. J Clin Oncol 2001;19:4097.

Capecitabine + Oxaliplatin (CAPOX, XELOX)

Regimen 1

Capecitabine	850–1000 mg/m^2 P.O.	b.i.d. d1–14
Oxaliplatin	130 mg/m^2 IV over 2 hours	d1
Q3w until progression or severe toxicity		

Reference:
Cassidy J et al. J Clin Oncol 2008;26:2006.
Diaz-Rubio E et al. J Clin Oncol 2007;25:4224.
Hochster, HS et al. J Clin Oncol 2008;26:3523.

Regimen 2		
Capecitabine	1000 mg/m^2 P.O.	b.i.d. d1–14
Oxaliplatin	70 mg/m^2 IV over 2 hours	d1, 8
Q3w until progression or severe toxicity		
After the 6th cycle, oxaliplatin is administrated only on d1		

Reference:
Mayer RJ et al. J Clin Oncol 2007;25:4165.
Porschen R et al. J Clin Oncol 2007;25:4217.

Regimen 3		
Capecitabine	1750 mg/m^2 P.O.	b.i.d. d1–7 and 14–21
Oxaliplatin	85 mg/m^2 IV over 2 hours	d1 and 14
Q4w		

Reference: Scheithauer W et al. J Clin Oncol 2003;21:1307.

Capecitabine + Bevacizumab

Capecitabine	850–1250 mg/m^2 P.O.	b.i.d. x 14 days
Repeat every 3 weeks		
Bevacizumab	5 mg/kg IV over 30–90 min d1 weekly	
Q3w		

Reference: VanCutsem E et al. J Clin Oncol 2001;19:4097.

FOLFIRI

Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU	d1
5-FU	400 mg/m^2 IV bolus d1, and then 2400 mg/m^2 IV over 46 hrs	
Irinotecan	180 mg/m^2 IV over 90 min	d1
Q2w		

Reference:
Fuchs CS et al. J Clin Oncol 2007;25:4779.
Van Cutsem E et al. 2007 ASCO annual meeting. Abstract 4000.
Andre T et al. Eur J Cancer 1999;35(9):1343-7.

FOLFIRI + Bevacizumab

Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU	d1
5-FU	400 mg/m^2 IV bolus d1, and then 2400 mg/m^2 IV over 46 hrs	
Irinotecan	180 mg/m^2 IV over 90 min	d1
Bevacizumab	5 mg/kg IV d1	
Q2w		

Reference: Fuchs CS et al. J Clin Oncol 2007;25:4779.

FOLFIRI + Cetuximab (for patients with wild-type KRAS)

Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU d1 q2w
5-FU	400 mg/m^2 IV bolus d1, and then 2400 mg/m^2 IV over 46 hrs q2w
Irinotecan	180 mg/m^2 IV d1 q2w
Cetuximab	400 mg/m^2 IV loading d1, and then 250 mg/m^2 IV qw
Cetuximab	500 mg/m^2 IV over 2 hrs d1 q2w

Reference:
Van Cutsem E et al. 2008 ASCO annual meeting. Abstract 2.
Van Cutsem E et al. 2007 ASCO annual meeting. Abstract 4000.
Cunningham D et al. NEJM 2004;351:337.
Martin-Martorell P et al. Br J Cancer 2008;99:455.

FOLFIRI + Panitumumab

Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU d1
5-FU	400 mg/m^2 IV bolus d1, and then 2400 mg/m^2 IV over 46 hrs, continuous infusion
Irinotecan	180 mg/m^2 IV over 30–90 min d1
Panitumumab	6 mg/kg IV over 60 min d1
Q2w	

Reference: Peeters M et al. J Clin Oncol 2010;28:4706.

Bolus/infusional 5-FU + LV (Roswell park regimen)

Leucovorin	500 mg/m^2 IV over 2 hrs, D1, 8, 15, 22, 29 and 36
5-FU	500 mg/m^2 IV bolus 1 h after the start of leucovorin, D1, 8, 15, 22, 29 and 36
Repeat every 8 wks	

Reference: Wolmark N et al. J Clin Oncol 1993;11:1879.

Simplified biweekly infusional 5-FU + LV (sLV5FU2)

Leucovorin	400 mg/m^2 IV over 2 hrs, D1, followed by
5-FU	400 mg/m^2 IV and then 1200 mg/m^2 x 2 days (total 2400 mg/m^2 over 46–48 hrs) continuous infusion
Repeat every 2 weeks	

Reference: Andre T et al. Eur J Cancer 1993;35(9):1343.

Weekly	
Leucovorin	20 mg/m^2 IV over 2 hrs, D1, followed by
5-FU	500 mg/m^2 IV bolus injection 1 h after start of leucovorin. Repeat weekly.

Reference: Jager E et al. J Clin Oncol 1996;14:2274.

5-FU	2600 mg/m^2 by 24 h infusion plus leucovorin 500 mg/m^2
Repeat every week	

Reference: Douillard JY et al. Lancet 2000;355:1041.

Irinotecan

Regimen 1 (qw)	
Irinotecan	125 mg/m^2 IV qw
Regimen 2 (q3w)	
Irinotecan	350 mg/m^2, or 300 mg/m^2 if >70 years of age, ECOG performance status 2 or prior pelvic radiation, IV q3w

Reference:
Cunningham D et al. Lancet 1998;352:1413.
Fuchs CS et al. J Clin Oncol 2003;21:807.

IROX

Regimen 1 (qw)	
Oxaliplatin	85 mg/m^2 IV over 2 hrs d1 followed by
Irinotecan	200 mg/m^2 over 30 or 90 minutes IV
Q3w	

Reference: Haller DG et al. J Clin Oncol 2008;26:4544.

FOLFOXIRI

Irinotecan	165 mg/m^2 IV over 1 h	d1
Oxaliplatin	85 mg/m^2 IV over 2 hrs	d1
Leucovorin	200 mg/m^2 IV over 2 hrs	d1
5-FU	3200 mg/m^2 civi over 48 hrs	d1–2
Q2w x 12 cycles		

Reference: Falcone A et al. J Clin Oncol 2007;25:1670.

Irinotecan	125 mg/m^2 IV over 30–90 min	d1, 8
Q3w		

Reference:
Cunnigham D et al. Lancet 1998;352:1413.
Fuchs S et al. J Clin Oncol 2003;21:807.

Irinotecan	125 mg/m^2 IV over 30–90 min	d1, 8
Q3w		

Cetuximab (for patients with wild-type KRAS)

Cetuximab	400 mg/m^2 IV loading, then 250 mg/m^2 IV qw till disease progression
Premedication	Diphenhydramine (Benadryl) 50 mg IV 30–60 min before cetuximab

Note: Approved by FDA on 10/2/07.
Reference:
Jonker DJ et al. N Engl J Med 2007;357-2040.
Lenz HJ et al. J Clin Oncol 2006;24:4914.
Cunningham, D et al. N Engl J Med 2004;351:337.

Cetuximab-Irinotecan (for patients with wild-type KRAS)

Cetuximab	400 mg/m^2 IV loading over 2 hours, then 250 mg/m^2 IV over 1 hour qw
or Cetuximab	500 mg/m^2 IV q2w

Reference: Martin-Martorell P et al. Br J Cancer 2008;99:455.

Irinotecan	350 mg/m^2 IV over 90 min q3w or 180 mg/m^2 IV q2w or 125 mg/m^2 IV d1, 8 q3w
x 4 wks every 6 wks	
Continue treatment until disease progression or unacceptable toxicity	

Reference:
Sobrero AF et al. J Clin Oncol 2008;26:2311.
Cunningham, D et al. N Engl J Med 2004;351:337.

Panitumumab (KRAS wild-type gene only)

Panitumumab	6 mg/kg IV over 60 min	q2w

Note: FDA approved on 9/27/06.
Reference: Cutsem EV et al. J Clin Oncol 2007;25:1658.

FOLFOX4

Leucovorin	200 mg/m^2 IV over 2 hrs before 5-FU, d1 and 2
5-FU	400 mg/m^2 IV bolus and then 600 mg/m^2 IV over 22 hrs, d1 and d2
Oxaliplatin	85 mg/m^2 IV d1
Q2w	

Reference:
Nordlinger B et al. 2007 ASCO annual meeting. LBA5.
Goldberg RM et al. J Clin Oncol 2006;24:4085.
Goldberg RM et al. J Clin Oncol 2006;24:3347.
Goldberg, RM et al. J Clin Oncol 2004;22:23.

FUFOX

Oxaliplatin	50 mg/m^2 IV over 2 hours followed by
Leucovorin	500 mg/m^2 IV over 2 hours followed by
5-FU	2000 mg/m^2 IV over 22 hours
D1, 8, 15 and 22	
Q5w until progression or severe toxicity	
After the 4th cycle, oxaliplatin is administrated only on d1 and 15	

Reference: Porschen R et al. J Clin Oncol 2007;25:4217.

FUOX

5-FU	2250 mg/m^2 IV over 48 hours d1, 8, 15, 22, 29, 36
Oxaliplatin	85 mg/m^2 IV over 2 hours d1, 15, 29
Q6w until progression or severe toxicity	

Reference: Diaz-Rubio E et al. J Clin Oncol 2007;25:4224.

COI

Capecitabine	1000 mg/m^2 P.O.	b.i.d. d2–6
Oxaliplatin	85 mg/m^2 IV	d2
Irinotecan	180 mg/m^2 IV	d1
Q2w		

Reference: Bajetta E et al. Ann Oncol 2007;18:1810.

FOLFOX4 + Bevacizumab

Leucovorin	200 mg/m^2 IV over 2 hrs before 5-FU, d1 and 2
5-FU	400 mg/m^2 IV bolus and then 600 mg/m^2 IV over 22 hrs, d1 and d2
Oxaliplatin	85 mg/m^2 IV over 2 hrs d1
Bevacizumab	5–10 mg/kg IV over 30–90 min d1
Q2w	

Reference:
Saltz LB et al. 2007 Gastrointestinal Cancers Symposium. Abstract 238.
Giantonio, BJ et al. J Clin Oncol 2007;25:1539.

FOLFOX4 + Cetuximab (for patients with wild-type KRAS)

Leucovorin	200 mg/m^2 IV over 2 hrs before 5-FU, d1 and 2 q2w
5-FU	400 mg/m^2 IV bolus and then 600 mg/m^2 IV over 22 hrs, d1 and d2 q2w
Oxaliplatin	85 mg/m^2 IV over 2 hrs d1q2w
Cetuximab	400 mg/m^2 IV loading over 2 hours d1, and then 250 mg/m^2 IV over 1 hour qw
Until progression	

Reference:
Bokemeyer C et al. 2008 ASCO annual meeting. Abstract 4000.
Tabernero J et al. J Clin Oncol 2007;25:5225.
Bokemeyer C et al. 2007 ASCO annual meeting. Abstract 4035.

FOLFOX6 + Bevacizumab

Leucovorin	400 mg/m^2 IV over 2 hrs before 5-FU d1
5-FU	400 mg/m^2 IV bolus d1 followed by 2400 mg/m^2 IV over 46 hrs
Oxaliplatin	100 mg/m^2 IV d1
Bevacizumab	5 mg/kg IV d1
Q2w	

Modified FOLFOX7 with intermittent Oxaliplatin + Bevacizumab

Leucovorin	200 mg/m^2 IV	d1
5-FU	2400 mg/m^2 IV over 46 hrs	
Oxaliplatin	85 mg/m^2 IV	d1
Bevacizumab	5 mg/kg IV	d1
Q2w x 8 cycles		
Alternating with		
Leucovorin	200 mg/m^2 IV	d1
5-FU	2400 mg/m^2 IV over 46 hrs	
Bevacizumab	5 mg/kg IV	d1
Q2w x 8 cycles		

Reference: Grothey A et al. 2008 ASCO annual meeting. Abstract 4010.

IFL + Bevacizumab

Leucovorin	20 mg/m^2 IV bolus qw x 4 wks every 6 wks
5-FU	500 mg/m^2 IV bolus qw x 4 wks every 6 wks
Irinotecan	125 mg/m^2 IV qw x 4 wks every 6 wks
Bevacizumab	5 mg/kg IV q2w

Reference: Hurwitz, H et al. N Engl J Med 2004;350:2335.

LV + 5-FU + Irinotecan + Bevacizumab

Leucovorin	200 mg/m^2 IV over 2 hrs before 5-FU, d1 and 2
5-FU	400 mg/m^2 IV bolus and then 600 mg/m^2 IV over 22 hrs, d1 and 2
Irinotecan	180 mg/m^2 IV d1
Bevacizumab	5 mg/kg IV d1
Q2w	

XELIRI + Bevacizumab

Capecitabine	1000 mg/m^2 (750 mg/m^2 for pts >65) P.O. b.i.d. x 14 days q3w
Irinotecan	250 mg/m^2 (200 mg/m^2 for pts >65) IV d1 q3w
Bevacizumab	7.5 mg/kg IV d1 q3w

Reference: Patt, YZ et al. 2004 ASCO annual meeting. Abstract 3602.

CapIri

Capecitabine	1000 mg/m^2 P.O.	b.i.d. x 14 days
Irinotecan	100 mg/m^2 IV	d1, 8
Q22d		

Reference: Grothey A, et al. 2004 ASCO annual meeting. Abstract 3534.

XELOX + Bevacizumab

Oxaliplatin	130 mg/m^2 IV over 2 hours	d1
Capecitabine	1000–850 mg/m^2 P.O.	b.i.d. d1–14
Bevacizumab	7.5 mg/kg IV over 30–90 min	d1
Q3w until progression or unacceptable toxicity		

Reference:
Punt CJ et al. 2008 ASCO annual meeting. LBA4011.
Saltz LB et al. J Clin Oncol 2008;26:2013.
Hochster, HS et al. J Clin Oncol 2008;26:3523.

5-FU + LV + Bevacizumab (Roswell park regimen)

5-FU	500 mg/m^2 IV bolus qw x 6 wks every 8 wks x 6 cycles
Leucovorin	500 mg/m^2 IV over 2 hrs qw x 6 wks every 8 wks x 6 cycles
Bevacizumab	5 mg/kg IV over 30–90 min q2w x 48 weeks

Reference: Kabbinavar, F et al. J Clin Oncol 2003;21:60.

5-FU + LV + Bevacizumab (Mayo clinic regimen)

5-FU	425 mg/m^2/d IV bolus	d1–5 q4w
Leucovorin	20 mg/m^2/d IV bolus	d1–5 q4w
Bevacizumab	5 mg/kg IV	q2w

Capecitabine

Capecitabine	1000–1250 mg/m^2 P.O.	b.i.d. x 14 days q3w
till disease progression		

Reference:
Van Cutsem, E et al. J Clin Oncol 2001;19:4097.
Hoff, PM et al. J Clin Oncol 2001;19:2282.

Uracil-Tegafur + Leucovorin

Uracil-Tegafur	100 mg/m^2 P.O. every 8 hours x 4 weeks
Leucovorin	30 mg P.O. every 8 hours x 4 weeks
Avoid food 1 hour before and 1 hour after each dose	
Q5w until disease progression or unacceptable toxicity	

Reference: Hochster HS et al. J Clin Oncol 2007;25:5397.

CBI (for patients with wild-type KRAS)

Cetuximab	400 mg/m^2 IV loading over 2 hours, then 250 mg/m^2 IV qw
Bevacizumab	5 mg/kg IV q2w
Irinotecan	350 mg/m^2 IV q3w or 180 mg/m^2 IV q2w or 125 mg/m^2 IV qw x 4 wks every 6 wks

Reference: Saltz LB et al. J Clin Oncol 2007;25:4557.

CB (for patients with wild-type KRAS)

Cetuximab	400 mg/m^2 IV loading over 2 hours, then 250 mg/m^2 IV qw
Bevacizumab	5 mg/kg IV q2w

Reference: Saltz LB et al. J Clin Oncol 2007;25:4557.

RECTAL CANCER
NEOADJUVANT CHEMORADIATION

5-FU + RT

5-FU	1000 mg/m^2/d civi x 5 days during the first and fifth weeks of radiotherapy
Concurrent radiotherapy	50.4 Gy
Surgery in 4–6 weeks	
5-FU	500 mg/m^2/d civi d1–5 q4w x 4 cycles

Reference: Sauer, R et al. N Engl J Med 2004;351:1731.

5-FU + LV + RT

5-FU	350 mg/m^2/d IV over 20 min	d1–5
	during the first and fifth weeks of radiotherapy	
Leucovorin	20 mg/m^2/d IV	d1–5
	during the first and fifth weeks of radiotherapy	
Concurrent radiotherapy 45 Gy in 25 fractions of 1.8 Gy over 5 weeks		
Surgery in 3–10 weeks		
3–10 weeks after surgery:		
5-FU	350 mg/m^2/d IV	d1–5 q3w x 4 cycles
Leucovorin	20 mg/m^2/d IV	d1–5 q3w x 4 cycles

Reference:
Collette L et al. J Clin Oncol 2007;25:4379.
Minsky BD et al. J Clin Oncol 2007;25:4339.
Bosset JF et al. N Eng J Med 2006;355:1114.
Gerard J et al. J Clin Oncol 2006;24:4602.

Capecitabine + RT

Regimen 1

Capecitabine	825 mg/m^2 P.O.	b.i.d. x 7 days/week
Concurrent radiotherapy	50–52.5 Gy	
Surgery 4–8 weeks later		
Adjuvant capecitabine	1250 mg/m^2 P.O.	b.i.d. x 14 days q3w for 4 cycles

Reference:
Krishnan S et al. Int J Radiat Oncol Bio Phy 2006;66:762.
Kim JC et al. Int J Radiat Oncol Bio Phy 2006;63:346.
De Paoli A et al. Ann Oncol 2006;17:246.

Regimen 2

Capecitabine	900 mg/m^2 P.O.	b.i.d. x 5 days/week
Concurrent radiotherapy	1.8 Gy/d to a total of 45 Gy	
Surgery 4–6 weeks later		

Reference: Craven I et al. Br J Cancer 2007;97:1333.

XELOX + RT

Regimen 1		
Capecitabine	825 mg/m^2 P.O.	b.i.d. d1–14 and 22–35
Oxaliplatin	50 mg/m^2 IV over 2 hrs	d1, 8, 22, 29
Concurrent radiotherapy	1.8 Gy/d to a total of 50.4 Gy	
Surgery 4–6 weeks later		
4–6 weeks after surgery:		
Capecitabine	1000 mg/m^2 P.O.	b.i.d. d1–14
Oxaliplatin	130 mg/m^2 IV	d1
Q3w x 4 cycles		

Reference:
Rodel C et al. J Clin Oncol 2007;25:110.
Rodel C et al. J Clin Oncol 2003;21:3098.

Regimen 2		
Capecitabine	825 mg/m^2 P.O.	b.i.d. on each day of radiation
Oxaliplatin	50 mg/m^2 IV over 2 hrs	qw x 5 weeks
Concurrent radiotherapy	1.8 Gy/d to a total of 45 Gy over 5 weeks	
Surgery 6–8 weeks later		
Adjuvant 5-FU and leucovorin recommended if positive lymph node at surgery		

Reference: Machiels JP et al. Ann Oncol 2005;16:1898.

5-FU + Oxaliplatin + RT

5-FU	200 mg/m^2/d civi throughout radiotherapy	
Oxaliplatin	60 mg/m^2 IV over 1 hour qw	
Concurrent radiotherapy	1.8 Gy/d to a total of 45 Gy over 5 weeks	
Surgery 4–6 weeks later		
Adjuvant 5-FU and leucovorin recommended		

Reference:
Ryan DP et al. J Clin Oncol 2006;24:2557.
Aschele C et al. Ann Oncol 2005;16:1140.

ADJUVANT CHEMORADIATION/CONCURRENT CHEMOTHERAPY/RT

5-FU + RT

Regimen 1		
4–6 weeks after surgery		
5-FU	500 mg/m²/d IV bolus	d1–5 and d36–40
Beginning on day 64, concurrent radiotherapy 45 Gy		
and		
5-FU	225 mg/m²/d civi	throughout radiotherapy
then		
5-FU	450 mg/m²/d IV bolus	d134 to 138 and d169 to 173

Reference: O'Connell, MJ et al. N Engl J Med 1994;331:502.

Regimen 2		
20–70 days after surgery		
5-FU	500 mg/m²/d IV bolus	d1–5 and d29–33
Beginning on day 57, concurrent radiotherapy 45 Gy		
and		
5-FU	225 mg/m²/d civi	throughout radiotherapy
28 days after completion of chemoradiaton,		
5-FU	450 mg/m²/d IV bolus	d1–5 q4w x 2 cycles

Reference: Smalley SR et al. J Clin Oncol 2006;24:3542.

Regimen 3		
20–70 days after surgery		
5-FU	300 mg/m²/d civi	d1–42
2 weeks later, concurrent radiotherapy 45 Gy		
and		
5-FU	225 mg/m²/d civi throughout radiotherapy, starting on day 57	
28 days after completion of chemoradiaton,		
5-FU	300 mg/m²/d civi	for 56 days

Reference: Smalley SR et al. J Clin Oncol 2006;24:3542.

5-FU/Leucovorin + RT

5-FU	400 mg/m^2 IV bolus + leucovorin 20 mg/m^2 IV bolus x 4d during wk 1 and 5 of XRT	

Reference: Tepper JE et al. J Clin Oncol 2002;20:1744.

Capecitabine + RT

Capecitabine	825 mg/m^2 P.O.	b.i.d. x 5 or 7 days/week + XRT x 5 wks

Reference:
Roh MS et al. J Clin Oncol 2011;29 (S):3503.
Hofheinz R et al. J Clin Oncol 2011;29 (S):3504.

Postoperative adjuvant chemotherapy and Advanced or Metastatic disease

The chemotherapy regimes are the same as recommended for colon cancer

PART - I
Solid Tumor

Endometrial Cancer

ENDOMETRIAL CANCER

Cancer of the endometrium is the most common gynecologic malignancy and accounts for 6% of all cancers in women. It is a highly curable tumor. As per the NCI data, 47,130 new cases and 8,010 deaths are estimated in the US in year 2012.

The degree of tumor differentiation has an important impact on the natural history of this disease and on treatment selection. An increased incidence of endometrial cancer has been found in association with prolonged, unopposed estrogen exposure. In contrast, combined estrogen and progesterone therapy prevents the increase in risk of endometrial cancer associated with unopposed estrogen use.

The pattern of spread is partially dependent on the degree of cellular differentiation. Well-differentiated tumors tend to limit their spread to the surface of the endometrium; myometrial extension is less common. In patients with poorly differentiated tumors, myometrial invasion occurs much more frequently. Myometrial invasion is frequently a harbinger of lymph node involvement and distant metastases and is often independent of the degree of differentiation. Metastatic spread occurs in a characteristic pattern. Spread to the pelvic and para-aortic nodes is common. Distant metastases can occur and most commonly involve the lungs, inguinal and supraclavicular nodes, liver, bones, brain, and vagina.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Ziel HK, Finkle WD: N Engl J Med 293(23):1167-70, (1975).
Jick SS, Walker AM, Jick H: Epidemiology 4(1):20-4, (1993).
Jick SS: Epidemiology 4(4):384, (1993).
Bilezikian JP: J Womens Health 3(4):273-282, (1994).
Hendrickson M et al. Gynecol Oncol 13(3):373-92, (1982).
Nori D et al. Int J Radiat Oncol Biol Phys 13(4):489-97, (1987).

PRIMARY TUMOR (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	*	Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one-half of the myometrium

T1b	IB	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus**
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

**FIGO staging no longer includes Stage 0 (Tis)*
***Endocervical glandular involvement only should be considered as stage I and not Stage II.*

REGIONAL LYMPH NODES (N)

TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

DISTANT METASTASIS (M)

TNM	FIGO	
M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes intraperitoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)

STAGE GROUPING

GROUP	T	N	M
0*	Tis	N0	M0
I	T1	N0	M0
I	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC1	T1–T3	N1	M0
IIIC2	T1–T3	N2	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

**FIGO no longer includes Stage 0 (Tis)*
Carcinosarcomas should be staged as carcinoma.
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Adjuvant chemotherapy for stage III and IVA cancer
- Adjuvant chemotherapy for carcinosarcoma
- Hormonal therapy for stage IVB (metastatic) cancer
- Chemotherapy for stage IVB (metastatic) cancer
- Miscellaneous

ADJUVANT CHEMOTHERAPY FOR STAGE III AND IVA CANCER

Adriamycin + Cisplatin

Doxorubicin	60 mg/m^2 IV	q3w x 7 cycles
Cisplatin	50 mg/m^2 IV	q3w x 8 cycles

Reference: Randall, ME et al. J Clin Oncol 2006;24:36.

ADJUVANT CHEMOTHERAPY FOR CARCINOSARCOMA

CIM

Cisplatin	20 mg/m²/d IV	d1–4
Ifosfamide	1.5 g/m²/d IV	d1–4
Mesna		120 mg/m² IV loading dose
followed by		
	1.5 g/m²/d IV	d1–4
Q3w x 3 cycles		

Reference: Wolfson AH et al. 2006 ASCO annual meeting. Abstract 5001.

HORMONAL THERAPY FOR STAGE IVB (METASTATIC) CANCER

Megestrol acetate

Megestrol acetate	200 mg P.O.	qd

Reference: Thigpen, JT et al. J Clin Oncol 1999;17:1736.

Tamoxifen

Tamoxifen	20 mg P.O.	b.i.d.

Reference: Carlson, JA Jr et al. Am J Obstet Gynecol 1984;149:149.

Tamoxifen + Megestrol acetate

Megestrol acetate	80 mg P.O.	b.i.d. x q3w alternating with
Tamoxifen	20 mg P.O.	b.i.d. x q3w

Reference: Carlson, JA Jr et al. Am J Obstet Gynecol 1984;149:149.

Tamoxifen + Medroxyprogesterone acetate (MPA)

Tamoxifen	40 mg P.O.	daily
MPA	200 mg P.O. daily alternating weekly cycles	

Reference: Whitney CW et al. Am Gynecol Oncol. 2004 Jan;92(1):4-9.

Anastrozole

Anastrozole	1 mg/d P.O. x 28 d

Reference: Rose PG et al. Gynecol Oncol. 2000 Aug;78(2):212-6.

Arzoxifene

Arzoxifene	20 mg/d P.O. x 8 w

Reference: Rose PG et al. Gynecol Oncol. 2000 Aug;78(2):212-6.

CHEMOTHERAPY FOR STAGE IVB (METASTATIC) CANCER

Carboplatin

Carboplatin	400 mg/m^2 IV	
Q4w		

Reference: van Wijk, FH et al. Eur J Cancer 2003;39:78.

Paclitaxel

Paclitaxel	110–200 mg/m^2 IV	
Q3w		

Reference:
Ball, HG et al. Gynecol Oncol 1996;62:278.
Lissoni, A et al. Ann Oncol 1996;7:861.
Lincoln, S et al. Gynecol Oncol 2003;88:277.

Topotecan

Topotecan	1.2–1.5 mg/m^2/d IV	d1–5
Q3w		

Reference: Wadler, S et al. J Clin Oncol 2003;21:2110.

Dactinomycin

Dactinomycin	2 mg/m^2 IV	
Q4w		

Reference: Moore, DH et al. Gynecol Oncol 1999;75:473.

Carboplatin + Paclitaxel

Carboplatin	AUC 5–7 IV	d1
Paclitaxel	175 mg/m^2 IV	d1
Q4w		

Reference: Hoskins, PJ et al. J Clin Oncol 2001;19:4048.

Carboplatin + Paclitaxel

Carboplatin	AUC 5 IV	d1
Paclitaxel	175 mg/m^2 IV	d1
Q3w x 6–9 cycles		

Reference:
Pectasides D et al. Gynecol Oncol. 2008 May;109(2):250-4. Epub 2008 Mar 4.
Sorbe B et al. Int J Gynecol Cancer. 2008 Jul-Aug;18(4):803-8. Epub 2007 Oct 18.

Carboplatin + Weekly Paclitaxel

Carboplatin	AUC 2 IV	d1
Paclitaxel	80 mg/m^2 IV	d1, 8, 15 of 28d cycle

Reference: Secord AA et al. Int J Clin Oncol. 2007 Feb;12(1):31-6. Epub 2007 Feb 25.

Cisplatin + Paclitaxel

Cisplatin	75 mg/m^2 IV	d1
Paclitaxel	175 mg/m^2 IV	d1
Q3w		

Reference: Dimopoulos, MA et al. Gynecol Oncol 2000;78:52.

Doxorubicin + Cisplatin + Paclitaxel

Doxorubicin	45 mg/m^2 IV	d1
Cisplatin	50 mg/m^2 IV	d1
Palictaxel	160 mg/m^2 IV	d2
Filgrastim support		
Q3w		

Reference: Fleming, GF et al. J Clin Oncol 2004;22:2159.

Ifosfamide + Paclitaxel (for carcinosarcoma)

Ifosfamide	1.6 g/m^2/d (1.2 g/m^2/d if patients received prior radiation) IV	d1–3
Paclitaxel	135 mg/m^2 IV over 3 hrs	d1
Mesna	2 g IV over 12 hrs beginning 15 min before ifosfamide	
Filgrastim	5 mcg/kg S.C. d4 till ANC $>$2000	
Q3w x 8 cycles		

Reference: Homesley HD et al. J Clin Oncol 2007;25:526.

Cisplatin-Vinorelbine

Cisplatin	80 mg/m^2 IV	day I
Vinorelbine	25 mg/m^2 IV	day 1, 8
Repeat every 3 weeks for 3 cycles.		

Reference: Gebbia V et al. Ann Oncol12(6):767-72, (2001).

PEF (Rrecurrent or metastatic endometrial carcinoma)

Cisplatin	35 mg/m^2 IV	day 1–3
Etoposide	80 mg/m^2 IV	day 1–3
5-FU	600 mg/m^2 IV	day 1–3
Repeat every 1 month.		

Reference: Pierga JY et al. Gynecol OncoI60(1):59-63, (1996).

JMF-M (Rrecurrent or metastatic endometrial carcinoma)

Carboplatin	300 mg/m^2 IV	day1
Merhotrexate	30 mg/m^2 IV	day 1
5-FU	500 mg/m^2 IV	day 1
Medroxy progesterone acetate	300 mg P.O.	day 1
Repeat every 3 weeks for 2 cycles.		

Reference: Bafaloukos D et al. Oncology 56(3):198-201, (1999).

MISCELLANEOUS

Doxorubicin (Advanced and/or recurrent adenocarcinoma)

Doxorubicin	60 mg/m^2	day1
Repeat every 4 weeks		

Reference: Aapro MS et al. Annals of Oncology 14:441-448, (2003).

Pegylated Liposomal Doxorubicin

Doxorubicin	50 mg/m^2	day1
Repeat every 4 weeks		

Reference: Muggia FM et al. J Clin Oncol. 2002 May 1;20(9):2360-4.

Doxorubicin-Cispiatin (Advanced and/or recurrent adenocarcinoma)

Doxorubicin	60 mg/m^2 IV	day 1
Cisplatin	50 mg/m^2 IV	day 1
Repeat every 4 weeks.		

Reference: Aapro MS et al. Annals of Oncology 14:441-448, (2003).

Doxorubicin-Paclitaxel (Stage III, stage IV or recurrent endometrial carcinoma)

Doxorubicin	50 mg/m^2 IV (Bolus or brief infusion)	day 1
Paclitaxel with	150 mg/m^2 1V 24 hrs infusion	day 1
	(4 hr after the administration of doxorubicin)	
G-CSF support		
Repeat every 3 weeks.		

Reference: Fleming GF et al. Annals of Oncology 15:1173-1178, (2004).

Chemotherapy-Hormone Therapy (Sequential) (advanced or recurrent endometrial cancer)

Carboplatin	300 mg/m^2 IV	day 1
Repeat every 4 weeks for 6 cycles.		
Megesterol acetate	20 mg P.O. b.i.d.	day 1
Tamoxifen	80 mg P.O. b.i.d.	day 1
Repeat every 3 weeks.		

Reference: Pinelli DM et al. Gynecol OncoI60(3):462-7, (1996).

Bevacizumab

Bevacizumab	15 mg/kg IV	q3w

Reference: Aghajanian C et al. J Clin Oncol. 2011 Jun 1;29(16):2259-65. Epub 2011 May 2.

PART - I
Solid Tumor

Esophageal Cancer

ESOPHAGEAL CANCER

As per the NCI data, approximately 17,460 new cases and 15,070 estimated deaths from esophageal cancer are reported in United States in year 2012. The incidence has risen in recent decades, coinciding with a shift in histologic type and primary tumor location. Risk factors for squamous cell carcinoma of the esophagus have been identified (e.g., tobacco, alcohol, diet) but the risk factors associated with esophageal adenocarcinoma are less clear. The presence of Barrett's esophagus is associated with an increased risk of developing adenocarcinoma of the esophagus, and chronic reflux is considered the predominant cause of Barrett's metaplasia.

Esophageal cancer is a treatable disease, but it is rarely curable. The overall 5-year survival rate in patients ranges from 5% to 30%. The occasional patient with very early disease has a better chance of survival. Severe dysplasia in distal esophageal Barrett's mucosa often has in situ or even invasive cancer within the dysplastic area. Following resection, these patients usually have excellent prognoses.

Primary treatment modalities include surgery alone or chemotherapy with radiation therapy. Combined modality therapy (i.e., chemotherapy plus surgery, or chemotherapy and radiation therapy plus surgery) is under clinical evaluation. Effective palliation may be obtained in individual cases with various combinations of surgery, chemotherapy, radiation therapy, stents, photodynamic therapy, and endoscopic therapy with laser.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Devesa SS et al. Cancer 83(10):2049-53, (1998).
Blot WJ, McLaughlin JK: Semin Oncol 26 (5 Suppl 15):2-8, (1999).
Tietjen TG, Pasricha PJ, Kalloo AN: Gastrointest Endosc Clin N Am 4(4): 851-62, (1994).
Lightdale CJ et al. Gastrointest Endosc 42(6):507-12, (1995).
Kubba AK: Digestion 60(1):1-10, (1999 Jan-Feb).
Heier SK, Heier LM: Gastrointest Endosc Clin N Am 4(2):327-52, (1994).
Bourke MJ et al. Gastrointest Endosc 43(1):29-32, (1996).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia *
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

**High-grade dysplasia includes all non-invasive neoplastic epithelium that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastases involving 1 to 2 nodes
N2	Regional lymph node metastases involving 3 to 6 nodes
N3	Regional lymph node metastases involving 7 or more nodes

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

STAGE GROUPING: SQUAMOUS CELL CARCINOMA*

GROUP	T	N	M	Grade	Tumor Location**
0	Tis (HGD)	N0	M0	1	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

**or mixed histology including a squamous component or NOS*
***Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus*

STAGE GROUPING: ADENOCARCINOMA

GROUP	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Neoadjuvant chemoradiation followed by surgery for resectable cancer
- Perioperative chemotherapy for resectable adenocarcinoma of esophagogastric junction and lower esophagus
- Advanced esophageal cancer
- Chemotherapy for stage IV (metastatic) cancer

NEOADJUVANT CHEMORADIATION +/- SURGERY FOR RESECTABLE CANCER

5-FU + Cisplatin + RT

5-FU	800 mg/m^2/d civi	d1 - 5 starting on d1, 22, 43, 64, 92
Cisplatin	15 mg/m^2/d IV over 1 h	d1 - 5 starting on d1, 22, 43, 64, 92
Radiotherapy	2 Gy/d to 66 Gy	over 6.5 weeks

Reference: Bedenne L et al. J Clin Oncol 2007;25:1160.

5-FU + Cisplatin + RT + Surgery

5-FU	15 mg/kg/d IV over 16 hours	d1 - 5 week 1 and 6
Cisplatin	75 mg/m^2 IV over 8 hours	d7 week 1 and 6
Concurrent RT	2.67 Gy/d to 40 Gy	over 3 weeks
Surgery		

Reference: Walsh TN et al. N Eng J Med 1996;335:462.

5-FU + Cisplatin + Vinblastine + RT + Surgery

5-FU	300 mg/m^2/d civi	d1 - 21
Cisplatin	20 mg/m^2/d civi	d1 - 5 and 17 - 21
Vinblastine	1 mg/m^2/d IV bolus	d1 - 4 and 17 - 20
Concurrent radiotherapy 45 Gy		
Surgery		

Reference: Urba SG et al. J Clin Oncol 2001;19:305.

PERIOPERATIVE CHEMOTHERAPY FOR RESECTABLE ADENOCARCINOMA OF ESOPHAGOGASTRIC JUNCTION AND LOWER ESOPHAGUS

ECF + surgery + ECF

Epirubicin	50 mg/m^2 IV	d1
Cisplatin	60 mg/m^2 IV	d1
5-FU	200 mg/m^2/d civi	
Q3w x 3 cycles		
Surgery 3-6 weeks after chemotherapy		
6-12 weeks after surgery, repeat the chemotherapy:		
Epirubicin	50 mg/m^2 IV	d1
Cisplatin	60 mg/m^2 IV	d1
5-FU	200 mg/m^2/d civi	
Q3w x 3 cycles		

Reference: Cunningham D et al. N Eng J Med 2006;355:11.

FP + Surgery +/- FP

5-FU	800 mg/m^2/d civi	d1-5
Cisplatin	100 mg/m^2 IV over 1 h	d1 or d2
Q4w x 2-3 cycles		
Surgery 4-6 weeks after chemotherapy		
4-6 weeks after surgery, repeat the chemotherapy if response to preoperative chemotherapy or stable disease with pN+:		
5-FU	800 mg/m^2/d civi	d1-5
Cisplatin	100 mg/m^2 IV over 1 h	d1 or d2
Q4w x 3-4 cycles		

Reference: Boige V et al. 2007 ASCO annual meeting. Abstract 4510.

ADVANCED ESOPHAGEAL CANCER

5-FU + Cisplatin + RT

(Concurrent chemoradiation for locally advanced cancer)

5-FU	1000 mg/m^2/d civi	d1-4 of week 1, 5, 8 and 11
Cisplatin	75 mg/m^2 IV	d1 of week 1, 5, 8 and 11
Radiotherapy	50 Gy	

Reference: Herskovic A et al. N Eng J Med 1992;326:1593.

Interferon-5FU

5-Fluorouracil	750 mg/m^2/day continuous infusion	day 1 to 5
	followed by a weekly outpatient bolus of 750 mg/m^2	
Interferon alfa-2a	9 million units	three times a week
		from day 1

Reference: Kelsen D, Lovett D, Wong J, et al. J Clin Oncol 10;269-274, (1992).

Epirubicin-Cisplatin-5FU (ECF)

Epirubicin	50 mg/m^2 IV	day 1 every 3 weeks
Cisplatin	50 mg/m^2 IV	day 1 every 3 weeks
5-FU	200 mg/m^2/day IV	for 6 months

Reference:
Webb et al. J Clin Oncol 15:1997:261-267
Zaniboni et al. Cancer 76, 1995:1694-1699

DEFINITIVE CHEMOTHERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER

5-FU + Cisplatin

5-FU	1000 mg/m^2/d civi	d1–5
Cisplatin	100 mg/m^2 IV	d1
Q3w		

Reference: Bleiberg, H et al. Eur J Cancer 1997;33:1216.

Cisplatin + Paclitaxel

Cisplatin	75 mg/m^2 IV	d2
Paclitaxel	200 mg/m^2 civi over 24 hrs	d1
Q3w		
G-CSF support		

Reference: Ilson, DH et al. Cancer J 2000;6:316.

Cisplatin + Irinotecan

Cisplatin	30 mg/m^2 IV
Irinotecan	65 mg/m^2 IV
Qw	

Reference: Ilson, DH et al. J Clin Oncol 1999;17:3270.

Epirubicin + Cisplatin + 5-FU (ECF)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Cisplatin	60 mg/m^2 IV	d1 q3w x 8 cycles
5-FU	200 mg/m^2/d civi	for 6 months

Reference:
Cunningham D et al. N Eng J Med 2008;358:36.
Ross, P et al. J Clin Oncol 2002;20:1996.

Epirubicin + Cisplatin + Capecitabine (ECX)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Cisplatin	60 mg/m^2 IV	d1 q3w x 8 cycles
Capecitabine	625 mg/m^2 P.O.	b.i.d. x 6 months

Reference: Cunningham D et al. N Eng J Med 2008;358:36.

Oxaliplatin + Capecitabine

Oxaliplatin	130 mg/m^2 IV	d1
Capecitabine	850–1000 mg/m^2 P.O.	b.i.d. x 14 days
Q3w		

Reference:
Meerten EV et al. Br J Cancer 2007;96:1348.
Jatoi A et al. Ann Oncol 2006;17:29.

Epirubicin + Oxaliplatin + 5-FU (EOF)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Oxaliplatin	130 mg/m^2 IV over 2 hours	d1 q3w x 8 cycles
5-FU	200 mg/m^2/d civi	x 6 months

Reference: Cunningham D et al. N Eng J Med 2008;358:36.

Epirubicin + Oxaliplatin + Capecitabine (EOX)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Oxaliplatin	130 mg/m^2 IV over 2 hours	d1 q3w x 8 cycles
Capecitabine	625 mg/m^2 P.O.	b.i.d. x 6 months

Reference: Cunningham D et al. N Eng J Med 2008;358:36.

Paclitaxel

Paclitaxel	250 mg/m^2 civi over 24 hrs
Q3w	
Filgrastim support	

Reference: Ajani, JA et al. J Natl Cancer Inst 1994;86:1086.

Vinorelbine

Vinorelbine	25 mg/m^2 IV	
Qw		

Reference: Conroy, T et al. J Clin Oncol 1996;14:164.

Docetaxel

Docetaxel	70 mg/m^2/IV infusion over 1-2 hrs	
To be repeated every 3 weeks		

Reference: Muro K et al. Ann Oncol. 2004 Jun;15(6):955-9

Paclitaxel-Cisplatin-5-FU

Paclitaxel	175 mg/m^2 IV 3 hr infusion	day1
Cisplatin	20 mg/m^2 IV	day 1-5
5 FU	750-1000 mg/m^2 IV. continuous infusion	day 1-5
To be repeated every 4 weeks		

Reference: Ilson et al. J Clin Oncol, 16;1998:1826-1834

Cisplatin-Vinorelbine

Cisplatin	80 mg/m^2 IV, over 30 min infusion	day 1
Vinorelbine	20-25 mg/m^2 IV, 5-10 min infusion	day 1 & 8
Cycle to be repeated every 3 weeks		

Note: Prehydration and post hydration with cisplatin therapy is recommended.
Reference: Conrov T et al. Ann Oncol, 13:721-729, (2002).

Docetaxel-Vinorelbine (Recurrent squamous cell esophageal carcinoma)

Docetaxel	80 mg/m^2/day/IV	day 1
Vinorelbine	20 mg/m^2 IV	day 1
To be repeated every 3 weeks		

Reference: Airoldi M et al. Med Oncol. 2003;20(1):19-24.

PART - I
Solid Tumor

Ewings Family of Tumors

EWINGS FAMILY OF TUMORS

EFTs include Ewing's tumor of bone (ETB or Ewing's sarcoma of bone), extraosseous Ewing's (EOE), primitive neuroectodermal tumor (PNET or peripheral primitive neuroepithelioma), and Askin's tumor (PNET of the chest wall). EFTs occur most frequently in the second decade of life and account for 4% of childhood and adolescent malignancies. The incidence in boys is slightly greater than in girls (ratio of 1.1:1). ETB is estimated to comprise 60% of the EFTs. The sites of origin for ETB are: lower extremity (41%), pelvis (26%), chest wall (16%), upper extremity (9%), spine (6%), skull (2%). For the EOE, the most common sites are: trunk (32%), extremity (26%), head and neck (18%), retroperitoneum (16%), other sites (9%). Major prognostic factors for patients with Ewing sarcoma are pretreatment factors (including site. size, age, gender, serum lactate dehydrogenase, metastases, standard cytogenetics, and molecular pathology) and treatment response factors

Reference:
Ewing Sarcoma Family of Tumors Treatment (PDQ®): National Cancer Institute, available at: http://www.cancer.gov/cancertopics/pdq/treatment/ewings/healthprofessional/allpages

CHEMOTHERAPY REGIMENS
FIRST LINE THERAPY (PRIMARY/NEOADJUVANT/ ADJUVANT THERAPY)

VAC/IE

Vincristine	2 mg/m^2 IV	
Doxorubicin	75 mg/m^2 IV bolus infusion	daily
Cyclophosphamide followed by Mesna	1200 mg/m^2	daily
Ifosfamide	1800 mg/m^2	daily for 5 days with Mesna
Etoposide	100 mg/m^2	daily for 5 days

Reference: Grier HE et al. N Engl J Med. 2003 Feb 20;348(8):694-701.

VAI

Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 1, 8, 15, 22
Doxorubicin	30 mg/m^2 IV	day 1, 2, 43, 44
Iphosphamide	3000 mg/m^2 IV	days 1, 2, 22, 23, 43, 44
Actinomycin-D	0.5 mg/m^2/d x 3 IV	days 22, 23, 24

Reference: Paulussen M et al. J Clin Oncol. 2001 Mar 15;19(6):1818-29.

VIDE

Vincristine	1.5 mg/m^2 (max single dose 2 mg) IV	days 1
Iphosphamide	3000 mg/m^2 IV	days 1, 2, 3
Doxorubicin	20 mg/m^2 IV	day 1, 2, 3
Etoposide	150 mg/m^2/d x 3 IV	days 1, 2, 3
Followed by Mesna prophylaxis and G-CSF support		

Reference: Jeurgens C et al. Pediatr Blood Cancer. 2006 Jul;47(1):22-9.

PRIMARY THERAPY FOR METASTATIC DISEASE AT INITIAL PRESENTATION

CVD

Cyclophosphamide	1200 mg/m^2 IV	days 1, 2, 22, 23, 43, 44
Vincristine	2 mg/m^2 (max 2 mg) IV	days 1, 8, 15, 22
Dactinomycin	1.25 mg/m^2/d x 3 IV	days 22, 23, 24

Reference: Miser JS, Krailo MD et al. J Clin Oncol. 2004 Jul 15;22(14):2873-6.

SECOND LINE THERAPY

Cyclophosphamide + Topotecan

Cyclophosphamide	250 mg/m^2/day IV over 30 min
Topotecan	0.75 mg/m^2/day IV over 30 min
Hydration	either P.O. or IV
Repeated on days 1–5 of treatment cycle	
Filgrastim	5 mcg/kg daily S.C. beginning on day 6 until ANC3 1500 mL

Reference:
Robert L. Saylors III, J. Clin. Oncol. 2001, 19(5):3463-3469
Hunold A et al. Pediatr Blood Cancer. 2006 Nov;47(6):795-800.

Temozolomide-Irinotecan (Recurrent/progressive Ewing sarcoma)

Temozolomide	100 mg/m^2/day x 5
Irinotecan	20 mg/m^2/day x 5 (x 2)

Reference: Casey DA et al. Pediatr Blood Cancer. 2009 Dec;53(6):1029-34.

ICE-CAV

2 courses of ICE		
Ifosfamide	1.8 g/m^2	daily for 5 days
Carboplatin	400 mg/m^2	daily for 2 days
Etoposide	100 mg/m^2	daily for 5 days

Reference: Giuseppe MM et al. Cancer, 2006; Vol 106, No. 8, Pages 1838-1845

Gemcitabine-Docetaxel (Pediatric Ewing sarcomas)

Gemcitabine	1000 mg/m^2 over 90 minutes	day 1, 8
Docetaxel	100 mg/m^2 over 2 to 4 hours	day 8
To be repeated every three weeks.		

Reference: Mora J et al. J Pediatr Hematol Oncol. 2009 Oct;31(10):723-9.

Docetaxel (Pediatric patients with recurrent Ewing sarcoma)

Docetaxel	125 mg/m^2 IV over 1 hour
To be repeated every 3 weeks for a maximum of 12 courses	

Reference: Zwerdling T et al. Cancer 2006 Apr 15;106(8):1821-8.

ICE-CAV

2 courses of ICE		
Ifosfamide	1.8 g/m^2	daily for 5 days
Carboplatin	400 mg/m^2	daily for 2 days
Etoposide	100 mg/m^2	daily for 5 days
Followed by 2 courses of CAV		
Cyclophosphamide	1500 mg/m^2	daily for 2 days
Doxorubicin	75 mg/m^2 IV over 72 hours	daily
Vincristine	1.5 mg/m^2 IV over 72 hour	

Note: Courses to be repeated every 21 to 28 days after patients achieved full hematologic recovery. G-CSF was administered at a dose of 5 µg/kg daily until patients achieved neutrophil recovery.
Reference: Giuseppe MM et al. Cancer, 2006; Vol 106, No. 8, Pages 1838-1845

VIP

Etoposide	75 mg/m^2 IV	for 5 days
Ifosfamide	1200 mg/m^2 IV	for 5 days
Cisplatin	20 mg/m^2 IV	for 5 days

Reference: Weshi EI et al. Am J Clin Oncol. 2004 Oct;27(5):529-34

MAID

Doxorubicin	15 mg/m^2/d civi	d1–4
Ifosfamide	2 g/m^2/d civi	d1–3
Dacarbazine	250 mg/m^2/d civi	d1–4
Mesna	2.5 g/m^2/d civi	d1–4
Q3w		

Reference: Antman, K et al. Cancer 1998;82:1288.

VACA AND MODIFICATIONS

Study IESS-I

Phase 1 (weeks 0–8)		
Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 1, 8, 15, 22, 29, 36
Cyclophosphamide	500 mg/m^2 IV	days 1, 8, 15, 22, 29, 36
Doxorubicin	60 mg/m^2 IV	day 36
Plus radiotherapy		

Phase 2 (weeks 9–68)		
Dactinomycin	0.015 mg/kg IV	days 1–5
Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 15, 22, 29, 36, 43
Cyclophosphamide	500 mg/m^2 IV	days 15, 22, 29, 36, 43
Doxorubicin	60 mg/m^2 IV	day 43
To be replaced after a therapy free interval of 3 weeks 6 times		

Phase 3 (weeks 69–98)		
Dactinomycin	0.015 mg/kg IV	days 1–5, 7
Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 15, 22, 29, 36, 43
Cyclophosphamide	500 mg/m^2 IV	days 15, 22, 29, 36, 43
To be replaced after a therapy free interval of 3 weeks 3 times		

Reference:
CANGIR et al. Cancer 1990(66):887-893
NESBIT et al. J. Clin. Oncol. 1990(8):1664-1674

Study IESS-II

Phase I (weeks 0–9)		
Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 1, 22, 29, 36, 43
Doxorubicin	75 mg/m^2 IV	day 2, 44
Cyclophosphamide	500 mg/m^2 IV	days 23, 30, 37
5-fluorouracil	300 mg/m^2 IV	days 23, 30, 37

Phase 2 (weeks 10–15)		
Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 1, 8, 15, 22
Cyclophosphamide	500 mg/m^2 IV	days 2, 9, 16, 23
5-fluorouracil	300 mg/m^2 IV	days 2, 9, 16, 23
Plus radiotherapy		

Phase 3a (weeks 15–51)		
Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 1, 22, 29, 36, 43
Doxorubicin	75 mg/m^2 IV	day 2
5-fluorouracil	300 mg/m^2 IV	days 23, 30, 37, 44
Cyclophosphamide	500 mg/m^2 IV	days 23, 30, 37, 44
To be repeated 4 times		

Phase 3b (weeks 52–103)		
Vincristine	1.5 mg/m^2 (max 2 mg) IV	days 1, 22, 29, 36, 43
Dactinomycin	2 mg/m^2 IV	day 2
Cyclophosphamide	500 mg/m^2 IV	days 23, 30, 37, 44
5-fluorouracil	300 mg/m^2 IV	days 23, 30, 37, 44
To be repeated 6 times		

Reference:
Burgert et al. J. Clin. Oncol. 1990,(8):1514-1524
Cangir et al. Cancer 1990,(66):887-893

Intergroup Study II-TRT 1

Regimen A		
Vincristine	1.5 mg/m^2 IV (max. 2.0 mg)	days 1 and 22
Doxorubicin	75 mg/m^2 IV	day 2
Cyclophosphamide	1400 mg IV (total)	day 23

Regimen B		
Vincrisitine	1.5 mg/m^2 IV (max. 2.0 mg)	days 1 and 22
Dactinomycin	0.45 mg/m^2/day IV (max. 0.5 mg/day)	days 1 to 5
Cyclophosphamide	1400 mg IV (total)	day 23

Note: Regimen A is begun on day 1. On day 42, surgery is considered. If not performed, then radiation therapy is begun with simultaneous doses of vincristine and doxorubicin. Chemotherapy resumes on day 63 for four additional cycles of regimen A followed on day 231 by seven cycles of regimen B. Therapy concludes on day 525 if no surgery was done and day 541 if surgery was performed and followed by radiation therapy. See the original report for details.
Reference: Evans RG, et al. J Clin Oncol 9:1173-1180, (1991).

SE 91 CNR Protocol

Induction therapy (0–6 weeks)		
VAdrC		
Doxorubicin	40 mg/m^2 IV over 4 hr	for 2 days
Cyclophosphamide	1200 mg/m^2 IV over 30 min	
with Mesna		
Vincristine	5 mg/m^2 IV (max 2 mg)	days 1, 8 of each induction cycle
Two courses every 3 weeks alternating with one course of VAI		

VAI		
Vincristine	5 mg/m^2 IV push	days 1, 8 of each induction cycle
Actinomycin-D	1.5 mg/m^2 IV push	during induction
Ifosfamide	1800 mg/m^2 IV over 1 hr	for 5 days
Local therapy was performed after 9 weeks of induction therapy		
Surgery and radiotherapy was given to patients with unresectable tumor		

MAINTENANCE CHEMOTHERAPY

Phase I a

VadrC (9, 15 weeks)		
Doxorubicin	40 mg/m^2 IV over 4 hr	for 2 days
Cyclophosphamide	1200 mg/m^2 IV over 30 min with Mesna	
Vincristine	5 mg/m^2 IV (max 2 mg)	days 1 of each maintenance cycle
Two courses every 3 weeks alternating with one course of VAI		

VAI (12 week)		
Vincristine	5 mg/m^2 IV push	day 1 of each cycle
Actinomycin-D	1.25 mg/m^2 IV push	
Ifosfamide	1800 mg/m^2 IV over 1 hr	for 5 days

Phase I b (18week)

VAdrC		
Doxorubicin	40 mg/m^2 IV over 4 hr	for 2 days
Cyclophosphamide	1200 mg/m^2 IV over 30 min with Mesna	
Vincristine	5 mg/m^2 IV (max 2 mg)	days 1 of each maintenance cycle
One course every 3 weeks alternating with one course of VAI		

VAI (21 week)		
Vincristine	5 mg/m^2 IV push	days 1of each cycle
Actinomycin-D	1.25 mg/m^2 IV push	
Ifosfamide	1800 mg/m^2 IV over 1 hr	for 5 days

Phase II

EI (24, 30, 36 weeks)		
Etoposide	100 mg/m^2 IV over 1 hr	for 5 days
Ifosfamide	1800 mg/m^2 IV over 1 hr	for 5 days
with Mesna		
Repeat 3 courses every 3 weeks alternating with VAC		

VAC (27, 33 weeks)		
Vincristine	5 mg/m^2 IV push	day 1of each cycle
Actinomyci-D	1.25 mg/m^2 IV push	
Cyclophosphamide	1200 mg/m^2 IV over 30 min with Mesna	
Repeat 2 courses every 3 weeks		
Doxorubicin administration ended at 24th week (total dose 400 mg/m^2)		

Reference: Pasquale Rosito et al. Cancer 1999, 86(3):421-428

For non metastatic Ewing's sarcoma

Vincristine	2 mg/m^2 IV	
Doxorubicin	75 mg/m^2 IV bolus	
Cyclophosphamide	1200 mg/m^2 IV	
with mesna		
Doxorubicin is substituted by Actinomycin D 1.25 mg/m^2/dose when total doxorubicin reached 375 mg/m^2		
Ifosfamide	1800 mg/m^2 IV/day	for 5 days
with mesna		
Etoposide	100 mg/m^2 IV/day	for 5 days
Repeat every 3 weeks for a total of 17 courses		

Reference: Holcombe E. Grier, N. Eng. J. Med 2003, 348:694-701

Et-2 (UKCCSG/-MRC study)

		IVAD3	IVAD2	IVA
Ifosfamide	3000 mg/m^2	x 3 days	x 2 days	x 2 days
Vincristine	2 mg/m^2	x 1 day	x 1 day	x 1 day
Doxorubicin	20 mg/m^2	x 3 days	x 2 days	-
Dactinomycin	1.5 mg/m^2	-	-	x 1 day

Note: Repeat IVAD3 every 3 weeks x 3, followed by definitive treatment of primary, then IVAD2 to repeated every 3 weeks x 2, then IVA to be repeated every 3 weeks
Reference: Craft et al. Am J. Pediatr. Hematol. Oncol. 1993, 15 (Suppl. A):31-35.

Primitive neuroectodermal tumor of bone

Cyclophosphamide	1200 mg/m^2 IV	d1, followed by mesna
Doxorubicin	75 mg/m^2 IV bolus	d1,
	change to dactinomycin 1.25 mg/m^2 IV d1 when total doxorubicin reaches 375 mg/m^2	
Vincristine	2 mg IV	d1
Alternating with		
Ifosfamide	1.8 g/m^2/d IV	d1–5, given with mesna
Etoposide	100 mg/m^2/d IV	d1–5
Q3w x 17 cycles		

Reference: Holcombe E et al. N Engl J Med 2003;348:694.

Peripheral neuroectodermal tumours (PNET)

Induction		
Ifosfamide	1,600 mg/m^2 IV over 15 min	days 1–5
(with mesna uroprotection)		
Etoposide	100 mg/m^2 IV over 1 hour	days 1–5
To be repeated every 3 weeks x 3 (weeks 0, 3, 6)		
Cyclophosphamide	150 mg/m^2 P.O.	days 1–7
Doxorubicin	35 mg/m^2 IV	day 8
To be repeated every 3 weeks x 3 (weeks 9, 12, 15)		
Surgery and/or radiotherapy follows) on week 17		

Maintenance		
Alternating cycles of ifosfamide, etoposide (weeks 25, 39, 53) and cyclophosphamide, doxorubicin (weeks 28, 31, 42, 45, 56, 59) as for induction and		
Vincristine	1.5 mg/m^2 IV (max 2 mg)	weekly
Dactinomycin	1.5 mg/m^2 IV (max 2 mg)	every 2 weeks*
(Weeks 18*, 19, 20*, 21, 22*, 23,*, 34*, 35, 36*, 37, 38*, 48*, 49, 50*, 51, 52*)		

Reference: Gururangan et al. J. Pediatr. Hematol, Oncol. 1988,(20):55-61

PART - I
Solid Tumor

Gall Bladder Cancer

GALL BLADDER CANCER

As per the NCI data 9,810 new cases and 3,200 deaths from gallbladder (and other biliary) cancer are estimated in the United States. Cancer that arises in gallbladder is uncommon. The most common symptoms caused by gallbladder cancer are jaundice, pain, and fever.

In patients whose superficial cancer (T1 or confined to the mucosa) is discovered on pathological examination of tissue after gallbladder removal for other reasons, the disease is often cured without further therapy. In patients who present with symptoms, the tumor is rarely diagnosed preoperatively. In such cases, the tumor often cannot be removed completely by surgery and the patient cannot be cured, though palliative measures may be beneficial. For patients with T2 or greater disease, extended resection with partial hepatectomy and portal node dissection may be an option. Cholelithiasis is an associated finding in the majority of cases, but <1% of patients with cholelithiasis develop this cancer.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Chao TC, Greager JA: J Surg Oncol 46(4):215-21, (1991).
Shoup M, Fong Y: Surg Oncol Clin N Am 11(4):985-94, (2002).
Sasson AR et al. Am Surg 67(3):277-83; discussion 284, (2001).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein.

N2 Metastases to periaortic, pericaval, superior mesentery artery and/or celiac artery lymph nodes

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T1–3	N1	M0
IVA	T4	N0–1	M0
IVB	Any T	N 2	M0
	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

FELv

5-FU	500 mg/m^2 bolus IV	day 1 - 3
followed by		
Etoposide	120 mg/m^2 IV over 40 min	day 1 - 3
Leucovorin	60 mg/m^2 bolus IV	day 1 - 3
To be repeated every third week		

Reference: Glimelius B et al. Ann Oncol 1996;7:593-600

FLv

5-FU	500 mg/m^2 bolus IV	day 1, 2
After 40 minutes		
Leucovorin	60 mg/m^2 bolus IV	day 1, 2
To be repeated every second week		

Reference: Glimelius B et al. Ann Oncol 1996;7:593-600

FAM

5-FU	200 mg/m^2 IV
Doxorubicin	15 mg/m^2 IV
Mitomycin-C	5 mg/m^2 IV
D1, 8, 15, 22 q5w x 2	

Reference: Takada et al. Hepatogastroenterology 1998;45:2020

Gemcitabine + Oxaliplatin

Gemcitabine	900 mg/m^2 IV d1, 8
Oxaliplatin	80 mg/m^2 IV d1, 8
Q3w	

Reference: Dwary et al. J Clin Oncol 2009;27(S):4521.

Gemcitabine + Cisplatin

Gemcitabine	1000 mg/m^2 IV d1, 8
Cisplatin	25 mg/m^2 IV d1, 8
Q4w	

Reference: Valle JW et al. NEJM 2010;362:1273.

Capecitabine + Oxaliplatin

Capecitabine	1000 mg/m^2 P.O. b.i.d. d1-14
Oxaliplatin	130 mg/m^2 IV d1
Q3w	

Reference: Valle JW et al. NEJM 2010;362:1273.

Capecitabine + Cisplatin

Capecitabine	1250 mg/m^2 P.O. b.i.d. d1–14
Cisplatin	60 mg/m^2 IV d1
Q3w	

Reference:
Hong YS et al. Cancer Chemother Pharmacol. 2008 Jun;62(1):77-84.
Kim TW et al. Ann Oncol. 2003 Jul;14(7):1115-20.

Epirubicin + Cisplatin + Capecitabine

Epirubicin	50 mg/m^2 IV d1
Cisplatin	60 mg/m^2 IV d1
Capecitabine	1000 mg/m^2 P.O. b.i.d. d1–14
Q3w	

Reference: Park SH et al. Cancer. 2006 Jan 15;106(2):361-5.

Gemcitabine

Regimen # 1

Gemcitabine	2200 mg/m^2 IV over 30 min
Every 2 weeks for 6 months	

Reference: Penz et al. Ann Oncol 2001 Feb;12(2):183-6

Regimen # 2

Gemcitabine	1000 mg/m^2 IV over 30 min
Every week for 3 wk followed by a week rest	
Repeat cycle every 28 days	

Reference: Gallardo et al. Ann Oncol 2001, Vol 12, Issue 10 1403-1406

Capecitabine

Capecitabine	1000 mg/m^2 P.O. days 1–14
Repeat cycle every 21 days	

Reference: Patt YZ et al. Cancer. 2004 Aug 1;101(3):578-86

MF

Mitomycin	6 mg/m^2 IV (at the time of surgery)
After surgery 5 FU IV would be administered in 2 courses of treatment for 5 consecutive days during postoperative weeks 1 & 3.	
5-Fluorouracil	310 mg/m^2 IV
From post-operative week 5 until disease recurrence	
5-Fluorouracil	100 mg/m^2 P.O./daily

Reference: Takada T et al. Cancer Treat Rev. 2003 Apr;29(2):135-7.

PART - I
Solid Tumor

Gastric Cancer

GASTRIC CANCER

As per the NCI, gastric cancer ranks 14th in incidence among the major types of cancer malignancies with an estimated incidence of 21,130 new cases and 10,620 deaths reported in US in year 2009. The precise etiology is unknown but acknowledged risk factors for gastric cancer includes Helicobacter pylori gastric infection, advanced age, male gender, diet low in fruits and vegetables, diet high in salted, smoked, or preserved foods, chronic atrophic gastritis, intestinal metaplasia, pernicious anemia, gastric adenomatous polyps, family history of gastric cancer, cigarette smoking, menetrier's disease (giant hypertrophic gastritis), familial adenomatous polyposis.

The prognosis is related to tumor extent and includes both nodal involvement and direct tumor extension beyond the gastric wall. In localized distal gastric cancer, more than 50% of patients can be cured. The overall survival rate in these patients at 5 years ranges from almost no survival for patients with disseminated disease to almost 50% survival for patients with localized distal gastric cancers confined to resectable regional disease. Even with apparent localized disease, the 5-year survival rate of patients with proximal gastric cancer is only 10% to 15%. Although the treatment of patients with disseminated gastric cancer may result in palliation of symptoms and some prolongation of survival, long remissions are uncommon.

Reference:
American Cancer Society.: Cancer Facts and Figures 2009.
Kurtz RC, Sherlock P: Semin Oncol 12(1):11-8, (1985).
Scheiman JM, Cutler AF: Am J Med 106(2):222-6, (1999).
Fenoglio-Preiser CM et al. Semin Oncol 23(3):292-306, (1996).
Siewert JR et al. Ann Surg 228(4):449-61, (1998).
Nakamura K et al. Cancer 70(5):1030-7, (1992).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria

T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures*,**,***

T4 Tumor invades serosa (visceral peritoneum) or adjacent structures**,***

T4a Tumor invades serosa (visceral peritoneum)

T4b Tumor invades adjacent structures

**A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T4.*

***The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.*

****Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.*

REGIONAL LYMPH NODES (N)

NX Regional lymph node(s) cannot be assessed

N0 No regional lymph node metastasis*

N1 Metastasis in 1 to 2 regional lymph nodes

N2 Metastasis in 3 to 6 regional lymph nodes

N3 Metastasis in 7 or more regional lymph nodes

N3a Metastasis in 7 to 15 regional lymph nodes

N3b Metastasis in 16 or more regional lymph nodes

**A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.*

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
IV	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Neoadjuvant chemotherapy
- Adjuvant chemoradiation for stage IB, II, III and non-metastatic IV cancer
- Chemotherapy for locally advanced unresectable and metastatic cancer
- Miscellaneous

NEOADJUVANT CHEMOTHERAPY

UFT (uracil plus futrafur)

UFT	300–600 mg P.O./day	1–6 weeks before surgery

Reference: Nio Y et al. Gastric Cancer. 1999 May;2(1):64-73

ADJUVANT CHEMORADIATION FOR STAGE IB, II, III AND NON-METASTATIC IV CANCER

5-FU + LV + RT

5-FU	425 mg/m^2/d IV	d1–5
Leucovorin	20 mg/m^2/d IV	d1–5
One month later		
5-FU	400 mg/m^2/d	d1–4 and last 3 days of RT
Leucovorin	20 mg/m^2/d IV	d1–4 and last 3 days of RT
Radiotherapy	1.8 Gy/d to 45 Gy	
One month after completion of RT		
5-FU	425 mg/m^2/d IV	d1–5 q4w x 2 cycles
Leucovorin	20 mg/m^2/d IV	d1–5 q4w x 2 cycles

Reference: Macdonald, JS et al. N Engl J Med 2001;345:725.

CHEMOTHERAPY FOR LOCALLY ADVANCED UNRESECTABLE AND METASTATIC CANCER

Epirubicin + Cisplatin + 5-FU (ECF)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Cisplatin	60 mg/m^2 IV	d1 q3w x 8 cycles
5-FU	200 mg/m^2/d civi	x 6 months

Reference:
Cunningham D et al. N Eng J Med 2008;358:36.
Roth AD et al. J Clin Oncol 2007;25:3217.
Webb, A et al. J Clin Oncol 1997;15:261.
Br J Cancer (1999) April 80(1-2)269-272

Epirubicin + Cisplatin + Capecitabine (ECX)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Cisplatin	60 mg/m^2 IV	d1 q3w x 8 cycles
Capecitabine	625 mg/m^2 P.O.	b.i.d. x 6 months

Reference: Cunningham D et al. N Eng J Med 2008;358:36.

Epirubicin + Oxaliplatin + 5-FU (EOF)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Oxaliplatin	130 mg/m^2 IV over 2 hours	d1 q3w x 8 cycles
5-FU	200 mg/m^2/d civi	x 6 months

Reference: Cunningham D et al. N Eng J Med 2008;358:36.

Epirubicin + Oxaliplatin + Capecitabine (EOX)

Epirubicin	50 mg/m^2 IV bolus	d1 q3w x 8 cycles
Oxaliplatin	130 mg/m^2 IV over 2 hours	d1 q3w x 8 cycles
Capecitabine	625 mg/m^2 P.O.	b.i.d. x 6 months

Reference: Cunningham D et al. N Eng J Med 2008;358:36.

5-FU + LV + Oxaliplatin (FLO)

Oxaliplatin	85 mg/m^2 IV over 2 hours	d1
Leucovorin	200 mg/m^2 IV over 2 hours	d1
5-FU	2600 mg/m^2 civi over 24 hours	
Q2w until progression or limiting toxicity		

Reference:
Al-Batran SE et al. J Clin Oncol 2008;26:1435.
Al-Batran, SE et al. J Clin Oncol 2004;22:658.

Cisplatin + 5-FU

Cisplatin	100 mg/m^2 IV	d1
5-FU	1000 mg/m^2/d civi	d1–5
Q4w		

Reference:
Ajani JA et al. J Clin Oncol 2007;25:3205.
Ajani JA et al. J Clin Oncol 2007;25:3210.
Custem EV et al. J Clin Oncol 2006;24:4991.

Cisplatin + Capecitabine

Regimen # 1

Cisplatin	80 mg/m^2 IV over 3 hrs	d1
Capecitabine	1000 mg/m^2 P.O. b.i.d.	d1–14
Q3w		

Reference: Kang Y et al. 2006 ASCO Annual Meeting. Abstract LBA4018.

Regimen # 2

Capecitabine	1250 mg/m^2 P.O./twice daily	day 1–14
Cisplatin	60 mg/m^2 IV	day 1
Repeat the cycle every 3 weeks		

Reference: Kim TW et al. Ann Oncol. 2002 Dec;13(12):1893-8

Cisplatin + Irinotecan

Regimen # 1		
Cisplatin	30 mg/m^2 IV	d1
Irinotecan	65 mg/m^2 IV	d1
Qw for 4 wks every 6 wks		

Reference: Ajani, JA et al. Cancer 2002;94:641.

Regimen # 1		
(In pretreated patients with unresectable or recurrent gastric cancer)		
Irinotecan	70 mg/m^2 IV	day 1, 15
Cisplatin	80 mg/m^2 IV	day 1
Repeat the cycle every 4 weeks.		

Reference: Ueda S et al. Gastric Cancer. 2006;9(3):203-7.

Cisplatin + Paclitaxel

Regimen # 1		
Cisplatin	60 mg/m^2 IV	d1
Paclitaxel	160 mg/m^2 IV	d1
Q2w		

Reference: Kornek, GV et al. Br J Cancer 2002;86:1858.

Regimen # 2		
Paclitaxel	145 mg/m^2 3 hr IV	day 1
Cisplatin	60 mg/m^2 IV	days 1
Repeat the cycle every 3 weeks		

Reference: Lee KW et al. Jpn J Clin Oncol. 2005 Dec;35(12):720-6.

Cisplatin + Docetaxel

Cisplatin	75 mg/m^2 IV	d1
Docetaxel	75 - 85 mg/m^2 IV	d1
Q3w		

Reference:
Roth AD et al. J Clin Oncol 2007;25:3217.
Ajani JA et al. J Clin Oncol 2005;23:5660.
Ridwelski, K et al. Ann Oncol 2001;12:47.

5-FU + LV + Irinotecan

Regimen 1		
Irinotecan	180 mg/m^2 IV	d1
Leucovorin	200 mg/m^2 IV over 2 hrs	d1 and 2
5-FU	400 mg/m^2 IV bolus	
	followed by	
	600 mg/m^2 civi over 22 hrs	d1 and 2
Q2w		

Reference: Bouche, O et al. J Clin Oncol 2004;22:4319.

Regimen 2		
Irinotecan	80 mg/m^2 IV over 30 min	d1
Leucovorin	500 mg/m^2 IV over 2 hrs	d1
5-FU	2000 mg/m^2 IV over 22 hrs	d1
Qw x 6 wks every 7 wks		

Reference: Dank M et al. 2005 ASCO Annual Meeting. Abstract 4003.

5-FU + Cisplatin + Docetaxel

Cisplatin	75 mg/m^2 IV	d1
Docetaxel	75 mg/m^2 IV	d1
5-FU	750 mg/m^2/d civi	d1–5
Q3w		

Reference:
Ajani JA et al. J Clin Oncol 2007;25:3205.
Ajani JA et al. J Clin Oncol 2007;25:3210.
Roth AD et al. J Clin Oncol 2007;25:3217.
Custem EV et al. J Clin Oncol 2006;24:4991.
Ajani JA et al. J Clin Oncol 2005;23:5660.

Irinotecan + Docetaxel + Oxaliplatin

Irinotecan	150 mg/m^2 IV	d1
Docetaxel	60 mg/m^2 IV	d1
Oxaliplatin	85 mg/m^2 IV	d2
Q3w		

Reference: Lauro LD et al. Br J Cancer 2007;97:593.

FAMTX

Methotrexate	1500 mg/m^2 IV	d1
5-FU	1500 mg/m^2 IV bolus	d1 1 hour after MTX
Doxorubicin	30 mg/m^2 IV bolus	d15
Q4w		

Reference:
Cocconi G et al. Ann Oncol 2003;14:1258.
Vanhoefer U et al. J Clin Oncol 2000;18:2648.
Webb A et al. J Clin Oncol 1997;15:261.
Wils JA et al. J Clin Oncol 1991;9:837.

Capecitabine

Capecitabine	1250 mg/m^2 P.O.	b.i.d. for 2 wks
Q3w		

Reference: Hong, YS et al. Ann Oncol 2004;15:1344.

Cisplatin + Irinotecan + Bevacizumab

Cisplatin	30 mg/m^2 IV over 30 min	d1, 8
Irinotecan	65 mg/m^2 IV over 30 min	d1, 8
Bevacizumab	15 mg/kg IV	d1
Q3w		

Reference: Shah MA et al. J Clin Oncol 2006;24:5201.

FUFOX + Cetuximab

5-FU	2000 mg/m^2 IV	d1, 8, 15, 22 q36d
Leucovorin	200 mg/m^2 IV	d1, 8, 15, 22 q36d
Oxaliplatin	50 mg/m^2 IV	d1, 8, 15, 22 q36d
Cetuximab	400 mg/m^2 IV	loading, then 250 mg/m^2 IV qw

Reference: Lordick F et al. 2007 ASCO annual meeting. Abstract 4526.

Docetaxel

Docetaxel	75–100 mg/m^2 IV over 1 hr infusion
Repeat cycle every 21 days	

Reference: Serena DC et al. Acta Oncologica Vol. 42, No. 7, pp. 6933/700, (2003).

Irinotecan

Irinotecan	125 mg/m^2 IV over 90 min infusion	day 1, 8, 15 & 22
Repeat cycle every 6 weeks		

Reference: Chun JH et al. Jpn J Clin Oncol. 2004 Jan;34(1):8-13

5-Flurouracil

5 FU	800 mg/m^2/day IV C.I	day 1-5
Repeat cycle every 4 weeks		

Reference: Ohtsu A et al. J Clin Oncol 21:54-59. 2003

Cisplatin-5 FU-Doxorubicin

Doxorubicin	40 mg/m^2 IV	day 1
5-fluorouracil	300 mg/m^2 IV	days 1-5
Cisplatin	60 mg/m^2 IV	day 1 with hydration
Repeat the cycle every 5 weeks.		

Reference: Moertel CG et al. J Clin Oncol 4:1053-1057, (1986).

Etoposide-LCV-5 FU (ELF)

Etoposide	20 mg/m^2 IV	over a 50 min period	day 1 to 3.
5-fluorouracil	500 mg/m^2 IV	bolus midway through the leucovorin infusion.	
Leucovorin	300 mg/m^2 IV	over a 10 min period	days 1 to 3

Note: Give leucovorin immediately following etoposide. Repeat the course every 3 or 4 weeks.
Reference: Vonhoefer et al. J Clin Oncol 18(14):2648-2657, (2000).

PELF

Cisplatin	40 mg/m^2 d1/wk
5-fluorouracil	500 mg/m^2
Epi Doxorubicin	35 mg/m^2
6S-Stereoisomer of Leucovorin	250 mg/m^2
Glutathione	1.5 g/m^2
Filgrastism	5 mg/m^2 S.C. d2/wk
Regimen may not be tolerable, use of G-CSF is recomended	

Reference: Cascinu et al. J Clin Oncol 15(11):3313-3319, (1997).

Paclitaxel-Cisplatin-5 FU

Paclitaxel	175 mg/m^2 3 hr IV	day 1
5-fluorouracil	750 mg/m^2 IV continuous infusion	days 1–5
Cisplatin	20 mg/m^2 IV	days 1–5
Repeat the cycle every 4 weeks.		

Reference: Kim et al. Cancer 85:295-301, (1999).

MISCELLANEOUS

FEMTX

Methotrexate	1500 mg/m^2 IV 30 min infusion	day 1
5 FU	1500 mg/m^2 IV 30 min infusion	day 1
(1 hr after methotrexate)		
Epirubicin	70 mg/m^2 IV	day 15
Leucovorin Rescue	30 mg/m^2 every 6 hours (oral or IV)	days 2 & 3 (8 doses)
Repeat the cycle every 29 days.		

Reference: Nitti D et al. Annals of Oncology 17:262-269, (2006).

PART - I
Solid Tumor

Gastrointestinal Stromal Tumor

GASTROINTESTINAL STROMAL TUMOR

Soft tissue sarcomas are malignant tumors that may arise in any of the mesodermal tissues of the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%). Rarely, these tumors arise in the gastrointestinal tract or gastrointestinal stroma, and a small percentage of these are called gastrointestinal stromal tumors (GISTs). Malignant GISTs can occur from the esophagus to the rectum but occur most commonly in the stomach and small intestine.

The prognosis for patients with adult soft tissue sarcomas depends on several factors, including the patient's age and the size, histologic grade, and stage of the tumor. Factors associated with a poorer prognosis include age older than 60 years, tumors larger than 5 cm, or high-grade histology.

Reference:
Adult Soft Tissue Sarcoma Treatment (PDQ®): National Cancer Institute. Available at http://www.cancer.gov/cancertopics/pdq/treatment/adult-soft-tissue-sarcoma/healthprofessional/allpages

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm but not more than 10 cm
T4	Tumor more than 10 cm in greatest dimension

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis
M1a	Lung
M1b	Other distant sites

STAGE GROUPING: GASTRIC GIST

GROUP	T	N	M	Mitotic Rate
IA	T1 or T2	N0	M0	Low
IB	T3	N0	M0	Low
II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
IIIA	T3	N0	M0	High
IIIB	T4	N0	M0	High
IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

STAGE GROUPING: SMALL INTESTINAL GIST

GROUP	T	N	M	Mitotic Rate
IA	T1 or T2	N0	M0	Low
II	T3	N0	M0	Low
IIIA	T1	N0	M0	High
	T4	N0	M0	Low
IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Imatinib

Imatinib	400–600 mg P.O.	qd

Reference:
Blanke CD et al. J Clin Oncol 2008;26:626.
Blanke CD et al. J Clin Oncol 2008;26:620.
Nilsson B et al. Br J Cancer 2007;96:1656.

Sunitinib Malate

Sunitinib	50 mg P.O.	qd x 4 wks every 6 wks

Reference:
Demetri GD et al. Lancet 2006;368:1329.
Faivre S et al. J Clin Oncol 2006;24:25.

PART - I
Solid Tumor

Gestational Trophoblastic Tumor

GESTATIONAL TROPHOBLASTIC TUMOR

Gestational trophoblastic tumors (GTTs) are rare but highly curable tumors arising from the products of conception in the uterus. The prognosis for cure is good even when the disease has spread to distant organs, especially when only the lungs are involved. The probability of cure depends on histologic type (mole, invasive mole, or choriocarcinoma), extent of spread of the disease, level of the human chorionic gonadotropin (HCG) titer duration of disease from the initial pregnancy event to start of treatment, specific sites of metastases, nature of antecedent pregnancy & extent of prior treatment.

Human chorionic gonadotropin is normally produced during pregnancy and elevated abnormally in the blood and urine of patients. It is a sensitive marker to indicate the presence or absence of disease before, during, and after treatment. The most common antecedent pregnancy is that of a hydatidiform mole, usually a genetic disorder of pregnancy in which only placental-like tissue is present.

Choriocarcinoma mostly follows a molar pregnancy but it can also follow a normal pregnancy, ectopic pregnancy, or abortion, and should always be considered when a patient has continued vaginal bleeding in the postdelivery period. Other common signs include bizarre neurologic symptoms in a female within the reproductive age group and asymptomatic lesions on routine chest x-ray.

Reference:
Gestational Trophoblastic Tumors Treatment (PDQ®): National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/gestational-trophoblastic/healthprofessional/allpages

PRIMARY TUMOR (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to uterus
T2	II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension

REGIONAL LYMPH NODES (N)

There is no regional nodal designation in the staging of these tumors. Nodal metastases should be classified as metastatic (M1) disease.

DISTANT METASTASIS (M)

TNM	FIGO	
M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1		Distant metastasis
M1a	III	Lung metastasis
M1b	IV	All other distant metastasis

STAGE GROUPING

GROUP	T	M	RISK SCORE
I	T1	M0	Unknown
IA	T1	M0	Low risk
IB	T1	M0	High risk
II	T2	M0	Unknown
IIA	T2	M0	Low risk
IIB	T2	M0	High risk
III	Any T	M1a	Unknown
IIIA	Any T	M1a	Low risk
IIIB	Any T	M1a	High risk
IV	Any T	M1b	Unknown
IVA	Any T	M1b	Low risk
IVB	Any T	M1b	High risk

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Low risk group (WHO score ≤ 4)
- Low risk group (charing cross scoring system 0–8)
- Medium risk cases (WHO score 4–7)
- High risk cases (WHO score ≥ 8)
- High risk gestational trophoblastic tumours (charing cross scoring system > 8)
- Salvage therapy for drug resistant choriocarcinoma
- Miscellaneous

LOW RISK GROUP (WHO SCORE ≤ 4)

Methotrexate

Methotrexate	0.4 mg/kg IV	days 1–5
To be repeated every 2 weeks.		

Reference: Lurain JR et al. Am J Obstet Gynecol. 1995 Feb;172(2 Pt 1):574-9.

MTX-FA/Dactinomycin

Methotrexate	50 mg/m^2 I.M.	days 1, 3, 5, 7 (at 12:00 hours)
Folinic acid	7.5 mg/m^2 P.O.	days 2, 4, 6, 8 (at 18:00 hours)
Or (in cases of impaired kidney and/or liver function)		
Dactinomycin	12 μg/kg IV	days 1–5
(max. single dose 0.5 mg daily)		
To be repeated every 14 to 21 days		

Note: Treatment period: Up to complete regression of the tumour and negative HCG titre, followed by another 1-2 courses as a safety margin.
Reference: Bagshaw et al. Br. J. Obstet Gynecol. 96(1989):795-802

Etoposide

Etoposide	200 mg/m^2 daily for 5 days
Repeated after a minimum resting period of 7 days	

Reference: Wong LC et al. Cancer. 1986 Jul 1;58(1):14-7.

LOW RISK GROUP (CHARING CROSS SCORING SYSTEM 0–8)

Methotrexate-Leucovorin/Dactinomycin

Methotrexate	50 mg/ml I.M.	day 1, 3, 5, 7
Leucovorin	7.5 mg/ml P.O.	day 2, 4, 6, 8
To be repeated every 14 days.		
Patients resistant to Methotrexate and hCG level < 100 IU/L		
Dactinomycin	0.5 mg daily IV	day 1–5
To be repeated every 14 days.		

Note: Treatment period: Up to complete regression of the tumor and negative HCG titre, followed by another 1-2 courses as a safety margin.
Reference: McNeish IA et al. J Clin Oncol 20(7):1838-1844, (2002).

MEDIUM RISK CASES (WHO SCORE 4-7)

Course A		
Etoposide	100 mg/m^2 IV	days 1 to 3

Course B		
Hydroxyurea	500 mg orally every 12 hours	day 1
Methotrexate	50 mg I.M. at 12 noon	days 2, 4, 6, 8
Folinic Acid	6 mg I.M. at 6 pm	days 3, 5, 7, 9
6-Mercaptopurine	75 mg orally	days 3, 5, 7, 9

Course C		
Dactinomycin	0.5 mg IV	days 1 to 5

Course D		
Vincristine	0.8 mg/m^2 IV	days 1 and 3
Cyclophosphamide	400 mg/m^2 IV	days 1 and 3

Note: Courses A, B and C are given in an 8 course sequence A, B, C, B, A, B, C, B. Repeat until the patient fails to respond. The ineffective course should then be replaced by course D. The course should be repeated at 7-day intervals, or on recovery of bone-marrow depression.
Reference: Newlands et al. Br. J. Obst. Gyn. 93:63-69, (1986).

HIGH RISK CASES (WHO SCORE > 8)

EMA/CO

Course 1		
Dactinomycin	0.5 mg/m^2 IV	days 1 and 3
Etoposide	100 mg/m^2 IV	days 1 and 3
Methotrexate	100 mg/m^2 IV	day 1 and
Methotrexate	200 mg/m^2 IV	day 1 (12 hour infusion)
Folinic acid	15 mg P.O. or I.M. b.i.d. for 4 doses, beginning 24 hours after the first methrotrexate dose	

Course 2		
Vincristine	1.0 mg/m^2 IV	day 8
Cyclophosphamide	600 mg/m^2 IV	day 8

Note: Course 1 and 2 are repeated in 6-day sequences (unless mucositis develops) up to CR or resistance. As a prophylactic treatment of the skull, intrathecal administration of 12.5 mg methotrexate on day 1 of course 2. (i.e. every alternate course).
Reference:
Bower et al. J. Clin. Oncol. 15(1997):2636-2643
Newlands ES et al. Br J Obstet Gynaecol. 1991 Jun;98(6):550-7.

HIGH RISK GESTATIONAL TROPHOBLASTIC TUMOURS (CHARING CROSS SCORING SYSTEM > 8)

EMA/CO

Course 1		
Dactinomycin	0.5 mg/m^2 IV	days 1 and 2
Etoposide	100 mg/m^2 IV	days 1 and 2
Methotrexate	300 mg/m^2 IV	day 1 (12 hr infusion)
Folinic acid	15 mg P.O. or I.M. b.i.d. for 4 doses, beginning 24 hours after the first methrotrexate dose.	

Course 2		
Vincristine	0.8 mg/m^2 IV	day 8
Cyclophosphamide	600 mg/m^2 IV	day 8

Note: Course 1 and 2 are repeated in 6-day sequences (unless mucositis develops) up to CR or resistance. As a prophylactic treatment of the skull, intrathecal administration of 12.5 mg methotrexate on day 1 of course 2. (i.e. every alternate course).
Reference: McNeish IA et al. J Clin OncoI20(7):1838-1844, (2002).

Triple MAC

Methotrexate	0.3 mg/kg I.M.	days 1 – 5
Dactinomycin	8 – 10 μg/kg IV	days 1 – 5
Chlorambucil	0.2 mg/kg P.O.	days 1 – 5
or		
Cyclophosphamide	250 mg IV	days 1 – 5
To be repeated every 15 – 21 days		

Reference: Soper, Semin. Oncol. 22(1995):172-184 (for review)

APE (Dactinomycin-Platinum-Etoposide)

Dactinomycin	300 μg/m^2 IV	days 1, 2, 3, 14, 15, 16
Etoposide	100 mg/m^2 IV or 200 mg/m^2 orally	days 1, 2, 3, 14, 15, 16
Cisplatin	100 mg/m^2 IV	day 1
With overhydration and mannitol diuresis		
Cycles to be repeated every 4 weeks		

Reference: Theodore C et al. Cancer 64:1824-1828. 1989.

PVB (Cisplatin-Vinblastine-Bleomycin)

Vinblastine	0.3 mg/kg IV	day 1
Bleomycin	15 mg/day civi	days 1, 2, 3,
Cisplatin	100 mg/m^2 IV	day 2
With overhydration and mannitol diuresis		
To be repeated at 2 1-day intervals		

Reference: Azab M, Cancer 64:1829-1832, (1989).

SALVAGE THERAPY FOR DRUG RESISTANT CHORIOCARCINOMA

EP/EMA

EP		
Day 1		
Etoposide	150 mg/m^2 IV in 250 mL NS over 30 minutes	
Cisplatin	25 mg/m^2 IV in 1 L NS 1 20 mmol KCl 4 hours	
Cisplatin	25 mg/m^2 IV in 1 L NS 1 20 mmol KCl 4 hours	
Cisplatin	25 mg/m^2 IV in 1 L NS 1 20 mmol KCl 4 hours	

EMA		
Day 1		
Etoposide	100 mg/m^2 IV in 250 mL NS over 30 minutes	
Methotrexate	300 mg/m^2 IV in 1 L NS over 12 hours	
Actinomycin D	0.5 mg IV bolus	
Day 2		
Folinic acid	15 mg orally or intramuscularly twice daily for 4 doses 24 hours after start of methotrexate	

Note. EP and EMA are alternated at weekly intervals. Close monitoring of renal function is essential.
Reference: Newlands ES et al. J Clin Oncol 18:854-859, (2000).

MISCELLANEOUS

Methotrexate (intramuscular)

Methotrexate	30 mg/m^2 I.M.	weekly
If no major toxicity was encountered, the weekly dose was escalated 5 mg/m^2 at three-week intervals until a maximum dose of 50 mg/m^2 each week was achieved.		

Reference: Homesley HD et al. Obstet Gynecol 72:413, (1988)

Ifosfamide-Carboplatin-Etoposide

Ifosfamide	1500 mg/m^2/d for 5 days
Carboplatin	200 mg/m^2/d for 5 days
Etoposide	250 mg/m^2/d for 5 days
Followed by bone marrow reinfusion	

Reference: Lotz JP et al. Cancer1995:75:874-85.

PEBA (Drug resistant choriocarcinoma)

Cisplatin	20 mg/m^2	day 1-4
Etoposide	100 mg/m^2	day 1-4
Bleomycin	10 mg/m^2	day 1-4
Adriyamycin	40 mg/m^2	day 1
To be repeated every three week.		
A total of six to eight cycles.		

Reference: Pai CL et al. Gynecologic Oncology 56, 231-234, (1995)

PART - I
Solid Tumor

Head and Neck Cancer

HEAD AND NECK CANCER

Head & Neck Cancer is the sixth most common form of cancer worldwide. It comprises of complex group of diseases including Squamous Cell Carcinomas of the oral cavity, pharynx and larynx.

LARYNGEAL CARCINOMA

As per the NCI, estimated 12,360 new cases and 3,650 deaths from laryngeal cancer in the US are reported in 2012. Primary subglottic cancers, which are quite rare, drain through the cricothyroid and cricotracheal membranes to the pretracheal, paratracheal, and inferior jugular nodes, and occasionally to mediastinal nodes.

A clear association has been made between smoking, excess alcohol ingestion, and the development of squamous cell cancers of the upper aerodigestive tract. For smokers, the risk of the development of laryngeal cancer decreases after the cessation of smoking but remains elevated even years later when compared to that of nonsmokers. Patients treated for laryngeal cancers are at highest risk of recurrence in the first 2 to 3 years. Recurrences after 5 years are rare and usually represent new primary malignancies.

LIP & ORAL CAVITY CANCER

Early cancers (stage I and stage II) of the lip and oral cavity are highly curable by surgery or by radiation therapy, and the choice of treatment is dictated by the anticipated functional and cosmetic results of treatment and by the availability of the particular expertise required of the surgeon or radiation oncologist for the individual patient. Advanced cancers (stage III and stage IV) of the lip and oral cavity represent a wide spectrum of challenges for the surgeon and radiation oncologist. Except for patients with small T3 lesions and no regional lymph node and no distant metastases or who have no lymph nodes larger than 2 cm, for whom treatment by radiation therapy alone or surgery alone might be appropriate, most patients with stage III or stage IV tumors are candidates for treatment by a combination of surgery and radiation therapy.

The rate of curability of cancers of the lip and oral cavity varies depending on the stage and specific site. Most patients present with early cancers of the lip, which are highly curable by surgery or by radiation therapy with cure rates of 90% to 100%. Small cancers of the retromolar trigone, hard palate, and upper gingiva are highly curable by either radiation therapy or surgery, with survival rates

of as much as 100%. Local control rates of as much as 90% can be achieved with either radiation therapy or surgery in small cancers of the anterior tongue, the floor of the mouth, and buccal mucosa.

Moderately advanced and advanced cancers of the lip also can be controlled effectively by surgery or radiation therapy or a combination of these. The choice of treatment is generally dictated by the anticipated functional and cosmetic results of the treatment. Moderately advanced lesions of the retromolar trigone without evidence of spread to cervical lymph nodes are usually curable and have shown local control rates of as much as 90%; such lesions of the hard palate, upper gingiva, and buccal mucosa have a local control rate of as much as 80%. In the absence of clinical evidence of spread to cervical lymph nodes, moderately advanced lesions of the floor of the mouth and anterior tongue are generally curable with survival rates of as much as 70% and 65%, respectively.

OROPHARYNGEAL CANCER

Worldwide, cancers of the oropharynx and hypopharynx account for an estimated 123,000 new cases per year, with an estimated mortality of 79,000 deaths. Cancers of the oropharynx and hypopharynx account for an estimated 123,000 new cases per year, with an estimated mortality of 79,000 deaths. Men are afflicted 3 to 5 times more often than women. Tobacco and alcohol abuse represent the most significant risk factors. Defective elimination of acetaldehyde, a carcinogen poses an additional risk factor.

The anterior tonsillar pillar and tonsil is the most common location for a primary tumor of the oropharynx. These cancers can progress across a broad region including the lateral soft palate, retromolar trigone and buccal mucosa, and tonsillar fossa. Soft palate tumors are primarily found on the anterior surface. Lesions in this area may remain superficial and in early stages. The lymphatic drainage is primarily to level II nodes.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Spaulding CA et al. Int J Radiat Oncol Biol Phys 13(7):963-8, (1987).
Spitz MR: Semin Oncol 21(3):281-8, (1994).
Bosetti C et al. Oral Oncol 42(9):866-72, (2006).
Wallner PE et al. Patterns of Care Study. Am J Clin Oncol 9(1):50-7, (1986).
Takagi M et al. Cancer 69(5):1081-7, (1992).
Parkin DM et al. Int J Cancer 94(2):153-6, (2001).
American Cancer Society.: Cancer Facts and Figures 2004.
Licitra L et al. Crit Rev Oncol Hematol 41(1):107-22, (2002).

LARYNX

PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage.

T4a Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumor limited to one vocal cord

T1b Tumor involves both vocal cords

T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

T3 Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage

T4a Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures Subglottis

T1 Tumor limited to the subglottis

T2 Tumor extends to vocal cord(s) with normal or impaired mobility

T3 Tumor limited to larynx with vocal cord fixation

T4a Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest Dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node, more than 6 cm in greatest dimension

**Note: Metastases at level VII are considered regional lymph node metastases.*

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

LIP AND ORAL CAVITY

PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor 2 cm or less in greatest dimension

T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumor more than 4 cm in greatest dimension

T4a Moderately advanced local disease. (Lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose (Oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone, [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)

T4b T4b Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N2a Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	Any T	N3	M0
	T4b	Any N	M0
IVC	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

PHARYNX

PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Nasopharynx

T1 Tumor confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension*

T2 Tumor with parapharyngeal extension*

T3 Tumor involves bony structures of skull base and/or paranasal sinuses

T4 Tumor with intracranial extension and/or involvement of involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

**Parapharyngeal extension denotes posterolateral infiltration of tumor.*

Oropharynx

T1 Tumor 2 cm or less in greatest dimension

T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis

T4a Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*

T4b Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

**Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.*

Hypopharynx

T1 Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension

T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx

T3 Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus

T4a Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue*

T4b Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

**Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.*

REGIONAL LYMPH NODES (N)

Nasopharynx

The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension*
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
N3	Metastasis in a lymph node(s)* $>$ 6 cm and/or extension to supraclavicular fossa
N3a	Greater than 6 cm in dimension
N3b	Extension to the supraclavicular fossa**

**Midline nodes are considered ipsilateral nodes.*
***Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder. Note that this would include caudal portions of Levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.*

Oropharynx and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

**Metastases at Level VII are considered regional lymph node metastases.*

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING: NASOPHARYNX

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IVB	Any T	N3	M0
IVC	Any T	Any N	M1

STAGE GROUPING: OROPHARYNX, HYPOPHARYNX

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

NASAL CAVITY AND PARANASAL SINUSES

PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Tis Carcinoma in situ

Maxillary Sinus

T1 Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone

T2 Tumor causing bone erosion or destruction includ ing extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates

T3 Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses

T4a Moderately advanced local disease. Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses

T4b Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

Nasal Cavity and Ethmoid Sinus

T1 Tumor restricted to any one subsite, with or without bony invasion

T2 Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion

T3 Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate

T4a Moderately advanced local disease. Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses

T4b Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node, more than 6 cm in greatest dimension

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

SALIVARY GLANDS

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension*
T4a	Moderately advanced disease Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

**Note: Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Concurrent chemoradiation for stage III, IVA and IVB cancer
- Concurrent targeted-radiation therapy for stage III, IVA and IVB cancer
- Neoadjuvant chemotherapy followed by chemoradiation or radiation for stage III, IVA and IVB cancer
- Concurrent chemoradiation for stage III, IVA and IVB nasopharyngeal cancer
- Chemotherapy for recurrent or metastatic cancer
- Targeted therapy for recurrent or metastatic cancer

CONCURRENT CHEMORADIATION FOR STAGE III, IVA AND IVB CANCER

PRIMARY SYSTEMIC THERAPY + CONCURRENT RT

Cisplatin + RT

Cisplatin	100 mg/m^2 IV	d1, 22 and 43
Concurrent radiotherapy	2 Gy/d to a total of 70 Gy	

Reference:
Forastiere A et al. J Clin Oncol 2006;24: Abstract 5517.
Forastiere AA et al. N Engl J Med 2003;349:2091.
Adelstein DJ et al. J Clin Oncol 2003;21:92.

5-FU + Cisplatin + RT

Cisplatin	20 mg/m^2/d civi	d1-4 and 22-25
5-FU	1000 mg/m^2/d civi	d1-4 and 22-25
Concurrent radiotherapy	2 Gy/d to a total of 70 Gy	

Reference: Adelstein DJ et al. Cancer 2000;88:876.

5-FU + Carboplatin + RT

Carboplatin	70 mg/m^2/d IV	d1-4, 22-25 and 43-46
5-FU	600 mg/m^2/d civi	d1-4, 22-25 and 43-46
Concurrent radiotherapy	2 Gy/d to a total of 70 Gy	

Reference:
Calais G et al. J Natl Cancer Inst 1999;15:2081.
Denis F et al. J J Clin Oncol. 2004 Jan 1;22(1):69-76. Epub 2003 Dec 2.
Bourhis J et al. Lancet Oncol. 2012 Feb;13(2):145-53. Epub 2012 Jan 18.

5-FU + RT

5-FU	1200 mg/m^2/d civi	d1-3 and 22-24
Concurrent radiotherapy	2 Gy/d to a total of 66 Gy	

Reference: Browman GP et al. J Clin Oncol 1994;12:2648.

Hydroxyurea + 5-FU + RT

Hydroxyurea	1 g b.i.d.
5-FU	800 mg/m^2/d civi
Concurrent radiotherapy	2 Gy/d to a total of 70 Gy

Reference: Garden AS et al. J Clin Oncol 2004 Jul 15;22(14):2856-64.

Paclitaxel + Cisplatin + RT

Paclitaxel	30 mg/m^2
Cisplatin	20 mg/m^2
Concurrent radiotherapy	2 Gy/d to a total of 70 Gy

Reference: Garden AS et al. J Clin Oncol 2004 Jul 15;22(14):2856-64.

Weekly Paclitaxel + Carboplatin + RT

Paclitaxel	45 mg/m^2/wk
Carboplatin	100 mg/m^2/wk
Concurrent radiotherapy	1.8 Gy/d to a total of 70.2 Gy

Reference: Suntharalingam M et al. J Int J Radiat Oncol Biol Phys. 2000 Apr 1;47(1):49-56.

POSTOPERATIVE CHEMORADIATION

Cisplatin + RT

Cisplatin	100 mg/m^2 IV	d1, 22 and 43
Concurrent radiotherapy	2 Gy/d to a total of 60-66 Gy over 6-6.6 wks	

Reference:
Cooper JS et al. N Engl J Med. 2004 May 6;350(19):1937-44.
Bernier J et al. N Engl J Med. 2004;350:1945.
Bernier J et al. Head Neck 2005;27:843.

Paclitaxel + Cisplatin + 5-FU

Paclitaxel	175 mg/m^2 IV	d1
Cisplatin	100 mg/m^2 IV	d1
5-FU	1000 mg/m^2/d	d1-5
Followed by		
Cisplatin	100 mg/m^2 IV	d1, 22, 43
With RT 70 Gy		

Reference: Hitt R et al. J Clin Oncol. 2005 Dec 1;23(34):8636-45. Epub 2005 Nov 7.

CONCURRENT TARGETED-RADIATION THERAPY FOR STAGE III, IVA AND IVB CANCER

Cetuximab + RT

Cetuximab	loading dose 400 mg/m^2 IV, 1 week before XRT, then
	250 mg/m^2 IV qw
Concurrent radiotherapy	2 Gy/d to a total of 70 Gy

Note: Approved by FDA on 3/1/2006
Reference: Bonner JA et al. N Engl J Med 2006;354:567.

NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CHEMORADIATION OR RADIATION FOR STAGE III, IVA AND IVB CANCER

TPF-Carboplatin + RT

Docetaxel	75 mg/m^2 IV over 1 hour	d1
Cisplatin	100 mg/m^2 IV over 30 min–3 hours	d1
5-FU	1000 mg/m^2/d civi	d1–4
Q3w x 3 cycles		
3–8 weeks later:		
Carboplatin	AUC 1.5 IV over 1 hour	qw x 7 weeks during RT
Concurrent RT	2 Gy/d to a total of 70–74 Gy	
6–12 weeks later:		
Surgical resection as needed		

Note: Approved by FDA on 9/28/07
Reference: Posner MR et al. N Eng J Med 2007;357:1705.

TPF-RT

Docetaxel	75 mg/m^2 IV over 1 hour	d1
Cisplatin	75 mg/m^2 IV over 1 hour	d1
5-FU	750 mg/m^2/d civi	d1–5
Q3w x 4 cycles		
4–7 weeks later, radiotherapy 1.8–2 Gy/d to a total of 66–70 Gy or accelarated/ hyperfractionated radiotherapy b.i.d. to a total of 70–74 Gy		
Surgical resection as needed before or after radiotherapy		

Note: Approved by FDA on 10/17/06.
Reference: Vermorken JB et al. N Eng J Med 2007;357:1695.

Cisplatin-5 FU + RT

Cisplatin	100 mg/m^2 IV infusion	day 1
5-Fluorouracil	1000 mg/m^2 (continuous infusion)	days 1 to 5
RT	64–70 Gy in 2 Gy per fraction 5 times/wk	

Reference: Lewin F et al. Radiother Oncol. 1997 Apr;43(1):23-8

Cisplatin-Epirubicin-Bleomycin

Cisplatin	100 mg/m^2 IV	day 1
Epirubicin	70 mg/m^2 IV	day 1
Bleomycin	15 mg IV bolus followed by 12 mg/m^2 IV civi	day 1–5
Repeat the cycle every 4 weeks. (neoadjuvant 2–3 courses)		
Followed by definitive radiation therapy with 70 Gy for 7 weeks		

Reference: BACHOUCHI et al. J. Natl. Cancer Inst. 82(1990):616-620

Paclitaxel-Carboplatin-THFX

Paclitaxel	135 mg/m^2 IV	day 1/wk for 6 weeks
Carboplatin	AUC 2	days 1 to 4/wk for 6 weeks
2 to 3 weeks after the last dose of carboplatin and paclitaxel		
5 cycles of concomitant chemoradiotherapy with TFHX (Paclitaxel, 5-FU, hydroxyurea and radiotherapy)		

Reference: Vokes et al. J Clin Oncol 21(2):320-326, (2003)

CONCURRENT CHEMORADIATION FOR STAGE III, IVA AND IVB NASOPHARYNGEAL CANCER

Cisplatin + RT-Cisplatin + 5-FU

Cisplatin	100 mg/m^2 IV	d1, 22 and 43
Concurrent radiotherapy	2 Gy/d to a total of 70 Gy	
Followed by		
Cisplatin	80 mg/m^2 IV	d1
5-FU	1000 mg/m^2/d civi	d1–4
Q4w x 3 cycles		

Reference:
Al-Sarraf, M et al. J Clin Oncol 1998;16:1310.
Chan AT et al. J Nat Clin Inst 2005;97:536.

Oxaliplatin + RT

Oxaliplatin	70 mg/m^2 IV over 2 hours	qw x 6
Concurrent radiotherapy	2 Gy/d to a total of 70–74 Gy	

Reference: Zhang L et al. J Clin Oncol 2005;23:8461.

Docetaxel + Cisplatin + 5-FU

Docetaxel	70 mg/m^2 IV	d1
Cisplatin	75 mg/m^2 IV	d1
5-FU	1000 mg/m^2/d	d1–4
Followed by		
Cisplatin	100 mg/m^2 IV	q3w
With RT		

Reference: Bae WK et al. Cancer Chemother Pharmacol. 2010 Feb;65(3):589-95.

CHEMOTHERAPY FOR RECURRENT OR METASTATIC CANCER

5-FU + Cisplatin + Bleomycin

Cisplatin	100 mg/m^2 IV	d1
5-FU	650 mg/m^2/d civi	d1–5
Bleomycin	15 mg IV	d1
	followed by	
	16 mg/m^2/d civi	d1–5
Q4w x 3 cycles		

Reference: Boussen, H et al. J Clin Oncol 1991;9:1675.

5-FU + Cisplatin + Bleomycin + Epirubicin

Bleomycin	10 mg IV bolus	d1
	followed by	
	12 mg/m^2/d civi	d1–4 in first 3 cycles only
5-FU	700 mg/m^2/d civi	d1–4
Epirubicin	70 mg/m^2 IV	d1
Cisplatin	100 mg/m^2 IV	d5
Q3w x 6 cycles		

Reference: Taamma, A et al. Cancer 1999;86:1101.

5-FU + Cisplatin + Epirubicin + Mitomycin

5-FU	800 mg/m^2/d civi	d1–4
Epirubicin	70 mg/m^2 IV	d1
Mitomycin	10 mg/m^2 IV	d1 in cycle 1, 3 and 5 only
Cisplatin	100 mg/m^2 IV	d1
Q4w x 6 cycles		

Reference: Hasbini, A et al. Ann Oncol 1999;10:421.

Cisplatin + Gemcitabine

Cisplatin	50 mg/m^2 IV	d1 and 8
Gemcitabine	1000 mg/m^2 IV	d1, 8 and 15
Q4w x 6 cycles		

Reference: Ngan, RK et al. Ann Oncol 2002;13:1252.

5-FU + Cisplatin

Cisplatin	100 mg/m^2 IV	d1
5-FU	1000 mg/m^2/d civi	d1–4
Q3w		

Reference:
Gibson MK et al. Clin Oncol. 2005 May 20;23(15):3562-7.
Forastiere AA et al. J Clin Oncol 1992;10:1245.
Jacobs C et al. J Clin Oncol. 1992 Feb;10(2):257-63.

5-FU + Carboplatin

Carboplatin	300 mg/m^2 IV	d1
5-FU	1000 mg/m^2/d civi	d1–4
Q4w		

Reference: Forastiere AA et al. J Clin Oncol 1992;10:1245.

Methotrexate

Regimen # 1

Methotrexate	40 mg/m^2 IV
Qw	

Reference: Forastiere AA et al. J Clin Oncol 1992;10:1245.

Regimen # 2

Methotrexate	40–60 mg/m^2 IV	once weekly

Reference:
DeCONTI and SCHOENFELD, Cancer 48(1981):1061-1072
VOGL et al. Cancer 56(1985):432-442

5-FU + LV + Cisplatin

Cisplatin	100 mg/m^2 IV	d1
5-FU	800 mg/m^2/d civi	d1–5
Leucovorin	50 mg/m^2 P.O. q6h	d1–5
Q4w		

Reference: Vokes EE et al. J Clin Oncol 1988;6:618.

Cisplatin + Capecitabine

Cisplatin	75 mg/m^2 IV	d1
Capecitabine	1000 mg/m^2 P.O.	b.i.d. x 2w
Q3w		

Reference: Hitt R et al. Br J Cancer 2004;91:2005.

Cisplatin + Paclitaxel

Regimen # 1	
Cisplatin	75 mg/m^2 IV
Paclitaxel	135 mg/m^2 civi x 24 hrs
Q3w	

Reference: Forastiere AA et al. J Clin Oncol 2001;19:1088.

Regimen # 2		
Paclitaxel	175 mg/m^2 IV 3 hr infusion	day 1
Cisplain	75 mg/m^2 IV 30 min infusion	day 2
Repeat the cycle every 3 weeks		

Reference: Adamo V et al. Oral Oncol. 2004 May;40(5):525-31

Carboplatin + Paclitaxel

Carboplatin	AUC 6 IV
Paclitaxel	200 mg/m^2 IV over 3 h
Q3w	

Reference: Clark JI et al. Cancer 2001;92:2334.

Carboplatin + Docetaxel

Carboplatin	AUC 6 IV
Docetaxel	65 mg/m^2 IV over 3 h
Q3w	

Reference: Samlowski WE et al. Cancer Cancer Invest. 2007 Apr-May;25(3):182-8.

Cisplatin + Docetaxel

Cisplatin	75 mg/m^2 IV
Docetaxel	75 mg/m^2 IV
Q3w	

Reference: Glisson BS et al. J Clin Oncol 2002;20:1593.

Paclitaxel

(Advanced squamous cell carcinoma of the head and neck)

Regimen # 1	
Paclitaxel	175 mg/m^2 3 h inf/wk

Reference: Gebbi et al. Eur J Cancer 32(1996):901-902

Regimen # 1	
Paclitaxel	250 mg/m^2 3 h inf/wk

Reference: Forastiere et al. Cancer 82(1998):2270-2274

Docetaxel

Docetaxel	100 mg/m^2 1 h inf/wk

Reference: Couteau C et al. Br J Cancer. 1999 Oct;81(3):457-62

Pegylated Liposomal Doxorubicin

Pegylated Liposomal Doxorubicin	30 mg/m^2 q3 wks and dose escalation of 5 mg/m^2 MTD 45–50 mg/m^2

Reference: Caponigro F, Ann Oncol. 2000 Mar;11(3):339-42

Ifosfamide-Cisplatin

Cisplatin	10 mg/m^2 IV infusion	days 1–5
Ifosfamide	1,500 mg/m^2 IV (30 min infusion)	days 1–5
(With mesna uroprotection)		
Repeat the cycle every 4 weeks.		

Reference: PAI et al. Oncology 50(1993):86-91

Paclitaxel-Cisplatin-Ifosfamide

Paclitaxel	175 mg/m^2 IV (3 h infusion)	day 1
Cisplatin	60 mg/m^2 IV infusion	day 1
Ifosfamide	1,000 mg/m^2 IV (2 hr infusion)	days 1–3
(with mesna uroprotection)		
Repeat the cycle every 3–4 weeks.		

Reference: SHIN et al. J Clin. Oncol. 16(1998):1325-1330

Paclitaxel-Gemcitabine

Paclitaxel	175 mg/m^2 IV	day 1
Gemcitabine	1000 mg/m^2	days 1 & 8
Repeat the cycle every 3 weeks		

Reference: Fountzilas G et al. Ann Oncol, 2006 Oct;17(10):1560-7. Epub 2006 Jun21

Cisplatin Methotrexate Bleomycin & Vincristine (CABO)

Cisplatin	50 mg/m^2 IV	day 4
Methotrexate	40 mg/m^2	day 1 & 15
Bleomycin	10 mg	day 1, 8 & 15.
Vincristine	2 mg	day 1, 8 & 15
Repeat the cycle every 3 weeks X 3 cycles		

Reference: Clavel M et al. Ann Oncol. 1994 Jul;5(6):521-6

Docetaxel Cisplatin 5 FU (TPF)

Docetaxel	75 mg/m^2	day 1
Cisplain	100 mg/m^2	day 1
5 FU	1000 mg/m^2 days 1 through 4 (total dose 4000 mg/m^2)	day 1, 22, & 43
Maximum of 3 cycles		

Reference: Baghi M et al. Anticancer Res. 2006 Jan-Feb;26(1B):585-90

TARGETED THERAPY FOR RECURRENT AND METASTATIC CANCER

Cetuximab

Cetuximab	loading dose 400 mg/m^2 IV over 2 hrs	
	followed by 250 mg/m^2 IV over 1 hr qw	

Reference: Vermorken JB et al. J Clin Oncol 2007;25:2171.

Cisplatin + Cetuximab

Cisplatin	75–100 mg/m^2 IV	d1 q3–4w
Cetuximab	loading dose 400 mg/m^2 IV over 2 hrs d1,	
	followed by 250 mg/m^2 IV over 1 hr qw	

Reference:
Burtness B et al. J Clin Oncol 2005;23:8646.
Herbst RS et al. J Clin Oncol 2005;23:5578.
Baselga J et al. J Clin Oncol 2005;23:5568.

Carboplatin + Cetuximab

Carboplatin	AUC 5 IV	q3w
Cetuximab	loading dose 400 mg/m^2 IV over 2 hrs d1,	
	followed by 250 mg/m^2 IV over 1 hr qw	

Reference:
Chan AT et al. J Clin Oncol 2005;23:3568.
Baselga J et al. J Clin Oncol 2005;23:5568.

Paclitaxel + Cetuximab

Paclitaxel	80 mg/m^2 IV	qw
Cetuximab	loading dose 400 mg/m^2 IV over 2 hrs d1,	
	followed by 250 mg/m^2 IV over 1 hr qw	

Reference: Hitt R et al. 2007 ASCO annual meeting. Abstract 6012.

5-FU + Cisplatin + Cetuximab

Cisplatin	100 mg/m^2 IV over 1 hour	d1q3w x 6 cycles
5-FU	1000 mg/m^2/d civi	d1–4 q3w x 6 cycles
Cetuximab	loading dose 400 mg/m^2 IV over 2 hours d1,	
	followed by 250 mg/m^2 IV over 1 hour ending at least 1 hour before chemotherapy qw until disease progression or unacceptable toxicity	

Reference: Vermorken JB et al. N Eng J Med 2008;359:1116.

5-FU + Carboplatin + Cetuximab

Carboplatin	AUC 5 IV over 1 hour	d1q3w x 6 cycles
5-FU	1000 mg/m^2/d civi	d1–4 q3w x 6 cycles
Cetuximab	loading dose 400 mg/m^2 IV over 2 hours d1,	
	followed by 250 mg/m^2 IV over 1 hour ending at least 1 hour before chemotherapy qw until disease progression or unacceptable toxicity	

Reference: Vermorken JB et al. N Eng J Med 2008;359:1116.

Cisplatin + Erlotinib

Erlotinib	100 mg P.O. qd to start 7 days before cisplatin until disease progression	
Cisplatin	75 mg/m^2 IV	q3w x 6 cycles

Reference: Siu L et al. J Clin Oncol 2007;25:2178.

Cisplatin + Docetaxel + Erlotinib

Cisplatin	75 mg/m^2 IV	d1 q3w x 6 cycles
Docetaxel	75 mg/m^2 IV	d1 q3w x 6 cycles
Erlotinib	150 mg P.O. qd until disease progression	
Filgrastim support		

Reference: Kim ES et al. 2007 ASCO annual meeting. Abstract 6013.

PART - I
Solid Tumor

Kaposi Sarcoma

KAPOSI SARCOMA

Kaposi's sarcoma (KS) was first described in 1872 by the Hungarian dermatologist, Moritz Kaposi. From that time until the current human immunodeficiency virus (HIV) disease epidemic identified with the Acquired Immunodeficiency Syndrome (AIDS), KS remained a rare tumor. While most of the cases seen in Europe and North America have occurred in elderly men of Italian or Eastern European Jewish ancestry, the neoplasm also occurs in several other distinct populations: young black African adult males, prepubescent children, renal allograft recipients, and other patients receiving immunosuppressive therapy.

The usual age at onset is between 50 and 70 years. Classic KS tumors usually present with one or more asymptomatic red, purple, or brown patch, plaque, or nodular skin lesion. The disease is often limited to single or multiple lesions usually localized to one or both lower extremities, especially involving the ankles and soles.

Classic Kaposi's sarcoma most commonly runs a relatively benign, indolent course for 10 to 15 years or more with slow enlargement of the original tumors and the gradual development of additional lesions. Venous stasis and lymphedema of the involved lower extremity are frequent complications. In long-standing cases, systemic lesions can develop along the gastrointestinal tract, in lymph nodes, and in other organs. The visceral lesions are generally asymptomatic and are most often discovered only at autopsy, though clinically, gastrointestinal bleeding can occur. As many as 33% of the patients with classic KS develop a second primary malignancy, which is most often non-Hodgkin's lymphoma.

Reference:
Friedman-Kien AE et al. Lancet 335(8682):168-9, (1990).
Safai B, Good RA: Clin Bull 10(2):62-9, (1980).
Reynolds WA et al. Medicine (Baltimore) 44(5):419-43, (1965).
Safai B et al. Cancer 45(6):1472-9, (1980).
Kaposi Sarcoma Treatment (PDQ®): National Cancer Institute, available at: http://www.cancer.gov/cancertopics/pdq/treatment/kaposis/healthprofessional/allpages#Reference2.1

AIDS CLINICAL TRIALS GROUP STAGING CLASSIFICATION

	Good Risk (0)	Poor Risk (1)
	(Any of the following)	(Any of the following)
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease [Note: Minimal oral disease is non-nodular KS confined to the palate.]	• Tumor-associated edema or ulceration • Extensive oral KS • Gastrointestinal KS • KS in other non-nodal viscera
Immune system (I)	CD4 cells ≥ = 200/microL	CD4 cells < 200 per cubic millimeter
Systemic illness (S)	No history of OIs or thrush [Note: OIs are opportunistic infections.]	History of OIs and/ or thrush
	No "B" symptoms [Note: "B" symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting >2 weeks.]	"B" symptoms present
	Performance status ≥70 (Karnofsky)	• Performance status <70 • Other HIV-related illness (e.g., neurological disease or lymphoma)

Reference:
Krown SE et al. J Clin Oncol 7(9):1201-7, (1989).
Krown SE et al. J Clin Oncol 15(9):3085-92, (1997).

TREATMENT GUIDELINES FOR KAPOSI'S SARCOMA

Disease status of KS	HN disease status	Treatment options
Minimal cutaneous disease	CD4 count < 200/μL; prior 01: B symptoms	Local Therapy
	CD4 count 200/μL; No prior 01; no B syrnptoms	Interferon and antivirals or Local Therapy
Cosmetically disturbing disease	Any	Local Therapy
Extensive cutaneous disease	CD4 count < 200/μL; prior 01	Chemotherapy
	CD4 count < 200/μL; no prior 01; no B syrnptoms	Interferon and antivirals or chemotherapy
Localized bulky or painful disease	Any	Radiation and or chemotherapy
Tumor-associated edema	Any	Chemotherapy
Symptomatic visceral disease	Any	Chemotherapy

CHEMOTHERAPY REGIMENS

- Intralesional chemotherapy
- Systemic therapy

INTRALESIONAL CHEMOTHERAPY

Vinblastine

Vinblastine (0.2 mg/mL)	0.1 mL per 0.5 cm of surface area of lesion (maximum, 4 mL)

Reference: Joel B. Epstein. Cancer, 71(5);1722-1725, (1993).

SYSTEMIC THERAPY

Pegylated liposomal doxorubicin

Pegylated liposomal doxorubicin	20 mg/m^2 IV	q3w

Reference:
Stewart S et al. J Clin Oncol 1998;16:683.
Northfelt DW et al. J Clin Oncol 1997;15:653.

Liposomal Daunorubicin

Regimen # 1

Liposomal Daunorubicin (DaunoXome)	40 mg/m^2 IV
Q2w	

Reference:
Gill, PS et al. J Clin Oncol 1996;14:2353.
Presant et al. Lancet 341:1242-1243, (1993).

Regimen # 2

Liposomal Danorubicin	60 mg/m^2 IV every 2 week

Reference: Tulpule A et al. J Clin Oncol16(10):3369-3374, (1998).

Paclitaxel

Paclitaxel	100 mg/m^2 IV over 3 hrs
Premedications:	
Dexamethasone	20 mg IV, reduce to 8 mg IV for subsequent cycles if no hypersensitivity reaction after the first treatment
Cimetidine	100 mg/m^2 IV
Diphenhydramine	50 mg IV
Q2w until CR, progression or unacceptable toxicity	

Reference: Gill PS et al. J Clin Oncol 1999;17:1876.

Docetaxel

Docetaxel	25 mg/m^2 IV	qw x 8 wks, then qow

Reference: Lim, ST. Cancer 2005;103:417.

Vinorelbine

Vinorelbine	30 mg/m^2 IV
Q2w	

Reference: Nasti, G et al. J Clin Oncol 2000;18:1550.

Etoposide

Etoposide	50 mg P.O. qd	d1–7
Q2w		

Reference: Evans, SR et al. J Clin Oncol 2002;20:3236.

Bleomycin + Vincristine

Bleomycin	15 IU/m^2 IV
Vincristine	2 mg IV
Q3w x 6 cycles	

Reference: Stewart S et al. J Clin Oncol 1998;16:683.

Doxorubicin + Bleomycin + Vinblastine

Doxorubicin	40 mg/m^2 IV	d1
Bleomycin	15 U/m^2 IV	d1, 15
Vinblastine	6 mg/m^2 IV	d1
Q4w		

Reference: Laubenstein LL et al. J Clin Oncol 1984;2:1115.

Irinotecan

Irinotecan	150 mg/m^2 IV	day1-10

Reference: Vaccher E et al. AIDS Nov 4;19(16):1915-6. 2005

Etoposide

Etoposide	150 mg/m^2 IV x 3 days every 4 week

Reference: Laubenstein LJ et al. J Clin Oncol 2(10):1115-1120, (1984).

Vinblastine-Bleomycin

Vinblastine	pto 10 mg IV
Bleomycin	15 IU I.M.
To repeat every 3 weeks.	

Reference: Brambilla L et al. J Eur Acad Dermatol Venereol: 2006 Oct;20(9):1090-4

PART - I
Solid Tumor

Kidney Cancer (Renal Cell Cancer)

KIDNEY CANCER (RENAL CELL CANCER)

Renal cell cancer (renal adenocarcinoma, or hypernephroma) can often be cured if it is diagnosed and treated when still localized to the kidney and to immediately surrounding tissue. As per the NCI data, 64,770 new cases and 13570 deaths from renal cell (kidney and renal pelvis) cancer in the US are estimated in year 2012.

The probability of cure is directly related to the stage or degree of tumor dissemination. Even when regional lymphatics or blood vessels are involved with tumor, a significant number of patients can achieve prolonged survival and probable cure. When distant metastases are present, disease-free survival is poor. Because a majority of patients are diagnosed when the tumor is still relatively localized and amenable to surgical removal, approximately 40% of all patients with renal cancer survive 5 years. Occasionally patients with locally advanced or metastatic disease may exhibit indolent courses lasting several years. Late tumor recurrence many years after initial treatment occasionally occurs. Renal cell cancer is one of the few tumors in which well-documented cases of spontaneous tumor regression in the absence of therapy exist, but this occurs very rarely and may not lead to long-term survival.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Sene AP, Hunt L, McMahon RF, et al. Br J Urol 70(2):125-34, (1992).
Renal Cell Cancer Treatment (PDQ®): National Cancer Institute, available at: http://www.cancer.gov/cancertopics/pdq/treatment/renalcell/healthprofessional

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney

T3 Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia

T3a Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia

T3b Tumor grossly extends into the vena cava below the diaphragm

T3c Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava

T4 Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Immunotherapy
- Molecular targeting therapy
- Chemotherapy or chemotherapy + immunotherapy

IMMUNOTHERAPY

Interferon α-2b

Interferon (IFN) α-2b	5 million IU/m^2 S.C.	tiw

Reference:
Flanigan, RC et al. N Engl J Med 2001;345:1655.
Mickisch, GH et al. Lancet 2001;358:966.

High-dose Interleukin-2

Interleukin-2 (IL-2)	600,000–720,000 IU/kg IV over 15 min	q8h for up to
14 doses in 5 days,		
Repeat the treatment following 5–9 days of rest (one course)		
Courses repeated every 6–12 weeks		

Reference:
Fyfe, G et al. J Clin Oncol 1995;13:688.
Yang, JC et al. J Clin Oncol 2003;21:3127.

Low-dose Interleukin-2

Interleukin-2 (IL-2)	72,000 IU/kg IV bolus	q8h up to 14 doses in 5 days
Repeat the treatment following 7–10 days of rest (one course)		
Courses repeated every 8 weeks		

Reference: Yang, JC et al. J Clin Oncol 2003;21:3127.

SC Interleukin-2

Interleukin-2 (IL-2)	250,000 IU/kg S.C.	qd x 5 days in the first week,
	followed by	
	125,000 IU/kg S.C.	qd x 5 days/w for 5 weeks
Courses repeated every 8 week		

Reference: Yang, JC et al. J Clin Oncol 2003;21:3127.

Interleukin-2 + Interferon α-2a

Induction Interleukin-2 (IL-2)	18 million IU/m^2/d	civi x 5 days
Repeat the treatment following 6 days of rest (one course)		
Course repeated once after 3 weeks rest		
Maintenance IL-2	18 million IU/m^2/d	civi x 5 days (one course), courses repeated 3 times with a 3 weeks rest between courses
Interferon (IFN) α-2a	6 million IU S.C.	tiw

Reference: Negrier, S et al. N Engl J Med 1998;338:1272.

Interferon α and interleukin-2

Interleukin-2	5 MIU/m^2/S.C. every 8 hrs (i.e 3 x day) on day 1, and then daily for 5 days/week over 4 weeks.
Interferon α	5.0 MIU/m^2 S.C. 3 times weekly for 4 weeks (on an outpatient basis)
Repeat every 6 weeks	

Reference: McDermott DF et al. Semin Oncol 33:583-587, (2006)

MOLECULAR TARGETING THERAPY

Bevacizumab

Bevacizumab	10 mg/kg IV	q2w

Reference:
Bukowski RM et al. J Clin Oncol 2007;25:4536.
Yang, JC et al. N Engl J Med 2003;349:427.

Bevacizumab + Interferon α-2a (NCCN category 1 option)

Bevacizumab	10 mg/kg IV	q2w until disease progression
Interferon (IFN) α-2a	9 million IU S.C.	tiw for 1 yr

Reference: Escudier B et al. Lancet 2007;370:2103.

Sorafenib (NCCN category 2A option)

Sorafenib	400 mg P.O.	b.i.d.

Note: Approved by FDA on 12/20/2005
Reference:
Choueiri TK et al. J Clin Oncol 2008;26:127.
Escudier B et al. N Eng J Med 2007;356:125.
Ratain MJ et al. J Clin Oncol 2006;24:2505.
Eisen T et al. J Clin Oncol, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 24, No 18S (June 20 Supplement), 2006:4524
Bukowski RM et al. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 25, No 18S (June 20 Supplement), 2007:5023

Sunitinib (NCCN category 1 option)

Sunitinib	50 mg P.O.	qd x 4 wks, repeat after 2 wks rest

Note: Approved by FDA on 2/2/07
Reference:
Motzer RJ et al. J Clin Oncol. 2009 Aug 1;27(22):3584-90. Epub 2009 Jun 1.
Gore M E et al. Lancet Oncol. 2009 Aug;10(8):757-63. Epub 2009 Jul 15.
*Rini BI et al. J Clin Oncol 2008;26:3743. *
Cella D et al. J Clin Oncol 2008;26:3763.
Choueiri TK et al. J Clin Oncol 2008;26:127.
Motzer RJ et al. N Eng J Med 2007;356:115.
Motzer RJ et al. J Clin Oncol 2006;24:16.
Motzer RJ et al. JAMA 2006;295:2516.

Pazopanib (NCCN category 1 option)

Pazopanib	800 mg P.O.	od

Note: Approved by FDA on 19/10/09
Reference: Sternberg CN et al. J Clin Oncol. 2010 Feb 20;28(6):1061-8. Epub 2010 Jan 25.

Temsirolimus (NCCN category 1 option)

Temsirolimus	25 mg IV over 30 min	qw

Note: Approved by FDA on 5/30/07.
Reference: Hudes G et al. N Eng J Med 2007;356-2271.

Everolimus (As subsequent therapy)

Everolimus	10 mg (two 5 mg tablets) P.O.	qd
until progression or unacceptable toxicity		

Reference:
Motzer RJ et al. Cancer. 2010 Sep 15;116(18):4256-65.
Motzer RJ et al. Lancet 2008;372:449.

Axitinib (As subsequent therapy)

Axitinib	5–10 mg P.O.	bd

Reference: Rini BI et al. Lancet 2011 Dec 3;378(9807):1931-9. Epub 2011 Nov 4.

Erlotinib (As subsequent therapy)

Erlotinib	150 mg P.O.	od

Reference: Gordon MS et al. J Clin Oncol. 2009 Dec 1;27(34):5788-93. Epub 2009 Nov 2.

CHEMOTHERAPY OR CHEMOTHERAPY + IMMUNOTHERAPY

Medroxyprogesterone

Medroxyprogesterone	300 mg P.O./daily
Treatment to be continues until disease progression/unacceptable toxicity.	

Reference: Lee CP et al. J Clin Oncol 24:898-903. 2006

Thalidomide

Thalidomide	100 mg P.O. nightly/daily for Ist 2 weeks
	200 mg P.O. nightly/daily for IInd 2 weeks
	300 mg P.O. nightly/daily for 2 IIIrd weeks
	thereafter 400 mg P.O. nightly/daily
Treatment to be continues until disease progression/unacceptable toxicity.	

Reference: Lee CP et al. J Clin Oncol 24:898-903. 2006

Thalidomide (Low dose)-Interferon α

Thalidomide	100 mg/day P.O.
Interferon α	3.0 MIU/day S.C.

Reference: Amato RJ et al. Annals of Oncology 16:7-15, (2005)

Interferon α-Vinblastine

Vinblastine	0.1 mg/m^2 every 3 week
Interferon α2a	3 x 106 U S.C. or I.M. 3 times a week for first week than 18 x 106U S.C. for subsequent weeks

Reference: Pyrhonen et al. J. Clin. Oncol. 17(1999)9:2859-2867

FUNIL-Thalidomide

5 FU	1750 mg/m^2 C.I over 24 hours	day 1
Interferon α	6.0 MIU/day S.C.	days 1, 3 & 5
Interleukin-2	6.0 MIU C.I	days 2 – 5

Note: To be given for first 4 weeks in 6 weeks cycle.

Thalidomide	200 mg/day P.O.

Note: Increasing by 200 mg/14 days to target 1200 mg/day.
Reference: Amato RJ et al. Annals of Oncology 16:7-15, (2005)

Vinblastin

Vinblastin	0.1 mg/m^2	every 3 week

Reference: Pyrhonen et al. J. Clin. Oncol. 17(1999)9:2859-2867

PART - I
Solid Tumor

Liver Cancer (Hepatocellular Cancer)

LIVER CANCER (HEPATO-CELLULAR CANCER)

ADULT PRIMARY LIVER CANCER

As per the NCI, 28,720 new cases and 20,550 deaths from liver and intrahepatic bile duct cancer are estimated in the US in 2012. It is associated with cirrhosis in 50% to 80% of patients; 5% of cirrhotic patients eventually develop hepatocellular cancer, which is often multifocal. Hepatocellular carcinoma is potentially curable by surgical resection, but surgery is the treatment of choice for only the small fraction of patients with localized disease. Prognosis depends on the degree of local tumor replacement and the extent of liver function impairment.

Hepatitis B infection and hepatitis C infection appear to be the most significant causes of hepatocellular carcinoma worldwide, particularly in patients with continuing antigenemia and chronic active hepatitis. Male patients older than 50 years and persons who consume more than 80 grams of alcohol per day having both hepatitis B and hepatitis C infection may be at particularly high risk. Exposures to Aflatoxin, vinyl chloride dust are other risk factors. The primary symptoms of the hepatocellular carcinoma are those of a hepatic mass. Among patients with underlying cirrhotic disease, a progressive increase in alpha-fetoprotein (AFP) and/or in alkaline phosphatase or a rapid deterioration of hepatic function may be the only clue to the presence of the neoplasm.

CHILDHOOD LIVER CANCER

Liver cancer, a rare malignancy in children and adolescents, is divided into 2 major histologic subgroups: hepatoblastoma and hepatocellular carcinoma. The incidence of hepatoblastoma in U.S has doubled in last 25 years. The cause for the increase is not known, but the increasing survival following very low birth weight premature births, which are known to be associated with hepatoblastoma may contribute. The age of onset of liver cancer in children is related to the histology of the tumor. Hepatoblastomas usually occur before 3 years of age, and about 90% of malignant liver tumors in children younger than 4 years are hepatoblastomas. In several Asian countries, the incidence of hepatocellular carcinoma in children is more than 10 times that in North America. The high incidence appears to be related to the high incidence of perinatally acquired Hepatitis B.

There is a clear association between hepatoblastoma and familial adenomatous polyposis (FAP); children in families that carry the FAP gene are at an 800-fold increased risk for hepatoblastoma, though it occurs in less than 1% of FAP family members.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Mor E et al. Ann Intern Med 129(8):643-53, (1998).
Blumberg BS et al. Am J Pathol 81(3):669-82, (1975).
Tsukuma H et al. N Engl J Med 328(25):1797-801, (1993).
Tagger A et al. Int J Cancer 81(5):695-9, (1999).
Alpert ME et al. Cancer 28(1):253-60, (1971).
Darbari A et al. Hepatology 38(3):560-6, (2003).
Ikeda H et al. Cancer 82(9):1789-96, (1998).
Chang MH et al. Clin Cancer Res 11(21):7953-7, (2005).
Iwama T, Mishima Y. Cancer 73(8):2065-8, (1994).
Garber JE et al. J Natl Cancer Inst 80(20):1626-8, (1988).
Giardiello FM et al. Gut 39(96):867-9, (1996).

LIVER (EXCLUDING INTRAHEPATIC BILE DUCTS)

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
T3a	Multiple tumors more than 5 cm
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum.

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

INTRAHEPATIC BILE DUCT

PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ (intraductal tumor)

T1 Solitary tumor without vascular invasion

T2a Solitary tumor with vascular invasion

T2b Multiple tumors, with or without vascular invasion

T3 Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion

T4 Tumor with periductal invasion

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis present

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IVA	T4	N0	M0
	Any T	N1	M0
IVB	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Single Agent Therapy
- Combination Therapy
- Intra-Arterial Chemotherapy

SINGLE AGENT THERAPY

Sorafenib

Sorafenib	400 mg (200 mg/tab, 2 tabs) P.O.	b.i.d.
until progression or unacceptable toxicity		

Note: Approved by FDA on 11/16/2007

Reference:

Chiu J et al. J Clin Oncol, 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 29, No 15_suppl (May 20 Supplement), 2011:4083
Marrero J A et al. J Clin Oncol, 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 29, No 15_suppl (May 20 Supplement), 2011:4001
Cheng A et al. Lancet Oncol. 2009 Jan;10(1):25-34. Epub 2008 Dec 16.
Abou-Alfa GK et al. J Natl Compr Canc Netw. 2009 Apr;7(4):397-403.
Pinter M et al. Oncologist. 2009 Jan;14(1):70-6. Epub 2009 Jan 14
Yau T et al. Cancer. 2009 Jan 15;115(2):428-36.
Llovet JM et al. N Engl J Med 2008;359:378.
Abou-Alfa GK et al. J Clin Oncol 2006;24:4293.
J. Bruix et al. J Clin Oncol 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition).

Vol 27, No 15S (May 20 Supplement), 2009:4580
Craxi A et al. J Clin Oncol 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 26, No 15S (May 20 Supplement), 2008:15591
Raoul J et al. J Clin Oncol 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 28, No 15_suppl (May 20 Supplement), 2010:4051

Capecitabine

Capecitabine	1000 mg/m^2 P.O.	b.i.d. x 14 days
Q3w		

Reference: Patt, YZ et al. Cancer 2004;101:578.

Doxorubicin

Doxorubicin	60–75 mg/m^2 IV
Q3w	

Reference:
Gish RG et al. J Clin Oncol 2007;25:3069.
Lai, CL et al. Cancer 1988;62:479.

Bevacizumab

Bevacizumab	5 mg/kg or 10 mg/kg IV	q2w
until progression or unacceptable toxicity		

Reference: Siegel AB et al. J Clin Oncol 2008;26:2992.

COMBINATION THERAPY

Bevacizumab + Capecitabine

Bevacizumab	7.5 mg/kg IV	d1
Capecitabine	800 mg/m^2 P.O. bd	b.i.d. d1–14 q3w

Reference: Hsu CH et al. Br J Cancer. 2010 Mar 16;102(6):981-6. Epub 2010 Feb 16.

Bevacizumab + Capecitabine + Oxaliplatin

Bevacizumab	5 mg/kg IV	d1
Oxaliplatin	130 mg/m^2 IV	d1
Capecitabine	825 mg/m^2 P.O. b.i.d.	d1–14 q3w

Reference: Sun W et al. Cancer. 2011 Jul 15;117(14):3187-92. doi: 10.1002/cncr.25889. Epub 2011 Jan 24.

5-FU + LV

5-FU	370 mg/m^2/d IV	d1–5
Leucovorin	200 mg/m^2/d IV	d1–5
Q4w		

Reference: Porta, C et al. Oncology 1995;52:487.

Capecitabine + Oxaliplatin (XELOX)

Capecitabine	1000 mg/m^2 P.O.	b.i.d. d1–14
Oxaliplatin	130 mg/m^2 IV	d1
Q3w		

Reference: Boige V et al. Br J Cancer 2007;97:862.

Cisplatin + Gemcitabine

Cisplatin	35 mg/m^2 IV	d1, 8
Gemcitabine	1250 mg/m^2 IV	d1, 8
Q3w		

Reference: Yang, TS et al. 2003 ASCO annual meeting. Abstract 1351.

Gemcitabine + Oxaliplatin + Bevacizumab (GEMOX-B)

Cycle 1 (14 days)		
Bevacizumab	10 mg/kg IV	d1
Cycle 2 and beyond		
Bevacizumab	10 mg/kg IV	d1, 15
Gemcitabine	1000 mg/m^2 IV at 10 mg/m^2/min	d2, 16
Oxaliplatin	85 mg/m^2 IV over 2 hours	d2, 16
Q4w		

Reference: Zhu AX et al. J Clin Oncol 2006;24:1898.

(PIAF) 5-FU-Cisplatin-Doxorubicin-Interferon α 2b

5-fluorouracil	400 mg/m^2 IV	days 1–4
Cisplatin	20 mg/m^2 IV	day 1–4
Doxorubicin	40 mg/m^2 IV	day 1
Interferon α 2b	5 MU/m^2	day 1–4

Reference: Leung et al. Clin Cancer Res 1999;5:1676-1681

5-FU-Interferon α 2b

5-fluorouracil	200 mg/m^2 IV/day	days 1–21
Interferon α 2b	4 x 106U/m^2 S.C.	three times weekly
Repeat cycle every 28 days		

Reference: Patt et al. JCO 2003;21:421-427

Epirubicin-Etoposide

Epirubicin	40 mg/m^2 IV	day 1
Etoposide	120 mg/m^2 IV	day 1
Repeat cycle every 28 days		

Reference: Bobbio-Pallavicini et al. Eur J Cancer 1997 Oct;33(11):1784-8

5-FU-Cisplatin-Mithotrexate-Interferon α 2b

Interferon α 2b	3 MU/m^2 S.C.	3 times per week
Cisplatin	75 mg/m^2 IV	day 1–4
Mithotrexate	30 mg/m^2 IV	day 1
5-fluorouracil	750 mg/m^2 intra hepatic arterial infusion	Weekly

Reference: Urabe et al. Oncology 1998 Jan-Feb;55(1):39-47

INTRA-ARTERIAL CHEMOTHERAPY

Hepatic artery infusion has been studied and appears to have an increased response rate compared with intravenous chemotherapy. Similarly chemoembolisation has been employed.

Reference:
Figueras J et al. Hepatology 1997;25:1485-1489
Lencioni R et al. Eur Radiol 1997;7:514-519

5-FU-Low dose Cisplatin

Cisplatin	10 mg/body/day	continuous arterial infusion
5-fluorouracil	250 mg/body/day	continuous arterial infusion

Note: This infusion chemotherapy was continued for five days and discontinued for two days, repeated over four weeks as one course
Reference: Takao T et al. Gan To Kagaku Ryoho. 1999 Oct;26(12):1836-40

5-FU-Adriamycin-Cisplatin

5-fluorouracil	500 mg/day C.I	day 1–5
Cisplatin	10 mg/day	day 1
Adriamycin	10 mg/day	day1

Reference: Kato H et al. Gan To Kagaku Ryoho. 2005 Oct;32(11):1842-5

PART - I
Solid Tumor

Lung Cancer

LUNG CANCER

Lung cancer is major cause of mortality and morbidity worldwide. As per the NCI data, 226,160 new cases and 160,340 deaths are estimated in the US in 2012. It comprises of two major subtypes, non small cell lung cancer and small cell lung cancer.

NON SMALL CELL LUNG CANCER

Non-small cell lung cancer (NSCLC) is a heterogeneous aggregate of histologies. The most common histologies are epidermoid or squamous carcinoma, adenocarcinoma, and large cell carcinoma. Risk factors that contribute to the development of lung cancer include smoking, exposure to second-hand smoke, radon, arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon progeny, air pollution and radiation therapy to the breast or chest.

At diagnosis, patients with NSCLC can be divided into 3 groups that reflect both the extent of the disease and the treatment approach. The first group of patients has tumors that are surgically resectable (generally stage I, stage II, and selected stage III patients). The second group includes patients with either locally (T3 – T4) and/or regionally (N2 – N3) advanced lung cancer. The final group includes patients with distant metastases (M1) that were found at the time of diagnosis.

SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) accounts for approximately 15% of bronchogenic carcinomas. The overall incidence and mortality rates of SCLC in the United States have decreased during the past few decades. Small cell carcinoma of the lung has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2 to 4 months. Compared with other cell types of lung cancer, small cell carcinoma has a greater tendency to be widely disseminated by the time of diagnosis and it tends to develop distant metastases.

Approximately 30% of patients with small cell carcinoma will have tumor confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. These patients are designated as having limited-stage disease, and most 2-year disease-free survivors come from this group. Patients with tumors that have spread beyond the supraclavicular areas are said to have extensive-stage disease and a worse prognosis than patients with limited-stage disease.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Wingo PA et al. J Natl Cancer Inst 91(8):675-90, (1999).
Govindan R et al. J Clin Oncol 24(28):4539-44, (2006).
Non-Small Cell Lung Cancer Treatment (PDQ®): National Cancer Institute. Available at; http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/allpages#Reference2.3
Small Cell Lung Cancer Treatment (PDQ®): National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/healthprofessional/allpages#Reference2.2

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Tis Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor ≤2 cm in greatest dimension
T1b	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm in greatest dimension
T2b	Tumor >5 cm but ≤7 cm in greatest dimension
T3	Tumor >7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (<2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

**The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion**
M1b	Distant metastasis

***Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.*

STAGE GROUPING

GROUP	T	N	M
Occult	TX	N0	M0
0	Tis	N0	M0
IA	T1a	N0	M0
	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0

IIB	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
IV	Any T	Any N	M1a
	Any T	Any N	M1b

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Non-small cell lung cancer
  - Induction chemoradiation and adjuvant chemotherapy for superior sulcus cancer
  - Adjuvant chemotherapy for stage II and III cancer
  - Concurrent chemoradiation for stage III cancer
  - Chemotherapy for stage IV (metastatic) cancer
- Small cell lung cancer
  - Limited stage
  - Extensive stage

NON-SMALL CELL LUNG CANCER INDUCTION CHEMORADIATION AND ADJUVANT CHEMOTHERAPY FOR SUPERIOR SULCUS CANCER

Induction chemoradiation		
Cisplatin	50 mg/m^2 IV	d1, 8, 29 and 36
Etoposide	50 mg/m^2 IV	d1–5 and 29–33
Radiotherapy	1.8 Gy/d over 5 weeks to 45 Gy	
Surgical resection	3–5 weeks later	
Adjuvant chemotherapy		
Cisplatin	50 mg/m^2 IV	d1, 8, 29 and 36
Etoposide	50 mg/m^2 IV	d1–5 and 29–33

Reference: Rusch VW et al. J Clin Oncol 2007;25:313.

ADJUVANT CHEMOTHERAPY FOR STAGE II AND III CANCER

Cisplatin + Etoposide or Vinorelbine or Vinblastine or Vindesine

Cisplatin	50 mg/m^2 IV	d1 and 8 q4w x 4 cycles,
	or	
	80 mg/m^2 IV	d1 q3w x 4 cycles,
	or	
	100 mg/m^2 IV	d1 q4w x 3–4 cycles,
	or	
	120 mg/m^2 IV	d1 q4w x 3 cycles
	plus	
Etoposide	100 mg/m^2/d IV	d1–3 q3–4w till completion of cisplatin,
	or	
Vinorelbine	25–30 mg/m^2 IV	qw till completion of cisplatin,
	or	
Vinblastine	4 mg/m^2 IV	qw d1–29, then q2w after d43 till completion of cisplatin,
	or	
Vindesine	3 mg/m^2 IV	qw d1–29, then q2w after d43 till completion of cisplatin
(Vinorelbine and Etoposide based regimens can be used for neoadjuvant therapy)		

Reference:
Butts CA et al. J Clin Oncol. 2010 Jan 1;28(1):29-34. Epub 2009 Nov 23.
Douillard JY et al. J Thorac Oncol. 2010 Feb;5(2):220-8.
Pignon JP et al. J Clin Oncol 2008;26:3552.
Fruh M et al. J Clin Oncol 2008;26:3573.

Chevalier TL et al. 2008 ASCO annual meeting. Abstract 7507.
Pepe C et al. J Clin Oncol 2007;25:1553.
Douillard J et al. Lancet Oncol 2006;7:719.
Winton T et al. N Engl J Med 2005;352:2589.
Arriagada R et al. N Eng J Med 2004;350:351.

OTHER ACCEPTABLE CISPLATIN-BASED ADJUVANT THERAPY REGIMENS (THESE REGIMENS CAN BE USED FOR NEOADJUVANT CHEMOTHERAPY FOR 3 CYCLES PRIOR TO LOCALIZED THERAPY)

Cisplatin + Gemcitaine

Cisplatin	75 mg/m^2 IV	d1
Gemcitabine	1250 mg/m^2 IV	d1, 8
Q3w		

Reference: Obe Y et al. Ann Oncol 2007;18:317

Cisplatin + Docetaxel

Cisplatin	75 mg/m^2 IV	d1
Docetaxel	75 mg/m^2 IV	
Q3w		

Reference: Fosella F et al. J Clin Oncol 2003;21(16):3016

Cisplatin + Pemetrexed {for adenocarcinoma and large cell carcinoma and NSCLC NOS(without specific histologic subtype)}

Cisplatin	75 mg/m^2 IV	d1
Pemetrexed	500 mg/m^2 IV	d1
Q3w x 4 cycles		

Reference: Scagliotti GV et al. J Clin Oncol 2008;26:3543

CHEMOTHERAPY REGIMEN FOR PATIENTS WITH COMORBIDITIES OR PATIENTS NOT ABLE TO TOLERATE CISPLATIN

Carboplatin + Paclitaxel (this regimen can be used for neoadjuvant chemotherapy)

Carboplatin	AUC 6 IV	d1
Paclitaxel	200 mg/m^2 IV	d1
Q3w x 4 cycles		

Reference: Strauss GM et al. J Clin Oncol 2008;26:5043.

CONCURRENT CHEMORADIATION/SEQUENTIAL CHEMORADIOTHERAPY/CONCURRENT CHEMORADIATION FOLLOWED BY CHEMOTHERAPY FOR STAGE III CANCER

Cisplatin + Etoposide + RT

Cisplatin	50 mg/m^2 IV	days 1, 8, 29 and 36
Etoposide	50 mg/m^2 IV	days 1–5, 29–33
Radiotherapy	1.8 Gy/d to 45 Gy	
If no disease progression, continue radiotherapy 2 Gy/d to 61 Gy		

Reference:
Hanna NH et al. 2007 ASCO annual meeting. Abstract 7512.
Gandara DR et al. J Clin Oncol 2003;21:2004.
Albain KS et al. J Clin Oncol. 2002 Aug 15;20(16):3454-60.

Weekly Carboplatin + Paclitaxel + RT-Carboplatin + Paclitaxel

Paclitaxel	45–50 mg/m^2 IV over 1 h	qw x 7 weeks
Carboplatin	AUC 2 IV over 30 min	qw x 7 weeks
Radiotherapy	2 Gy/d to 63–66 Gy over 7 weeks	
3 weeks later		
Paclitaxel	200 mg/m^2 IV over 3 hrs	q3w x 2 cycles
Carboplatin	AUC 6 IV over 30 min	q3w x 2 cycles

Reference:
Belani CP et al. J Clin Oncol 2005;23:5883.
Choy H et al. J Clin Oncol 1998;16:3316.

Cisplatin + Vinblastine

Cisplatin.	100 mg/m^2 IV	days 1 and 29
Vinblastine.	5 mg/m^2 IV	days 1, 8, 15, 22 and 29
Begin radiation therapy on day 50, and give 60 Gy over a 6-week period.		

Reference: Dillman RO, et al. N Engl J Med 323:940-945, (1990).

CHEMOTHERAPY FOR STAGE IV (METASTATIC) CANCER

Cisplatin-based regimens

Cisplatin + Irinotecan

Cisplatin	80 mg/m^2 IV	day 1
Irinotecan	60 mg/m^2 IV	day 1, 8, 15
Q4w		

Carboplatin + Paclitaxel

Carboplatin	AUC 6 IV	day 1
Paclitaxel	200 mg/m^2 IV over 3 hours	day 1
Q3w		

Cisplatin + Gemcitabine

Cisplatin	80 mg/m^2 IV	day 1
Gemcitabine	1000 mg/2 IV	days 1, 8
Q3w		

Cisplatin + Vinorelbine

Regimen 1		
Cisplatin	80 mg/m^2 IV	d1
Vinorelbine	25 mg/m^2 IV over 10 min	d1, 2
Q3w		

Reference: Obe Y et al. N Ann Oncol. 2007 Feb;18(2):317-23. Epub 2006 Nov 1.

Cisplatin + Paclitaxel

Regimen 1		
Paclitaxel	135 mg/m^2 IV over 24 hours	day 1
Cisplatin	75 mg/m^2 IV	day 2
Q3w		

Reference: Schiller JH et al. N Eng J Med 2002;346:92.

Regimen 2		
Paclitaxel	175 mg/m^2 IV over 3 hours	day 1
Cisplatin	70 mg/m^2 IV	day 1
Q3w x 4 cycles		

Reference: Park JO et al. J Clin Oncol 2007;25:5233.

Regimen 3		
Paclitaxel	175 mg/m^2 IV over 3 hours	day 1
Cisplatin	80 mg/m^2 IV	day 1
Q3w x 4 cycles		

Reference: Smit EF et al. J Clin Oncol. 2003 Nov 1;21(21):3909-17.

Cisplatin + Gemcitabine

Regimen 1		
Cisplatin	100 mg/m^2 IV	day 1
Gemcitabine	1000 mg/2 IV	days 1, 8, 15
Q4w		

Reference: Schiller JH et al. N Eng J Med 2002;346:92.

Regimen 2 (for elderly patients > 70 years of age)		
Cisplatin	60 mg/m^2 IV	day 1
Gemcitabine	1000 mg/m^2 IV	days 1, 8
Q3w		

Reference: Gridelli C et al. J Clin Oncol 2007;25:4663.

Regimen 3 (for elderly patients ≥ 70 years of age)		
Gemcitabine	1,000 mg/m^2 IV	days 1, 8, 15
Cisplatin	35 mg/m^2 IV	days 1, 8, 15
To be repeated every 4 weeks		

Reference: Berardi R et al. Oncology 2003;65(3):198-203.

Regimen 4		
Gemcitabine	1,250 mg/m^2 IV (30 min infusion)	days 1+8
Cisplatin	100 mg/m^2 IV	day 1
To be repeated every 3 weeks		

Reference: Cardenal et al. J Clin Oncol. 17(1999):12-18

Cisplatin + Docetaxel

Regimen 1		
Cisplatin	75 mg/m^2 IV	day 1
Docetaxel	75 mg/m^2 IV	day 1
Q3w		

Reference:
Fossella F et al. J Clin Oncol 2003;21:3016.
Schiller JH et al. N Eng J Med 2002;346:92.

Regimen 2		
Docetaxel	20 mg/m^2 IV	days 1, 8, 15
Cisplatin	25 mg/m^2 IV	day 1, 8 & 15
To be repeated every 4 weeks		

Reference: Ohe Y et al. Ann Oncol 2004;15:45-50

Carboplatin + Paclitaxel

Regimen 1		
Carboplatin	AUC 5 - 6 IV	day 1
Paclitaxel	175 - 225 mg/m^2 IV over 3 hours	day 1
Q3w		

Reference:
Lilenbaum R et al. J Clin Oncol 2008;26:863.
Schiller JH et al. N Eng J Med 2002;346:92.
Kelly K et al. N J Clin Oncol. 2001 Jul 1;19(13):3210-8.

Regimen 2		
Carboplatin	AUC 6 IV	day 1
Paclitaxel	100 mg/m^2 IV	qw x 3
Premedications for paclitaxel:		
Dexamethasone	20 mg IV	
Diphenhydramine	50 mg IV	
Cimetidine	300 mg IV	
	or	
Ranitidine	50 mg IV	
If no hypersensitivity reaction to paclitaxel during the first cycle, may change premedications to:		
Dexamethasone	8–10 mg IV	
Diphenhydramine	25 mg IV	
Cimetidine	300 mg IV	
	or	
Ranitidine	50 mg IV	
Q4w x 4 cycles		
Maintenance Paclitaxel	70 mg/m^2 IV with premedications as above until disease progression or intolarable toxicity	qw x 3 every 4 weeks

Reference: Belani CP et al. J Clin Oncol 2008;26:468.

Carboplatin + Docetaxel

Carboplatin	AUC 6 IV	day 1
Docetaxel	75 mg/m^2 IV	day 1
Q3w		

Reference:
Fossella F et al. J Clin Oncol 2003;21:3016.
Boooton R et al. Ann Oncol. 2006 Jul;17(7):1111-9. Epub 2006 Apr 7.

Carboplatin + Gemcitabine

Regimen 1		
Carboplatin	AUC 5 IV	day 1
Gemcitabine	1250 mg/m^2 IV	days 1, 8
Q3w		

Reference: Sederholm C et al. J Clin Oncol 2005;23:8380.

Regimen 2 (low dose carboplatin)		
Gemcitabine	1000–1250 mg/m^2 IV	days 1 & 8
Vinorelbine	AUC 4	day 1
To be repeated every 3 weeks		

Reference: Maestu I et al. Lung Cancer 2003 Dec;42(3):345-54.

Regimen 3		
Carboplatin	AUC 5 IV	day 1
Gemcitabine	1000 mg/m^2 IV	days 1, 8, 15
Q4w		

Reference: Danson S et al. Cancer. 2003 Aug 1;98(3):542-53

Cisplatin + Vinorelbine

Regimen 1		
Cisplatin	100 mg/m^2 IV	d1 q4w
Vinorelbine	25 mg/m^2 IV over 10 min	qw

Reference: Fossella F et al. J Clin Oncol 2003;21:3016.

Regimen 2		
Cisplatin	120 mg/m^2 IV	day 1 and 28, then q6w
Vinorelbine	30 mg/m^2 IV	qw

Reference: Smith TJ et al. J Clin Oncol 1995;13:2166.

Regimen 3 (for elderly patients >70 years of age)		
Cisplatin	40 mg/m^2 IV	day 1
Vinorelbine	25 mg/m^2 IV	days 1, 8
Q3w		

Reference: Gridelli C et al. J Clin Oncol 2007;25:4663.

Regimen 4		
Cisplatin	80 mg/m^2 IV	day 1
Vinorelbine	25 mg/m^2 IV at the 1st and 4th cycles (12.5 mg/m^2 during 2nd and 3rd cycles) on d1, 8, 15 q4w	

Reference: Zatloukal P et al. J Lung Cancer. 2004 Oct;46(1):87-98.

Carboplatin + Vinorelbine

Carboplatin	AUC 5 IV	day 1
Vinorelbine	30 mg/m^2 IV	day 1 and 8
Q3w		

Reference: Tan EH et al. Lung Cancer 2005;49:233.

Gemcitabine + Docetaxel

Gemcitabine	1100 mg/m^2 IV	d 1 and 8
Docetaxel	100 mg/m^2 IV	day 8
Q3w		
G-CSF support		d 9–15

Reference: Georgoulias V et al. Lancet 2001;357:1478.

Gemcitabine	1000 mg/m^2 IV	d 1 and 8
Docetaxel	85 mg/m^2 IV	day 8
Q3w		

Reference: Pujol JL et al. Ann Oncol. 2005 Apr;16(4):602-10. Epub 2005 Mar 1.

Gemcitabine + Vinorelbine

Gemcitabine	1000–1200 mg/m^2 IV	d 1 and 8
Vinorelbine	25–30 mg/m^2 IV	d 1 and 8
Q3w		

Reference:
Tan EH et al. Lung Cancer 2005;49:233.
Frasci G et al. J Clin Oncol 2000;18:2529.

Carboplatin + Pemetrexed

Carboplatin	AUC 5 IV	d1
Pemetrexed	500 mg/m^2 IV over 10 min	d1
Q3w x 4 cycles		
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350–1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.		
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed		

Reference: Gronberg BH et al. 2007 ASCO annual meeting. Abstract 7517.

Cisplatin + Pemetrexed

(especially for adenocarcinoma and large-cell carcinoma)

Cisplatin	75 mg/m^2 IV	d1
Pemetrexed	500 mg/m^2 IV over 10 min	d1
Q3w x 6 cycles		
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350–1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.		
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed		

Reference: Scagliotti GV et al. J Clin Oncol 2008;26:3543.

Bevacizumab + Carboplatin + Paclitaxel

Paclitaxel	200 mg/m^2 IV	d1 q3w x 6 cycles
Carboplatin	AUC 6 IV	d1 q3w x 6 cycles
Bevacizumab	15 mg/kg IV	d1 q3w till disease progression

Note: Approved by FDA on 10/11/2006
Reference:
Ramalingam SS et al. J Clin Oncol 2008;26:60.
Sandler, A et al. N Eng J Med 2006;355:2542.
Johnson DH, et al. J Clin Oncol 2004;22:2184.

Albumin-bound Paclitaxel

Albumin-bound Paclitaxel	260 mg/m^2 IV over 30 min	d1q3w

Reference: Green MR et al. J Clin Oncol 2008;26:60.

Nanoparticle Paclitaxel

Nanoparticle Paclitaxel	220 mg/m^2 IV over 60 min	d1q3w

Reference: Ranade AA et al. J Clin Oncol 26:2008 (May 20 suppl; abstr 1115)

Cisplatin + Gemcitabine + Bevacizumab

Cisplatin	80 mg/m^2 IV	d1q3w x 6 cycles
Gemcitabine	1250 mg/m^2 IV	d1, 8 q3w x 6 cycles
Bevacizumab	7.5–15 mg/kg IV	q3w till disease progression

Reference: Manegold C et al. 2007 ASCO annual meeting. LBA7514.

Paclitaxel + Carboplatin + Gemcitabine

Regimen 1

Paclitaxel	200 mg/m^2 IV	d1
Carboplatin	AUC 6 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1 and 8
Q3w x 6 cycles		

Reference: Paccagnella A et al. J Clin Oncol 2006;24:681.

Regimen 2

Paclitaxel	200 mg/m^2 IV	d1
Carboplatin	AUC 5 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1 and 8
Q3w		

Reference: Greco FA et al. Clin Lung Cancer. 2007 Sep;8(8):483-7.

Paclitaxel

Regimen 1 (q3w)

Paclitaxel	200 mg/m^2 IV	q3w

Reference: Tester WJ et al. Cancer 1997;79:724.

Regimen 2 (qw)

Paclitaxel	90 mg/m^2 IV	qw x 6 wks every 8 wks

Reference: Fidias P et al. Clin Cancer Res 2001;7:3942.

Docetaxel

Regimen 1

Docetaxel	35 mg/m^2 IV	qw x 3 weeks every 4 weeks

Reference:
Chen YM et al. Chest 2006;129:1031.
Schuette W et al. J Clin Oncol 2005;23:8389.

Regimen 2

Docetaxel	36 mg/m^2 IV	qw x 6 weeks every 8 weeks

Reference: Hainsworth JD et al. Cancer 2000;89:328.

Regimen 3

Docetaxel	75 mg/m^2 IV	q3w

Reference:
Ramlau R et al. J Clin Oncol 2006;24:2800.
Chen YM et al. Chest 2006;129:1031.
Schuette W et al. J Clin Oncol 2005;23:8389.

Docetaxel + Bevacizumab

Docetaxel	75 mg/m^2 IV over 1 hour
Bevacizumab	15 mg/kg IV
Q3w until progression or 52 weeks of treatment	

Reference: Herbst RS et al. J Clin Oncol 2007;25:4743.

Gemcitabine

Regimen 1

Gemcitabine	1000 mg/m^2 IV	d 1, 8 and 15
Q4w		

Reference: Manegold C et al. Ann Oncol 1997;8:525.

Regimen 2		
Gemcitabine	1250 mg/m^2 IV over 30–60 min	d1, 8
Q3w x 6 cycles		

Reference: Sederholm C et al. J Clin Oncol 2005;23:8380.

Vinorelbine

Vinorelbine	25 mg/m^2 IV	qw

Reference: Furuse K et al. Ann Oncol 1996;7:815.

Topotecan IV

Topotecan	1.5 mg/m^2/d IV	d1–5 q3w

Reference: Perez-Soler R et al. J Clin Oncol 1996;14:503.

Pemetrexed + Bevacizumab

Pemetrexed	500 mg/m^2 IV over 10 min
Bevacizumab	15 mg/kg IV
Q3w until progression or 52 weeks of treatment	
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350–1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.	
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed.	

Reference: Herbst RS et al. J Clin Oncol 2007;25:4743.

Erlotinib

Erlotinib	150 mg P.O.	qd at least 1 hour before or 2 hours after a meal

Reference:
Zhou C et al. Lancet Oncol. 2011 Aug;12(8):735-42. Epub 2011 Jul 23. (OPTIMAL Study)
Gridelli C et al. J Clin Oncol, 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 28, No 15_suppl (May 20 Supplement), 2010:7508 (TORCH study)
Wheatley-Price P et al. J Clin Oncol 2008;26:2350.
Lilenbaum R et al. J Clin Oncol 2008;26:863.
Bezjak A et al. J Clin Oncol 2006;24:3831.

Erlotinib + Bevacizumab

Erlotinib	150 mg P.O.	qd at least 1 hour before or 2 hours after a meal
Bevacizumab	15 mg/kg IV	q3w
Continue until progression or 52 weeks of treatment		

Reference: Herbst RS et al. J Clin Oncol 2007;25:4743.

Gefitinib

Gefitinib	250–500 mg P.O.	qd until progression or unacceptable toxicity

Reference:
Mok T et al. N Engl J Med. 2009 Sep 3;361(10):947-57. Epub 2009 Aug 19.
Inoue A et al. J Clin Oncol. 2009 Mar 20;27(9):1394-400. Epub 2009 Feb 17.
Kim ES et al. Lancet 2008;372:1809.
Sequist LV et al. J Clin Oncol 2008;26:2442.
Cappuzzo F et al. J Clin Oncol 2007;25:2248.
Inoue A et al. J Clin Oncol 2006;24:3340.
West HL et al. J Clin Oncol 2006;24:1807.

Crizotinib

Crizotinib	250 mg P.O.	b.i.d. daily x 3w cycles

Reference:
Crino et al. J Clin Oncol, 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 29, No 15_suppl (May 20 Supplement), 2011:7514

Maintenance Gefitinib

Chemotherapy for 3 cycles followed by		
Gefitinib	250 mg P.O.	qd

Reference: Hida T et al. 2008 ASCO annual meeting. LBA8012.

Sunitinib

Sunitinib	50 mg P.O.	qd for 4 weeks every 6 weeks

Reference: Socinski MA et al. J Clin Oncol 2008;26:650.

Cetuximab

Cetuximab	400 mg/m^2 IV over 2 hrs	first week,
	followed by	
	250 mg/m^2 IV over 1 h	qw

Reference: Hanna N et al. J Clin Oncol 2006;24:5253.

MAINTENANCE CHEMOTHERAPY

Carboplatin + Paclitaxel + Bevacizumab

Paclitaxel	200 mg/m^2 IV	d1 q3w x 6 cycles
Carboplatin	AUC 6 IV	d1 q3w x 6 cycles
Bevacizumab	15 mg/kg IV	d1 q3w till disease progression

Note: Approved by FDA on 10/11/2006
Reference: Sandler, A et al. N Eng J Med 2006;355:2542.

Pemetrexed + Bevacizumab

Carboplatin	AUC 6	
Pemetrexed	500 mg/m^2 IV over 10 min	
Bevacizumab	15 mg/kg IV	
Q3w x 6 cycles		
For patients with response or stable disease, continue pemetrexed and bevacizumab until disease progression or unacceptable toxicity.		

Reference: Patel JD et al. J Clin Oncol. 2009 Jul 10;27(20):3284-9. Epub 2009 May 11.

Pemetrexed

Chemotherapy x 4 cycles, followed by		
Pemetrexed	500 mg/m^2 IV over 10 min	q3w
	until progression or unacceptable toxicity	

Reference:
Paz-Ares LG et al. Lancet Oncol. 2012 Mar;13(3):247-55. Epub 2012 Feb 16. (PARAMOUNT trial)
Ciuleanu TE et al. Lancet 2009 Oct 24;374(9699):1432-40. Epub 2009 Sep 18.

Cetuximab + Cisplatin + Vinorelbine

(for EGFR IHC-positive patients who are not eligible for bevacizumab)

Cisplatin	80 mg/m^2 IV	d1 q3w x 6 cycles
Vinorelbine	25 mg/m^2 IV	d1, 8 q3w x 6 cycles
Cetuximab	400 mg/m^2 IV loading,	
	followed by	
	250 mg/m^2 IV	qw until progression or limiting toxicity

Reference: Pirker R et al. (FLEX trial): Lancet 2009 May 2;373(9674):1525-31.

Gemcitabine

Gemcitabine	1250 mg/m^2 IV	d 1, 8 q3w or
Until disease progression		

Reference:
Perol M et al. J Clin Oncol, 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 28, No 15_suppl (May 20 Supplement), 2010:7507

Erlotinib

Erlotinib	150 mg P.O.	qd at least 1 hour before or 2 hours after a meal

Reference:
Capuzzo F et al. Lancet Oncol. 2010 Jun;11(6):521-9. Epub 2010 May 20.
Janne PA et al. J Clin Oncol, 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 28, No 15_suppl (May 20 Supplement), 2010:7503

Docetaxel

Docetaxel	75 mg/m^2 IV	q3w

Reference: Fidias P et al. J Clin Oncol. 2009 Feb 1;27(4):591-8.

SECOND-LINE AND THIRD-LINE CHEMOTHERAPY

Docetaxel	75 mg/m^2 IV	q3w

Reference:
Fossella FV et al. J Clin Oncol. 2000 Jun;18(12):2354-62.
Shepherd FA et al. J Clin Oncol. 2000 May;18(10):2095-103.

Pemetrexed

Pemetrexed	500 mg/m^2 IV over 10 min	q3w
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350–1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.		
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed.		

Reference:
Hanna N et al. J Clin Oncol 2004;22:1589.
Demarinis F et al. Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 24, No 18S (June 20 Supplement), 2006:7133

Erlotinib

Erlotinib	150 mg P.O.	qd at least 1 hour before or 2 hours after a meal

Reference: Shepherd FA et al. N Eng J Med 2005:353:123.

Topotecan P.O.

Topotecan	2.3 mg/m^2/d P.O.	d1–5 q3w

Reference: Ramlau R et al. J Clin Oncol 2006;24:2800.

SMALL CELL LUNG CANCER

LIMITED STAGE

Cisplatin + Etoposide + RT

Regimen 1		
Cisplatin	60 mg/m^2 IV	d1
Etoposide	120 mg/m^2/d IV	d1 - 3
Q3w x 4 cycles		
Radiotherapy	1.8 Gy once daily to 54 - 61 Gy or 1.5 Gy twice daily to 45 Gy	

Reference: Turrisi AT 3rd et al. N Eng J Med 1999;340:265.

Regimen 2		
Cisplatin	80 mg/m^2 IV	d1
Etoposide	100 mg/m^2/d IV	d1 - 3
Q4w x 4 cycles		
Radiotherapy	1.5 Gy twice daily to 45 Gy	

Reference: Takada M et al. J Clin Oncol 2002;20:3054.

Cisplatin + Etoposide + RT-Cisplatin + Irinotecan

Cisplatin	80 mg/m^2 IV	d1
Etoposide	100 mg/m^2 IV	d1 - 3
Radiotherapy	1.5 Gy twice daily to 45 Gy	
4 weeks later		
Cisplatin	60 mg/m^2 IV	d1
Irinotecan	60 mg/m^2 IV	d1, 8 and 15
Q4w x 3 cycles		

Reference: saito H et al. J Clin Oncol 2006;24:5247.

Etoposide, Ifosfamide, Cisplatin (VIP)

Etoposide.	100 mg/m^2/day IV	days 1 to 3
Ifosfamide.	1,000 mg/m^2/day IV	days 1 & 2
Cisplatin.	100 mg/m^2 IV	day 1
To be administered with concurrent radiotherapy		

Reference: Woo IS et al. Jpn J Clin Oncol. 2000 Dec;30(12):542-6.

EXTENSIVE STAGE

Carboplatin + Etoposide

Regimen 1		
Carboplatin	300 mg/m^2 IV	d1
Etoposide	100 mg/m^2/d IV	d1–3
Q4w x 4 cycles		

Reference: Smith IE et al. J Clin Oncol 1987;5:185.

Regimen 2		
Carboplatin	AUC 5 IV	d1
Etoposide	100 mg/m^2/d IV	d1–3
Q4w x 6 cycles		

Reference: Quoix E et al. Ann Oncol 2001;12:957.

Regimen 3		
Carboplatin	AUC 5 IV over 1 h	d1
Etoposide	140 mg/m^2/d IV over 90 min	d1–3
Q3w		

Reference: Schmittel A et al. Ann Oncol 2006;17:663.

Regimen 4		
Carboplatin	AUC 5 IV	d1
Etoposide	80 mg/m^2/d IV	d1–3
Filgrastim support		
Q3–4 w x 4 cycles		

Reference: Okamoto H et al. Br J Cancer 2007;97:162.

Cisplatin + Etoposide

Regimen 1		
Cisplatin	80 mg/m^2 IV	d1
Etoposide	80 mg/m^2/d IV	d1–3
Q3w		

Reference: Ihde DC et al. J Clin Oncol 1994;12:2022.

Regimen 2		
Cisplatin	80 mg/m^2 IV	d1
Etoposide	100 mg/m^2/d IV	d1–3
Q3w x 4 cycles		

Reference:
Natale RB et al. 2008 ASCO annual meeting. Abstract 7512.
Echcrdt JR et al. J Clin Oncol 2006;24:2044.
Noda K et al. N Eng J Med 2002;346:85.

Regimen 3		
Cisplatin	60 mg/m^2 IV	d1
Etoposide	120 mg/m^2/d IV	d1–3
Q3w		

Reference: Hanna N et al. J Clin Oncol 2006;24:2038.

Regimen 4		
Cisplatin	25 mg/m^2/d IV	d1–3
Etoposide	80 mg/m^2/d IV	d1–3
Filgrastim support		
Q3–4w x 4 cycles		

Reference: Okamoto H et al. Br J Cancer 2007;97:162.

Cisplatin + Irinotecan

Regimen 1		
Cisplatin	60 mg/m^2 IV	d1
Irinotecan	60 mg/m^2 IV	d1, 8 and 15
Q4w x 4 cycles		

Reference:
Natale RB et al. 2008 ASCO annual meeting. Abstract 7512.
Noda K et al. N Eng J Med 2002;346:85.

Regimen 2		
Cisplatin	30 mg/m^2 IV	d1, 8
Irinotecan	65 mg/m^2 IV	d1, 8
Q3w		

Reference: Hanna N et al. J Clin Oncol 2006;24:2038.

Carboplatin + Irinotecan

Regimen 1		
Carboplatin	AUC 5 IV over 1 h	d1
Irinotecan	50 mg/m^2 IV over 30 min	d1, 8, 15
Q4w		

Reference: Schmittel A et al. Ann Oncol 2006;17:663.

Regimen 2		
Carboplatin	AUC 4 IV	d1
Irinotecan	175 mg/m^2 IV	d1
Q3w x 4 cycles		

Reference: Hermes A et al. 2007 ASCO annual meeting. Abstract 7523.

Cisplatin + Topotecan

Topotecan	1.7 mg/m^2/d P.O.	d1–5
Cisplatin	60 mg/m^2 IV	d5
Q3w x 4 cycles		

Reference: Echcrdt JR et al. J Clin Oncol 2006;24:2044.

Carboplatin + Paclitaxel

Carboplatin	AUC 2 IV over 15–30 min
Paclitaxel	80 mg/m^2 IV over 1 hour
Days 1, 8, 15	
Q4w x 6 cycles	

Reference: Neubauer M et al. J Clin Oncol 2004;22:1872.

ICE-V

Day 1	
Ifosfamide	5 g/m^2 IV over 24 hours with mesna
Carboplatin	300 mg/m^2 IV
Etoposide	120 mg/m^2 IV
Day 2	
Etoposide	120 mg/m^2 IV
Day 3	
Etoposide	240 mg/m^2 P.O.
Day 14	
Vincristine	1 mg/m^2 IV
Q4w x 6 cycles	

Reference: Thatcher N et al. J Clin Oncol 2005;23:8371.

Etoposide

Etoposide	50 mg/m^2 P.O.	qd x 3 weeks
q4w		

Reference: Johnson DH et al. J Clin Oncol 1990;8:1613.

Paclitaxel

Paclitaxel	80 mg/m^2 IV over 1 hour	qw x 6 wks every 8 wks

Reference: Yamamoto N et al. Anticancer Res 2006;26:777.

Topotecan P.O.

Topotecan	2.3 mg/m^2/d P.O.	d1–5
q3w		

Reference:
Eckardt JR et al. J Clin Oncol 2007;25:2086.
O'Brien M et al. J Clin Oncol 2006;24:5441.

Topotecan IV

Topotecan	1.5 mg/m^2/d IV over 30 minutes	d1-5 q3w

Reference:
Eckardt JR et al. J Clin Oncol 2007;25:2086.
Ardizzoni A et al. J Clin Oncol 1997;15:2090.

Amrubicin

Amrubicin	40 mg/m^2/d in 20 ml of normal saline IV over 5 min d1-3 q3w

Reference: Onoda S et al. J Clin Oncol 2006;24:5448.

Paclitaxel + Carboplatin

Paclitaxel	200 mg/m^2 IV infusion over 3 hrs	day 1
Carboplatin	AUC 6 IV infusion over 30 mins	day 2
To be repeated every 4 weeks		

Reference: Kakolyris S et al. Annals of Oncology 2001 Feb;12(2):193-7.

Cisplatin + Epirubicin

Cisplatin	100 mg/m^2 IV	On day 1
Etoposide	100 mg/m^2 IV	On day 1
To be repeated every 3 weeks (total of 6 cycle)		

Reference: Artal-Cortes A et al. Clin Lung Cancer. 2004 Nov;6(3):175-83

Irinotecan + Etoposide

Irinotecan	60 mg/m^2 IV	days 1, 8 & 15
Etoposide	80 mg/m^2 IV infusion 30-60 mins	days 2-4
To be repeated every 4 weeks		

Reference: Kudoh S et al. Lung cancer 2005 Aug;49(2):263-9. Epub 2005 Mar 17

Amrubicin + Cisplatin

Amrubicin	40 mg/m^2 IV over 5 mins	day 1-3
Cisplatin day 1	60 mg/m^2 IV infusion over 60-120 min	
To be repeated every 3 weeks (Total of 4-6 cycle)		

Reference: Ohe Y et al. Annals of Oncology 2005 16(3):430-436

CAV

Cyclophosphamide	1,000 mg/m^2 IV	day 1.
Doxorubicin	40 mg/m^2 IV	day 1.
Vincristine	1.0 mg/m^2 (max. 2.0 mg) IV	day 1.
Repeat every 3 weeks for six cycles.		

Reference: Roth BJ, et al. J Clin Oncol 10:282-291, (1992).

CODE

Cisplatin	25 mg/m^2 IV	day 1 every week for 9 weeks
Vincristine	1 mg/m^2 IV	day 1 of weeks 1, 2, 4, 6 and 8
Doxorubicin	40 mg/m^2 IV	day 1 of weeks 1, 3, 5, 7, and 9
Etoposide	80 mg/m^2 IV	day 1 of weeks 1, 3, 5, 7 and 9
Etoposide	80 mg/m^2 orally	days 2 and 3 weeks 1, 3, 5, 7 and 9
Prednisone	50 mg by mouth daily for 5 weeks, then alternate days to 9 weeks, and then taper over a 2-week period	
Cimetidine	600 mg orally twice daily for 9 weeks	
Co-trimoxazole	One double-strength tablet twice daily on weeks 2 to 11	
Ketoconazole	200 mg by mouth daily on weeks 2 to 11	

Note: When using ketoconazole, do not allow erythromycin or terfenadine to be administered.
Reference: Murray N, et al. J Clin Oncol 9:1632-1638, (1991).

Carboplatin, Etoposide, Paclitaxel

Carboplatin.	AUC 5 IV over 30 – 60 mins	day 4
Etoposide.	100 –125 mg/m^2 IV 30 min infusion	days 1 to 3
Paclitaxel	175 mg/m^2 IV over 3 hr infusion	day 4
Repeat every 3 weeks		

Reference: Martin R, Journal of the National Cancer Institute, Vol. 95, No. 15, 1118-1127, August 6, (2003)

PART - I
Solid Tumor

Melanoma

MELANOMA

Melanoma is a malignant tumor of melanocytes, which are the cells that make the pigment melanin and are derived from the neural crest. As per the NCI data, 76,250 new cases and 9,180 deaths from melanoma are estimated in the US in year 2012.

Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate. It occurs predominantly in adults, and more than 50% of the cases arise in apparently normal areas of the skin. Early signs in a nevus that would suggest malignant change include darker or variable discoloration, itching, an increase in size, or the development of satellites. Ulceration or bleeding are later signs. Melanoma in women occurs more commonly on the extremities and in men on the trunk or head and neck, but it can arise from any site on the skin surface.

A biopsy, preferably by local excision, should be performed for any suspicious lesions, and the specimens should be examined by an experienced pathologist to allow for microstaging. Suspicious lesions should never be shaved off or cauterized.

Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, presence of tumor infiltrating lymphocytes, number of regional lymph nodes involved, and ulceration or bleeding at the primary site affect the prognosis. Patients who are younger, female, with melanomas on the extremities generally have a better prognosis. It can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Metastases can involve any organs, but lungs and liver are more common sites. The risk of relapse decreases substantially over time but late relapses can also occur.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Corona R et al. J Clin Oncol 14(4):1218-23, (1996).
Balch CM et al. Ann Surg Oncol 7(2):87-97, (2000).
Manola J et al. J Clin Oncol 18(22):3782-93, (2000).
Balch CM et al. J Clin Oncol 19(16):3635-48, (2001).
Shen P et al. Ann Surg Oncol 7(2):114-9, (2000).
Tsao H, Cosimi AB, Sober AJ: Cancer 79(12):2361-70, (1997).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	Melanomas $<$1.0 mm in thickness
T1a	without ulceration and mitosis $<1/mm^2$
T1b	with ulceration or mitoses $>1/mm^2$
T2	Melanomas 1.01–2.0 mm
T2a	without ulceration
T2b	with ulceration
T3	Melanomas 2.01–4.0 mm
T3a	without ulceration
T3b	with ulceration
T4	Melanomas $>$4.0 mm
T4a	without ulceration
T4b	with ulceration

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1 node – micrometastasis* – macrometastasis** 2–3 nodes – micrometastasis* – macrometastasis**
N2c	in transit met(s)/satellite(s) without metastatic nodes
N3	Clinical: $\geq$1 node with in transit met(s)/satellite(s); pathologic: 4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)

**Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).*
***Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.*

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1a Metastases to skin, subcutaneous tissues, or distant lymph nodes

M1b Metastases to lung

M1c Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

STAGE GROUPING*

GROUP	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	Any N > N0	M0
IV	Any T	Any N	M1

**Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Adjuvant therapy
- Metastatic cancer

ADJUVANT THERAPY

Interferon α-2a

Interferon α-2a	3 x 106 MU/m^2/d IV x 3/w for 18 months,

Reference: Grob JJ et al. Lancet 1998 Jun 27;351(9120):1905-10.

Pegylated Interferon α-2b

Pegylated Interferon α-2b	6 ug/kg/wk S.C. x 8 wks,
	then
	3 ug/kg/wk S.C., for a total of 5 years

Reference: Eggermont AM et al. Lancet 2008 Jul 12;372(9633):117-26.

Interferon α-2b

Interferon α-2b	20 MU/m^2/d IV x 5/w for 4 wks,
	then
	10 MU/m^2/d S.C. x 3/w for 48 wks

Reference: Kirkwood JM et al. J Clin Oncol 1996;14:7.

Interferon α-2b

Interferon α-2b	15 MU/m^2/d IV x 5/w for 4 weeks.

Reference: Gogas H et al. 2007 ASCO annual meeting. Abstract 8505.

METASTATIC CANCER

Ipilimumab

Ipilimumab	3 mg/kg BW	q3w x 4.

Reference: Hodi FS et al. N Engl J Med. 2010 Aug 19;363(8):711-23.

Ipilimumab + Dacarbazine

Ipilimumab	10 mg/kg BW	w1, 4, 7, 10
Dacarbazine	850 mg/m^2/d IV	w1, 4, 7, 10
Followed by Dacarbazine alone q3w through w22		

Reference: Robert C et al. N Engl J Med. 2011 Jun 30;364(26):2517-26.

Vemurafenib

Vemurafenib	960 mg P.O. b.i.d.

Reference: Chapman PB et al. N Engl J Med. 2011 Jun 30;364(26):2507-16.

High-dose Interleukin-2

Interleukin-2 (IL-2)	600,000–720,000 U/kg IV over 15 min q8h for up to 14-doses in 5 days,	
repeat the treatment after 1–2 weeks of rest (one course).		
Courses repeated every 6–12 weeks		

Reference:
Smith FO et al. Clin Cancer Res. 2008 Sep 1;14(17):5610-8.
Tarhini AA et al. J Clin Oncol 2007;25:3802.
Atkins MB et al. J Clin Oncol 1999;17:2105.

Dacarbazine

Dacarbazine	250 mg/m^2/d IV	d1–5
Q3w		

Reference: Middleton, MR et al. J Clin Oncol 2000;18:158.

Dacarbazine (DTIC)

Dacarbazine	800 mg/m^2 IV	day I
	or	
	200 mg/m^2 IV	day 1–5
	or	
	2–4.5 mg/kg IV	day 1–10
To be repeated every 4 weeks.		

Reference:
Falkson et al. J Clin Oncol16:1743-1751, (1998).
Legha, Semin Oncol16 (suppll):34-44, (1989).

Temozolomide

Temozolomide	200 mg/m^2/d P.O.	d1–5
Q4w		

Reference: Middleton, MR et al. J Clin Oncol 2000;18:158.

Fotemustine

Fotemustine	100 mg/m^2 IV over 1 hr	qw x 3 wks
	followed by a 5 week rest, then	
	100 mg/m^2 IV	q3w

Reference: Avril MF et al. J Clin Oncol 2004;22:1118.

Temozolomide + Thalidomide

Temozolomide	75 mg/m^2 P.O.	qd x 6 wks every 8 wks
Thalidomide	100–400 mg P.O.	qd

Reference: Hwu WJ et al. J Clin Oncol 2003;21:3351.

Temozolomide + IFN

Temozolomide	200 mg/m^2/d P.O.	d-5 q4w
Interferon α-2b	5 MU/m^2 S.C.	tiw

Reference: Kaufmann R et al. J Clin Oncol 2005;23:9001.

Temozolomide + IL-2 + IFN + GM-CSF

Temozolomide	150-200 mg/m^2/d P.O.	d-5
IL-2 4	MU/m^2/d S.C.	d6-17
Interferon α-2b	5 MU/d S.C.	d6-17
GM-CSF	125 mcg/m^2/d (max 250 mcg/d) S.C.	d6-17
Q4w		

Reference: Robert WW et al. J Clin Oncol 2005;23:8992.

Carboplatin + Paclitaxel

Carboplatin	AUC 6 IV	d1 q3w
Paclitaxel	225 mg/m^2 IV	d1 q3w

Reference:
Flaherty KT et al. J Clin Oncol 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 28, No 15_suppl (May 20 Supplement), 2010:8511
Hauschild A et al. J Clin Oncol. 2009

Carboplatin + Weekly Paclitaxel

Carboplatin	AUC 2 IV	d1, 8, 15 q4w
Paclitaxel	100 mg/m^2 IV	qw

Reference: Rao RD et al. Cancer. 2006 Jan 15;106(2):375-82.

Cisplatin + Paclitaxel + Dacarbazine

Cisplatin	20 mg/m^2 IV
Paclitaxel	120 mg/m^2 IV
Dacarbazine	800 mg/m^2/d IV d1

Reference: Papadopoulos NE et al. Am J Clin Oncol. 2009 Oct;32(5):509-14.

Dacarbazine + Cisplatin + Carmustine

Dacarbazine	220 mg/m^2/d IV over 1 hr	d1-3 q3w
Cisplatin	25 mg/m^2/d IV over 30 min	d1-3 q3w
Carmustine	150 mg/m^2 IV over 2 hrs	d1 q6w

Reference: Creagan Et et al. J Clin Oncol 1999;17:1884.

CVD

Cisplatin	20 mg/m^2/d IV	d1–4 and 22–25
Vinblastine	2 mg/m^2/d IV	d1–4 and 22–25
Dacarbazine	800 mg/m^2 IV	d1, 22
Q6w		

Reference: Eton, O et al. J Clin Oncol 2002;20:2045.

CVD + IL-2 + IFN

Cisplatin	20 mg/m^2/d IV	d1–4 and 22–25
Vinblastine	1.5 mg/m^2/d IV	d1–4 and 22–25
Dacarbazine	800 mg/m^2 IV	d1, 22
IL-2	9 MU/m^2/d civi	d5–8, 17–20, 26–29
Interferon α-2b	5 MU/m^2/d S.C.	d5–9, 17–21, 26–30
Q6w		

Reference: Eton, O et al. J Clin Oncol 2002;20:2045.

CVD-Interferon α-IL-2

Cisplatin	20 mg/m^2 IV	day 1–4
Vinblastine	1.6 mg/m^2 IV	day 1–4
Dacarbazine	800 mg/m^2 IV	day 1
Interferon α	5 MIU S.C.	days 1–5, 7, 9, 11, 13
Interleukin-2	9 MIU IV continuous infusion	days 1–4
To be repeated every 3 weeks.		

Reference: Legha et al. J Clin Oncol16(5):1752-1759, (1998).

Oblimersen + Dacarbazine

Oblimersen	7 mg/kg/d civi	d1–5
Dacarbazine	1000 mg/m^2 IV over 1 h	d6
Q3w x 8 cycles		

Reference: Bedikian A et al. J Clin Oncol 2006;24:4738.

Temozolomide-Cisplatin

Temozolomide	200 mg/m^2/day P.O.	day 1–5
Cisplatin	75 mg/m^2/IV	day1
To be repeated every 4 weeks		

Reference: Tas F et al. Melanoma Res. 2005 Dec;15(6);543-8

Temozolomide-Interferon α-2b

Temozolomide	150 mg/m^2/day	day 1-5 Every 4 weeks
Interferon α2b	10 MU/m^2/S.C.	Twice weekly continuously
Treatment to be continued until disease progression or for a maximum of 12 months		

Reference: Garcia M et al. Melanoma Res. 2006 Aug;16(4);365-70

Temozolomide-Vinblastine-Cisplatin-Interferon α-Interleukin 2

Temozolomide	250 mg/m^2/day P.O.	day 1-5
Cisplatin	20 mg/m^2/IV	day1-4
Vinblastine	1.6 mg/m^2	day1-4
Interferon α	5 x 10 units/m^2 S.C.	day1-5
Interleukin2	18 x 10I.U/m^2 IV Cont infusion	day1-4
To be repeated every 4 weeks		

Reference: Ron IG et al. Melanoma Res. 2006 Feb;16(1);65-9

PART - I
Solid Tumor

Mesothelioma

MESOTHELIOMA

Since there is great variability in the time before diagnosis and the rate of disease progression in mesothelioma, prognosis is difficult to assess consistently. Important prognostic factors are stage, age, performance status, and histology. For those patients treated with aggressive surgical approaches, nodal status is an important prognostic factor. Median survival has been reported as 16 months for patients with malignant pleural disease and 5 months for patients with extensive disease. In some instances the tumor grows through the diaphragm making the site of origin difficult to assess. Effusions, both pleural and peritoneal, represent major symptomatic problems for at least 66% of the patients. A history of asbestos exposure is reported in about 70% to 80% of all cases of mesothelioma.

Reference:
Ruffie P et al. J Clin Oncol 7(8):1157-68, (1989).
Tammilehto L et al. Respiration 59(3):129-35, (1992).
Sugarbaker DJ et al. J Clin Oncol 11(6):1172-8, (1993).
Chailleux E et al. Chest 93(1):159-62, (1988).
Adams VI et al. Cancer 58(7):1540-51, (1986).

PRIMARY TUMOR (T)

IMIG Staging System for Diffuse Malignant Pleural Mesothelioma (MPM)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement

T1a No involvement of the visceral pleura

T1b Tumor also involving the visceral pleura

T2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:

- involvement of diaphragmatic muscle
- extension of tumor from visceral pleura into the underlying pulmonary parenchyma

T3 Locally advanced but potentially resectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:

- involvement of the endothoracic fascia
- extension into the mediastinal fat
- solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall
- non-transmural involvement of the pericardium

T4 Locally advanced technically unresectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:

- diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
- direct transdiaphragmatic extension of tumor to the peritoneum
- direct extension of tumor to the contralateral pleura
- direct extension of tumor to mediastinal organs
- direct extension of tumor into the spine
- tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes

N2 Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes

N3 Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

Cisplatin + Pemetrexed

Cisplatin	75 mg/m^2 IV over 2 hours	d1 30 min after pemetrexed
Pemetrexed	500 mg/m^2 IV over 10 min	d1
Q3w		
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350–1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.		
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed		

Reference: Vogelzang, NJ et al. J Clin Oncol 2003;21:2636.

Carboplatin + Pemetrexed

Carboplatin	AUC 5 IV over 30 min	d1 30 min after pemetrexed
Pemetrexed	500 mg/m^2 IV over 10 min	d1
Q3w		
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350–1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.		
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed		

Reference:
Castagneto B et al. Ann Oncol. 2008 Feb;19(2):370-3.
Ceresoli GL et al. J Clin Oncol 2006;24:1443.

Cisplatin + Gemcitabine

Cisplatin	100 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1, 8, 15
Q4w		

Reference: Nowak AK et al. Br J Cancer. 2002 Aug 27;87(5):491-6.

Pemetrexed

Pemetrexed	500 mg/m^2 IV over 10 min	d1 q3w
Start vitamin supplements 1 week before initial dose of pemetrexed until 21 days after last dose of pemetrexed. Folic acid 350–1000 mcg P.O. qd. Vitamin B12 1000 mcg I.M. every 9 weeks.		
Dexamethasone 4 mg twice daily the day before, the day of and the day after pemetrexed		

Reference:
Taylor P et al. J Thorac Oncol. 2008 Jul;3(7):764-71.
Scagliotti GV et al. J Clin Oncol 2003;21:1556.

Vinorelbine

Vinorelbine	30 mg/m^2 IV	qw x 12w

Reference: Muers MF et al. Lancet 2008 May 17;371(9625):1685-94.

SECOND-LINE CHEMOTHERAPY

Pemetrexed

Pemetrexed	500 mg/m^2 IV over 10 min	d1 q3w

Reference: Jassem J et al. J Clin Oncol 2008;26:1698.

Vinorelbine

Vinorelbine	30 mg/m^2 IV	qw x 6w

Reference: Stebbing J et al. Lung Cancer. 2009 Jan;63(1):94-7. Epub 2008 May 16.

Cisplatin + Gemcitabine

Cisplatin	100 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1, 8, 15
Q4w		

Reference: Manegold C et al. Ann Oncol 2005;16(6):927.

PART - I
Solid Tumor

Myelodysplastic Syndrome

MYELODYSPLASTIC SYNDROME

The myelodysplastic syndromes (MDS) are a group of disorders characterized by one or more peripheral blood cytopenias secondary to bone marrow dysfunction. The MDS are diagnosed in slightly more than 10,000 people in the United States yearly for an annual age-adjusted incidence of 3.4/100,000 people. The syndromes may arise de novo, or secondarily after treatment with chemotherapy and/or radiation therapy for other diseases. Secondary myelodysplasia usually has a poorer prognosis than does de novo myelodysplasia. Prognosis is directly related to the number of bone marrow blast cells and the amount of peripheral blood cytopenias. The MDS transforms to acute myeloid leukemia (AML) in about 30% of patients after various intervals from diagnosis and at variable rates. The acute leukemic transformation is much less responsive to chemotherapy than is de novo AML.

The MDS is characterized by abnormal bone marrow and blood cell morphology. Megaloblastic erythroid hyperplasia with macrocytic anemia, which is associated with normal vitamin B12 and folate levels, is frequently observed. Circulating granulocytes are frequently severely reduced, often hypogranular or hypergranular, and may display the acquired pseudo-Pelger-Huët abnormality. Early, abnormal myeloid progenitors are identified in the marrow in varying percentages, depending on the type of myelodysplastic syndrome. Abnormally small megakaryocytes (micromegakaryocytes) are seen in the marrow and hypogranular or giant platelets appear in the blood.

The MDS occur predominantly in older patients (usually >60 years), though patients as young as 2 years have been reported. Anemia, bleeding, easy bruising, and fatigue are common initial findings. Splenomegaly or hepatosplenomegaly may occasionally be present. Approximately 50% of the patients have a detectable cytogenetic abnormality, most commonly a deletion of all or part of chromosome 5 or 7, or trisomy 8. Although the bone marrow is usually hypercellular at diagnosis, 15% to 20% of patients present with a hypoplastic bone marrow. Hypoplastic myelodysplastic patients tend to have profound cytopenias and may respond more frequently to immunosuppressive therapy.

Reference:
Ma X et al. Cancer 109(8):1536-42, (2007).
uncer MA et al. Br J Haematol 82(2):347-53, (1992).
Gyger M et al. Am J Hematol 28(1):13-20, (1988).
Nand S, Godwin JE: Cancer 62(5):958-64, (1988).

CHEMOTHERAPY REGIMENS

- Single Agent
- Combination Therapy
- Supportive Care

SINGLE AGENT

Azacitidine

Regimen 1

Azacitidine	75 mg/m^2/d S.C.	qd x 7 days q4w

Reference:
Silverman LR et al. Cancer. 2011 Jun 15;117(12):2697-702.
Fenaux P et al. Lancet Oncol. 2009 Mar;10(3):223-32.
Silverman LR et al. J Clin Oncol 2006;24:3895.
List AF et al. 2008 ASCO annual meeting. Abstract 7006.
Silverman LR et al. J Clin Oncol 2002;20:2429.

Regimen 2

Azacitidine 5-2-2	75 mg/m^2/d S.C.	qd x 5 days
followed by 2 days no treatment, then 75 mg/m^2/d for 2 days)		
Azacitidine 5-2-5	75 mg/m^2/d S.C.	qd x 5 days
followed by 2 days no treatment, then 50 mg/m^2/d for 5 days);		
Azacitidine 5	75 mg/m^2/d S.C.	qd x 5 days

Reference:
Lyons RM et al. J Clin Oncol. 2009 Apr 10;27(11):1850-6.
Martin WG et al. Am J Hematol. 2009 Sep;84(9):560-4.

Decitabine

Regimen 1

Decitabine	20 mg/m^2/d IV over 1 h	d1-5 q4w

Reference: Kantarijian H et al. Blood 2007;109:52.

Regimen 2

Decitabine	15 mg/m^2 IV over 3 hrs	q8h x 3 days q6w

Reference:
Lubbert m et al. J Clin Oncol. 2011 May 20;29(15):1987-96.
Kantarjian H et al. Cancer 2006;106:1794.
Ruter B et al. Cancer 2006;106:1744.
Saba HI et al. Blood (ASH Annual Meeting Abstracts) 2005 106: Abstract 2515
Note: Approved by FDA on 5/2/2006

Lenalidomide

Lenalidomide	10 mg P.O.	qd day1–21 or
Lenalidomide	5 mg P.O.	qd day1–28
To repeat every 4 weeks		

Note: Approved by FDA on 12/27/2005
Reference:
Fenaux P et al. Blood. 2011 Oct 6;118(14):3765-76.
Raza A et al. Blood 2008;111:86.
List A et al. N Eng J Med 2006;355:1456.

Imatinib

(for MDS/MPD associated with PDGFR gene re-arrangements)

Imatinib	400 mg P.O.	qd

Note: Approved by FDA on 10/19/06.
Reference: David M et al. Blood 2007;109:61.

Antithymocyte globulin (ATG)

Antithymocyte globulin	40 mg/kg/d IV	d1–4

Reference:
Sloand EM et al. J Clin Oncol 2008;26:2505.
Molldrem JJ et al. Ann Intern Med 2002;137:156.
Steensma DP et al. Blood 2003;101:2156.

Cyclosporine

Cyclosporine	5–6 mg/kg/d P.O.	b.i.d.
Adjust for blood levels between 100 to 300 mg/mL		

Reference:
Sloand EM et al. J Clin Oncol 2008;26:2505.
Jonasova A et al. Br J Haematol 1998;100:304.

Recombinant Human Erythropoietin Alpha (rhEPO)

RhEPO	40,000–60,000 U/SC once weekly
Continue treatment till 12 weeks.	

Reference: Stasi R et al. Annals of Oncology 15:1684-1690. (2004)

Thalidomide

Thalidomide	start with lOO mg P.O. bedtime andincrease the dose as tolerated to
	400 mg P.O. over the next several weeks.

Reference: Raza A et al. Blood 98(4):958-965, (2001).

9 Nitro Camptothecin (9-NC)

9 NC	2 mg/m^2 P.O. daily 5 days a week every 4–6 weeks

Reference: Quintas-Cardama A et al. Cancer 107:1525-9, (2006)

Arsenic Trioxide

Arsenic Trioxide	0.25 mg/kg/day	day 1–5 per week forwk I & 2
Repeat the cycle every 4 weeks.		

Reference: List AF et al. The Oncologist 7 (suppl-l):39-49, (2002).

COMBINATION THERAPY

Aclarubicin/Cytosine Arabinoside/GCSF

Aclarubicin	14 mg/m^2/day IV	days 1–4
Cytosine Arabinoside	10 mg/m^2 S.C. every 12 hours	days 1–14
GCSF	200 mcg/m^2 S.C.	days 1–14

Reference: Li JM et al. Int J Hematol. Jul;82(1):48-54, (2005).

PCD

Pentoxifylline	800 mg t i.d.
Ciprofloxacin	500 mg b.i.d.
Dexamethasone	4 mg daily single dose in the morning

Reference: Raza S et al. J Interferon Cytokine Res 10:871-7, (1998).

Amifostine-PCD

Amifostine	200–400 mg/m^2 IV Three times/week
Pentoxifylline	800 mg t.i.d.
Ciprofloxacin	500 mg b.i.d.
Dexamethasone	4 mg daily single dose in the morning

Reference: Raza A et al. Blood 95(5):1580-1587, (2000).

Topotecan-Cytarabine

Topotecan	1.25 mg/m^2	day 1–5
Cytarabine	19/m^2	day 1–5

Reference:
Beran M, Semin Hemato1 36 (4 supp1 8):3-10, (1999).
Beran M, J Clin Oncol 17(9):2819-30, (1999).

BMT

Allogeneic treatment singly has demonstrated the ability to cure patients. The use of autologous stem cells is dependent on the ability to collect nonclonal hematopoietic stem cells.

Reference:
Wattel E et al. Leuk Res 21 (suppl l):552, (1997).
Andecson JE et al. Leuk Res 21 (suppl):551, (1997).

SUPPORTIVE CARE

With advanced age, poor health or lack of an unmatched donor supportive care with antibiotics and transfusions can be considered in symptomatic cases. Other agents like growth factors, hormonal therapy and differentiating agents like Retinoids, low dose cytarabine, vitamin D analogs and 5 Azacitidine can be tried.

Reference: Zuckerman KS et al. Curr Opin Hematol 4:183, (1993).

PART - I
Solid Tumor

Nephroblastoma (Wilms Tumor)

NEPHROBLASTOMA (WILMS TUMOR)

Wilms' tumor is a curable disease in the majority of affected children. Approximately 500 cases are diagnosed in the United States annually. More than 90% of patients survive 4 years after diagnosis. The prognosis is related not only to the stage of disease at diagnosis, the histopathologic features of the tumor, patient age, and tumor size, but also to the team approach to each patient by the pediatric surgeon, radiation oncologist, and pediatric oncologist. Wilms' tumor normally develops in otherwise healthy children; however, 10% of cases occur in individuals with recognized malformations. Children with Wilms' tumor may have associated anomalies, including hemihypertrophy, cryptorchidism, and hypospadias. Approximately 10% of patients with Wilms' tumor have a recognizable phenotypic syndrome (including overgrowth disease, aniridia, genetic malformations, and others). These syndromes have provided clues to the genetic basis of the disease. Wilms' tumor (hereditary or sporadic) appears to result from changes in 1 or more of several genes. The Wilms' tumor gene-1 (WT1) is located on the short arm of chromosome 11 (11p13). The normal function of WT1 is required for normal genitourinary development and is important for differentiation of the renal blastema. Germline WT1 mutations have been found in about 2% of phenotypically normal children with Wilms' tumor.

Reference:
Ritchey ML et al. Semin Surg Oncol 9(6):502-9, (1993)
Breslow N et al. Cancer 68(11):2345-53, (1991).
Ritchey ML et al. J Am Coll Surg 192(1):63-8; quiz 146, (2001).
Little SE et al. J Clin Oncol 22(20):4140-6, (2004).

PRIMARY TUMOR

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Unilateral tumor 80 cm^2 or less in area (including kidney)
T2	Unilateral tumor more than 80 cm^2 in area (including kidney)
T3	Unilateral tumor rupture before treatment
T4	Bilateral tumors

Note: The area is calculated by multiplying the vertical and horizontal dimensions of the radiologic shadow of the tumor and kidney.

REGIONAL LYMPH NODES

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

CHEMOTHERAPY REGIMENS

Ifosfamide + Etoposide

(Refractory/resistant cases)

Ifosfamide	2,000 mg/m^2 IV	days 1 to 3
Etoposide	100 mg/m^2 IV	days 1 to 3
Repeat every 2 to 3 weeks		

Reference: Kung et al. Proc. ASCO abstr. 1074, (1991).

Ifosfamide + Etoposide + Carboplatin

Ifosfamide	1800 mg/m^2 IV	days 0 to 4
Carboplatin	400 mg/m^2 IV	day 0 to 1
Etoposide	400 mg/m^2 IV	days 0 to 4
Hydration IV and Mesna		day 0 to 4
Repeat every 3 weeks		

Reference: AM Abu Ghosh et al. Annals of Oncology 2002, 13:460-469

SIOP-9 Protocol

Preoperative Chemotherapy

Vincristine	1.5 mg/m^2 IV	week 1–4
Actinomycin D	15 mcg/kg IV x 3days	week 1, 3

Post Operative Therapy		
Stage I (Favourable Histology) – No therapy		
Stage I (Standard Histology and Anaplastic Wilm's Tumor)		
Vincristine	1.5 mg/m^2 IV	weeks 1–4, 10, 11, 17, 18
Actinomycin D	15 mcg/kg IV x 3days	weeks 1, 10, 17
Stage II, N0, II N1, and III (Standard Histology)		
Vincristine	1.5 mg/m^2 IV	weeks 1–8, 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27
Actinomycin D	15 mcg/kg IV x 3days	weeks 2, 6, 11, 17, 23
Anthracycline	50 mg/m^2	weeks 4, 8, 14, 20, 26
Radiotherapy	15 Gy ± boost II N1 or III	week 2–3
Stage II, III Anaplastic Wilms tumor, I–III Clear cell sarcoma		
Vincristine	1.5 mg/m^2 IV	weeks 1–3, 5, 7, 10–12, 14, 15
Actinomycin D	30 mcg/kg IV	weeks 5, 14, 21, 28, 35
Anthracycline	50 mg/m^2 IV	weeks 1, 10, 17, 24, 31
Ifosfamide	3 g/m^2 IV for 2 days	weeks 3, 12, 19, 26, 33
Radiotherapy	30 Gy ± boost stage >I	weeks 5–9

Reference: MF Tournade et al. J. Clin. Oncol 2001, 19(2):488-500

Stage I Favourable Histology & Stage I Anaplastic Wilm's tumor (Low risk Group)

EE-4A Protocol (Pulse Intensive Treatment)		
Dactinomycin	45 mcg/kg IV	weeks 0, 3, 6, 9, 12, 15, 18
Vincristine	2 mg/m^2 IV	weeks 1–10, 13, 14, 24, 25

Stage II Favourable Histology Wilms tumor (Low risk Group)

K-4A Protocol (Pulse Intensive Treatment)		
Dactinomycin	45 mcg/kg IV	weeks 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60
Vincristine	1.5 mg/m^2 IV	weeks 1–10
Vincristine	2 mg/m^2 IV	weeks 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60

Stage III, IV Favourable Histology Wilms tumor, Stages I – IV Clear cell sarcoma of Kidney

DD-4A Protocol (Pulse Intensive treatment)		
Dactinomycin	45 mcg/kg IV	weeks 0, 6, 12, 18, 24, 30, 36, 42, 48, 51, 54
Doxorubicin	30 mg/m^2 IV	weeks 3, 9, 15, 21, 27, 33, 39, 45, 51
Vincristine	1.5 mg/m^2 IV	weeks 1–10
Vincristine	2 mg/m^2 IV	weeks 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54
XRT-Abdominal irradiation week 0		

Reference: DM Green et al. J. Clin. Oncol. 1998, 16:237-245

Children's Cancer Group-4921 protocol

Intensive sequential Chemotherapy		
Cyclophosphamide	440 mg/m^2/day IV	for 5 days
Etoposide	100 mg/m^2/day IV	for 5 days
Mesna and G-CSF for all patients		
Repeat for 2 cycles		
Followed by Chemotherapy		

High Risk Group		
Carboplatin	500 mg/m^2 IV/day	for 2 days
Etoposide	100 mg/m^2 IV/day	for 2 days
G-CSF		
Repeat for 2 cycles		

Low Risk Group	
Vincristine	2 mg/m^2 IV
Doxorubicin	45 mg/m^2 IV
Alternating with	
Vincristine	2 mg/m^2 IV
Actinomycin D	45 mcg/m^2 IV
Followed by surgery	

Reference: R. Tannous, Proc. Am. Soc. Clin. Oncol. 1995, NA

PART - I
Solid Tumor

Neuroblastoma

NEUROBLASTOMA

Neuroblastoma is predominantly a tumor of early childhood, with two thirds of the cases presenting in children aged 5 years and younger. Neuroblastoma originates in the adrenal medulla or the paraspinal sites where sympathetic nervous system tissue is present. These tumors can be divided into low-, intermediate-, and high-risk groups. Low- and intermediate-risk patients usually have localized disease or are infants younger than 18 months The most common presentation of neuroblastoma is an abdominal mass. The most common symptoms in high-risk patients are due to a tumor mass or to bone pain from metastases.

Some neuroblastomas cannot be differentiated, via conventional light microscopy, from other small round blue cell tumors of childhood, such as lymphomas, primitive neuroectodermal tumors, and rhabdomyosarcomas. Evidence for sympathetic neuronal differentiation may be demonstrated by immunohistochemistry, electron microscopy, or by finding elevated levels of serum catecholamines (e.g., dopamine and norepinephrine) or urine catecholamine metabolites, such as vanillylmandelic acid (VMA) or homovanillic acid (HVA). The minimum criterion for a diagnosis of neuroblastoma, as has been established by international agreement, is that it must be based on one of the following: (1) An unequivocal pathologic diagnosis made from tumor tissue by light microscopy (with or without immunohistology, electron microscopy, or increased levels of serum catecholamines or urinary catecholamine metabolites); or (2) The combination of bone marrow aspirate or trephine biopsy containing unequivocal tumor cells (e.g., syncytia or immunocytologically-positive clumps of cells) and increased levels of serum catecholamines or urinary catecholamine metabolites.

Prognosis for patients with neuroblastoma is related to their age at diagnosis, clinical stage of disease, site of the primary tumor, tumor histology and, in patients older than 1 year, regional lymph node involvement. The clinical characteristics of neuroblastoma in adolescents are similar to those observed in children. The only exception is that bone marrow involvement occurs less frequently, and there is a greater frequency of metastases in unusual sites such as lung or brain. Neuroblastoma in an adolescent or an adult has a worse long-term prognosis regardless of stage or site and, in many cases, a more prolonged course when treated with standard doses of chemotherapy.

Reference:
Neuroblastoma Treatment (PDQ®): National Cancer Institute, available at: http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/healthprofessional/allpages

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Single tumor 5 cm or less in greatest dimension
T2	Single tumor more than 5 cm but not more than 10 cm in greatest dimension
T3	Single tumor more than 10 cm in greatest dimension
T4	Multicentric tumors occurring simultaneously

Since it is often impossible to differentiate between the primary tumour and the adjacent lymph nodes, the T assessment relates to the total mass. When there is doubt between multicentricity and metastasis, the latter is presumed.

Note: Size is estimated clinically and/or radiologically. For classification the larger measurement should be used.

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

GROUP	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T3	Any N	M0
IVA	T1, T2, T3	Any N	M1
IVB	T4	Any N	Any M

INTERNATIONAL NEUROBLASTOMA STAGING SYSTEM (INNS)

Stage 1 Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (i.e., nodes attached to and removed with the primary tumor may be positive).

Stage 2A Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.

Stage 2B Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.

Stage 3 Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

Stage 4 Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S.

Stage 4S Localized primary tumor, as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (limited to infants younger than 1 year). Marrow involvement should be minimal (i.e., $<$10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered stage 4 disease. The results of the MIBG scan, if performed, should be negative for disease in the bone marrow.

Reference:
Brodeur GM et al. J Clin Oncol 11(8):1466-77, (1993).
Brodeur GM et al. J Clin Oncol 6(12):1874-81, (1988).
Castleberry RP, Shuster JJ, Smith EI: J Clin Oncol 12(11):2378-81, (1994).
Ikeda H et al. Br J Cancer 86(7):1110-6, (2002).

CHEMOTHERAPY REGIMENS

- Low risk
- Intermediate risk
- High risk
- Localized Neuroblastomas and Infants >1 year
- Recurrent and Refractory Neuroblastoma
- Advanced Neuroblastoma

LOW RISK

(Incl. Stage 1, 2 A/B and 4S with favorable histology)

Initial treatment with surgery

INTERMEDIATE RISK

(incl. Infants <1 year with stage 3, 4 and 4S and non-amplified MYCN oncogene status; patients ≥1–21 years with stage 3, non-amplified MYCN)

Children's Cancer Group Study CCG-3881

Induction

Week 0	Week 4	Week 7	Week 11	Week 15
CDEC	CPM	CPM	CDDP	CPM
	DOX	CDDP	ETOP	CDDP
		DOX		DOX

Consolidation

Week 18	Week 19	Week 19–21		
Surgery	CPM	Radiation		
	ETOP			

Maintenance

Week 22	Week 26	Week 30	Week 34	Week 38
CPM	CDDP	CPM	CDDP	Surgery if
DOX	ETOP	DOX	ETOP	residual tumor

CDEC

Cisplatin	60 mg/m^2 IV (6 h infusion)	day 0
Doxorubicin	30 mg/m^2 IV	day 2
Etoposide	100 mg/m^2 IV (1 h infusion)	days 2 + 5 days 3 + 4

CPM/DOX

Cyclophosphamide	150 mg/m^2 IV	for 7 days
Doxorubicin	35 mg/m^2 IV	day 1

CPM/CDDP/DOX

Cyclophosphamide	150 mg/m^2 IV	for 7 days
Cisplatin day 1	90 mg/m^2 IV (8 h infusion)	
Doxorubicin	35 mg/m^2 IV	day 1

CDDP/ETOP

Cisplatin	90 mg/m^2 IV (8 h infusion)	day 1
Etoposide	150 mg/m^2 IV (continuous infusion)	over 3 days

CPM/ETOP

Cyclophosphamide	150 mg/m^2 IV	for 7 days
Etoposide	150 mg/m^2 IV (continuous infusion)	over 3 days

Reference: Matthay et al. J. Clin. Oncol. 1998,(16):1256-1264

HIGH RISK

(Incl. Infants $<$1 year stage 3, 4 and 4S and amplified MYCN oncogene Status; patients $\geq$1–21 years stage 3 and amplified MYCN oncogene status and/or unfavourable histology and any stage 4)

Children's Cancer Group Study CCG 3891

Induction

Week 0	Week 4	Week 8	Week 12	Week 13
CDEC	CDEC	CDEC	BM harvest	CDEC
		Randomization		

Week 17	Week 18	Week 21
Surgery	CDEC	Radiation

Consolidation/ABMT			
Week 22	Week 26	Week 30	Week 34
CIDE	CIDE	CIDE	Randomization
Or			
CEM-TBI + ABMT			

Biotherapy/Follow-Up		
Week 34	Week 46	Week 58
13-CRA	13-CRA	Follow up
Or		
Follow-up	Follow-up	Follow-up

CIDE

Cisplatin	40 mg/m^2 IV (continuous infusion)	days 0 – 3
Ifosfamide	2,500 mg/m^2 IV (1 h infusion)	days 0 – 3
with mesna uroprotection		
Doxorubicin	10 mg/m^2 IV (continuous infusion)	days 0 – 3
Etoposide	125 mg/m^2 IV (continuous infusion)	days 0 – 3

CEM-TBI

Caboplatin	250 mg/m^2 IV (continuous infusion)	days 8 to 5
Etoposide	160 mg/m^2 IV (continuous infusion)	days 8 to 5
Melphalan	140 mg/m^2 IV	day 7 and
	70 mg/m^2 IV	day 6
Total body irradiation		day 3 to 1
Purged autologous bone marrow infusion		day 0

13-CRA

13-cis-retinoic acid	160 mg/m^2/d	on days 0 – 3 of each 28 days
divided twice daily for a total of 3 cycles/course for 2 courses		

Reference: MATTHAY et al. J. Clin. Oncol. 16(1998):1256-1264

Intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid

Initial Chemotherapy		
Cisplatin	60 mg/m^2 IV (6 hr)	day 0
Doxorubicin	30 mg/m^2 IV	day 2
Etoposide	100 mg/m^2 IV	day 2, 5
Cyclophosphamide	1000 mg/m^2 IV	day 3, 4
Repeat for 5 cycles at 28 day interval		
Surgery and radiotherapy for gross residual disease		
For transplantation group conditioning regimen of		
Carboplatin	1000 mg/m^2 IV	
Etoposide	640 mg/m^2 IV (96 hr infusion)	
Melphalan	140 mg/m^2 IV	7 day before transplantation
	70 mg/m^2 iv	6 day before transplantation
Total body radiation	333 cGy daily	x 3 days before transplantation
Purged Bone marrow	2 x 108 mononuclear cells/kg body weight	day 0
G-MCSF	250 mcg/m^2 IV	

Continuation therapy		
Cisplatin	160 mg/m^2 IV	for 3 cycles
Etoposide	500 mg/m^2 IV	
Doxorubicin	40 mg/m^2 IV (96 hr continuous infusion)	
Ifosfamide	2500 mg/m^2 IV (bolus)	day 0 – 3
Mesna	600 mg/m^2/dose IV every 3 hr	for 5 doses
G-CSF	5 mcg/m^2 S.C.	
After transplantation or end of continuation therapy (week 34)		
Patients without disease progression assigned		
13-Cis retinolic acid	160 mg/m^2/day P.O. (2 divided doses)	14 consecutive days
For 28 day cycle		

Reference: Katherine K. Matthay et al. The New Eng. J. Med. 1999, 341(16):1165-1173

LOCALIZED NEUROBLASTOMAS AND INFANTS > 1 YEAR

Cyclophosphamide + Doxorubicin

Cyclophosphamide	150 mg/m² P.O.	days 1-7
Doxorubicin	35 mg/m² IV	days 8
Repeat every 3 weeks for 5 courses		

Reference:
Castleberry et al. J. Clin. Oncol. 1992, (10):1299-1304
Nitschke et al. J. Clin. Oncol 1991, (9):1181-1188.

ICGNB-92 Protocol

(High Risk patients)

Defroxamine	4.0 g/m²	x 4 cycles
Defroxamine	7.5 g/m²	days 1-5 x 3 cycles
Cyclophosphamide	600 mg/m²	days 5-6
Thiotepa	30 mg/m²	days 5-7
Etoposide	450 mg/m²	days 5-7
Carboplatin	1 g/m²	days 6-7 x 4 cycles
Followed by surgery on day 150		
If residual tumor then radiotherapy or MIBG therapy		
or		
Carboplatin	800 mg/m²	day 1-2
Etoposide	300 mg/m²	day 1-2
For 2-4 cycles		

Reference: Garaventa A et al. Ann. of Oncol. 2002, 13:956-964

RECURRENT AND REFRACTORY NEUROBLASTOMA

Carboplatin + Etoposide

Carboplatin	500 mg/m²/day IV	day 1-2
Etoposide	100 mg/m²/day IV	day 1-3

Ifosfamide + Carboplatin

Ifosfamide	1.5 mg/m²/day IV	day 1-3
Carboplatin	400 mg/m² IV	day 4
Every 3 weeks		

Reference: Alvarado CS et al. J Paed Haematol Oncol;1997, 19(1):62-67

Topotecan

Topotecan	2 mg/m² IV 30 min infusion	for 5 days
Every 3 weeks		

Reference: Kretschmar CS et al. J Clin Oncol. 2004 Oct 15;22(20):4119-26

Paclitaxel

Paclitaxel	350 mg/m^2 IV 24 hr infusion	
Every 3 weeks		

Reference: Hurwitz CA et al. J Pediatr Hematol Oncol. 2001 Jun-Jul;23(5):277-81.

Cyclophosphamide-Topotecan

Cyclophosphamide	250 mg/m^2/dose IV 30 min infusion	day 1-5
Topotecan	0.75 mg/m^2/dose IV 30 min infusion	day 1-5
Repeat cycle every 21 days.		
To be administered along with Filgrastim support.		

Reference: Saylors RI 3rd et al. J Clin Oncol. 2001 Aug 1;19(15):3463-9

CTV

Cyclophosphamide	70 mg/kg IV over 6 hrs with hydration	day 1-2
Topotecan	2 mg/m^2 IV 30 min infusion	day 1-4
Vincristine	0.067 mg/kg IV bolus	Day 1
To be administered along with Filgrastim support.		

Reference: Kushner BH et al. Clinical Cancer Research. Vol. 10, 84-87, January 1, (2004)

CI

Cyclophosphamide	70 mg/kg IV over 6 hrs with hydration	day 1-2
Irinotecan	50 mg/m^2 IV over I hr infusion	day 1-5

Reference: Kushner BH et al. Clinical Cancer Research. Vol. 10, 84-87, January 1, (2004)

Ifosfamide-Carboplatin-Etoposide (ICE)

Ifosfamide	3 mg/m^2/day IV	day 1-3
Carboplatin	400 mg/m^2/day IV	day 1-2
Etoposide	160 mg/m^2/day IV	day 1-3
Every 3-4 weeks		

Reference: Loss JF et al. Pediatr Blood Cancer. 2004 Feb;42(2):139-44

Topotecan-Vincristine-Doxorubicin

Topotecan	1.5 mg/m^2/day IV 30 min infusion	day 1-5
Doxorubicin	45 mg/m^2 IV 48 hr infusion	day 5-6
Vincristine	2 mg/m^2 IV 48 hr infusion	day 5-6

Note: Doxorubicin & Vincristine to be administered 1 hr after the last dose of Topotecan.
Reference: Garaventa A et al. Cancer. 2003 Dec 1;98(11):2488-94.

ADVANCED NEUROBLASTOMA

OPEC

Vincristine	1.5 mg/m^2 IV	day 1
Cyclophosphamide	600 mg/m^2 IV	day 1
Cisplatinum	60 mg/m^2 IV	day 2
Teniposide (VM-26)	150 mg/m^2 IV	day 4
6–10 courses, repeated every 3 weeks		

Reference: Shafford E et al. J Clin Oncol, 1984;2:742

CADO

Vincristine	1.5 mg/m^2 IV	days 1 and 5
Cyclophosphamide	300 mg/m^2 IV	days 1–5
Doxorubicin	60 mg/m^2 IV	day 5
6–8 courses, repeated every 3 weeks		

Reference: Hartmann O et al. J Clin Oncol;1987, 5:1205

PE-CADO

Vincristine	1.5 mg/m^2 IV	days 1 and 5
Cyclophosphamide	300 mg/m^2 IV	days 1–5
Doxorubicin	60 mg/m^2 IV	day 5
Cisplatinum	100 mg/m^2 IV	day 21
Teniposide (VM-26)	150 mg/m^2 IV	day 23
3–4 courses, repeated every 3 weeks		

Reference: Bernhard JL et al. J Clin Oncol, 1987;5:1952

Chemotherapy + Surgery

(Neuroblastoma with Intraspinal extension)

Course A		
Curboplatinum	200 mg/m^2 IV/day	x 3 days
Etoposide	150 mg/m^2 IV/day	x 3 days

Course B		
Cyclophosphamide	300 mg/m^2 oral or IV/day	x 5 days
Vincristine	1.5 mg/m^2 IV x 2 days	day 1 and 5
(max dose 2 mg)		
Doxoruhicin	60 mg/m^2 IV x 1 day	day 5

Note: four alternating courses preoperatively and two alternating courses postoperatively.
Courses were administered every 21 days or as soon as the leukocyte count was >1000/μL, or platelets were >100,000/μL.
Reference: Plantaz D et al. Cancer, 1996, volume 78 issue 2, Pages 311 – 319

PART - I
Solid Tumor

Osteosarcoma

OSTEOSARCOMA

Osteosarcoma occurs predominantly in adolescents and young adults. Osteosarcoma accounts for approximately 5% of childhood tumors. In children and adolescents, more than 50% of these tumors arise from the bones around the knee. Osteosarcoma can rarely be observed in soft tissue or visceral organs. There appears to be no difference in presenting symptoms, tumor location, and outcome for younger patients (<10 years) compared with adolescents. The natural history of osteosarcoma has not changed over time, and fewer than 20% of patients with localized resectable primary tumors treated with surgery alone can be expected to survive free of relapse. Prognostic factors include site and size of the primary tumor and presence or absence of clinically detectable metastatic disease.

Reference:
Bacci G et al. J Pediatr Hematol Oncol 27(3):129-34, (2005).
Bacci G et al. J Pediatr Hematol Oncol 30(12):908-12, (2008).
Link MP et al. N Engl J Med 314(25):1600-6, (1986).
Eilber F et al. J Clin Oncol 5(1):21-6, (1987).
Bacci G et al. Acta Orthop Scand 74(4):449-54, (2003).
Pakos EE et al. Eur J Cancer 45(13):2367-75, (2009).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 8 cm or less in greatest dimension
T2	Tumor more than 8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis
M1a	Lung
M1b	Other distant sites

HISTOPATHOLOGICAL GRADING (G)

GX	Grade of differentiation cannot be assessed
G1	Well differentiated-Low Grade
G2	Moderately differentiated-Low Grade
G3	Poorly differentiated – High Grade
G4	Undifferentiated – High Grade

Ewing sarcoma is classified as G4.

STAGE GROUPING

GROUP	T	N	M			
IA	T1	N0	M0	G1, 2	Low grade	GX
IB	T2	N0	M0	G1, 2	Low grade	GX
IB	T3	N0	M0	G1, 2	Low grade	GX
IIA	T1	N0	M0	G3, 4	High grade	
IIB	T2	N0	M0	G3, 4	High grade	
III	T3	N0	M0	G3, 4*		
IVA	Any T	N0	M1a	Any G		
IVB	Any T	N1	Any M	Any G		
	Any T	Any N	M1b	Any G		

**Ewing's sarcoma is classified as G4.*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

FIRST LINE THERAPY (PRIMARY/NEOADJUVANT/ ADJUVANT THERAPY)

Cisplatin-Doxorubicin

European Osteosarcoma Intergroup (EOI)		
Doxorubicin	25 mg/m^2 IV	days 1–3
Cisplatin	100 mg/m^2 IV (continuous infusion)	day 1
To be repeated every 3 weeks (3 courses preoperative, surgery on day 63, followed after 2 weeks by 3 courses postoperative).		

Reference:
Bramwell V et al. J. Clin Oncol. 10(1992):1579
Lewis IJ et al. J. Nat Cancer Inst 2007;99:112
Souhami RL et al. Lancet 1997;350:917

Cisplatin-Doxorubicin

Cisplatin.	90 mg/m^2 IV over a 6-hour period with hydration IV
Doxorubicin	75 mg/m^2 IV 48 hours after cisplatin.

Note: Pretreatment and post-treatment hydration and mannitol diuresis are essential elements of the protocol. Treatments were repeated at 3-week intervals.
Reference: Pratt CB et al. Cancer 56:1930-1933, (1985).

COSS Protocols

	Doxorubicin	Methotrexate	Cisplatin	BCD	Ifosfamide
COSS-80	4 x 90 mg/m^2	14 x 12 g/m^2	4 x 20 mg/m^2	4 courses	None
COSS-82 (study arm)	None	8 x 12 g/m^2	None	4 courses	None
COSS-82 (control)	4 x 60 mg/m^2	8 x 12 g/m^2	4 x 120 mg/m^2	None	None
COSS-86 (low risk)	4 x 90 mg/m^2	12 x 12 g/m^2	4 x 120 mg/m^2	None	None
COSS-86 (high risk)	5 x 90 mg/m^2	14 x 12 g/m^2	5 x 120–150 mg/m^2	None	5 x 6 g/m^2

Note:
Patients treated on protocol COSS-80 were given either cisplatin or BCD.
Patients treated on protocol COSS-82 received an alternate salvage regimen postoperatively in case of poor response to preoperative treatment.
BCD = bleomycin, cyclophosphamide, dactinomycin
Reference:
Fuchs N et al. Ann Oncol 9(8):893, (1998)
Bacci G et al. J Clin Oncol 2000:18,4016
Winkler K et al. J Clin Oncol 1988;6:329
Bacci G et al. Ann Oncol 2003;14:1126

Cisplatin + Ifosfamide + Epirubicin

Preoperatively (3 cycles prior to surgery)		
Cisplatin	100 g/m^2 IV	d1
Epirubicin	90 g/m^2 IV	d1
Ifosfamide	2 g/m^2 IV over 2 hrs	d2–4
Mesna	500 mg/m^2 mixed with first dose of ifosfamide IV over 2 hrs,	
	followed by 2.4 g/m^2/d civi x 4 days	
Q3w		
Postoperatively (3 cycles after surgery)		

Reference: Basaran M et al. Oncology. 2007;72(3-4):255-60.

Ifosfamide

Ifosfamide	2 g/m^2 IV over 2 hrs	q12 hrs x 7 doses (total 14 g)
Mesna	500 mg/m^2 mixed with first dose of ifosfamide IV over 2 hrs,	
	followed by 2.4 g/m^2/d civi x 4 days	
Filgrastim	5 mcg/kg S.C.	qd starting on d4

Reference: Patel, SR et al. J Clin Oncol 1997;15:2378.

AD

Doxorubicin	15 mg/m^2/d civi	d1–4
Dacarbazine	250 mg/m^2/d civi	d1–4
Q3w		

Reference: Antman, K et al. J Clin Oncol 1993;11:1276.

MAID

Doxorubicin	15 mg/m^2/d civi	d1–4
Ifosfamide	2 g/m^2/d civi	d1–3
Dacarbazine	250 mg/m^2/d civi	d1–4
Mesna	2.5 g/m^2/d civi	d1–4
Q3w		

Reference:
Antman, K et al. J Clin Oncol 1993;11:1276.
Antman, K et al. Cancer 1998;82:1288.

Methotrexate

High-dose methotrexate (8.–12.0 g/m^2 along with leucovorin)
Methotrexate should only be high-dosed when methotrexate blood levels can be monitored. The pretreatment creatinine rate should be at least 70 mL/min.
Methotrexate administration and alkalization of urine: Before administration of high-dose methotrexate, 0.5 mEq/kg of sodium bicarbonate is infused IV over 15 to 30 minutes in an attempt to create alkaline urine. Allopurinol, 300 mg/day for 3 days, is given starting 1 day before the methotrexate infusion.

Methotrexate is dissolved in no more than 1,000 mL of 5% dextrose in water, with a final concentration of about 1 g/100 mL. The total dose ranges from 8 g/m^2 for patients over 40 years old to 12 g/m^2 for children and young adults.

Leucovorin rescue: Twenty four hours after the start of the methotrexate infusion, leucovorin, 15 to 25 mg, is administered P.O. every 6 hours for at least 10 doses, or intramuscularly if the oral medication is not tolerated.

Serum methotrexate levels: These levels should be followed and should fall about 1 log/day. When methotrexate concentration falls below 1 x 10 – 7 M, leucovorin may be safely discontinued. Intravenous hydration is required whenever oral intake is inadequate to produce sufficient urine output as previously defined, for abnormal serum methotrexate concentration, for persistent vomiting, or for early toxicity.

Reference: BRAMWELL, Semin. Oncol. 24(1997):561-571

DFCI-TCH Study III

Vincristine	2.0 mg/m^2 IV (max. 2.0 mg)
30 minutes later	
Methotrexate	7,500 mg/m^2 IV over a 6-hour period
Leucovorin	15 mg IV (beginning 2 hours after the methotrexate dose is completed) every 3 hours for eight doses and then 15 mg of oral leucovorin every 6 hours for eight doses
Doxorubicin	75 mg/m^2 IV every 3 weeks for six courses beginning with the fifth course of vincristine-methotrexate

Note: The vincristine-methotrexate-leucovorin (VML) protocol is administered every week for 4 weeks, then every 3 weeks with the addition of doxorubicin for six courses, then VML every week for 4 weeks, then every 3 weeks for six courses, and then every week for final four courses.
Reference: Goorin AM et al. J Clin Oncol 5:1178-1184, (1987).

VP/CY with CIS/DOX

Etoposide	200 mg/m^2 IV (72 hrs infusion)	Wk 0, 3, 13, 19, 25 & 31
Cyclophosphamide	300 mg/m^2 IV every 12 hrs x 6 doses	Wk 0, 3, 13, 19, 25 & 31
Cisplatin.	100 mg/m^2 IV	Weeks 6, 8, 16, 22, 28 & 34
Doxorubicin.	40 mg/m^2 IV	Weeks 6, 8, 16, 22, 28 & 34
Surgery is performed on week 10		

Reference: Cassano Wf et al. Cancer 68:1899-1902, (1991).

T10 Protocol

Preoperative		
Methotrexate	8,000 (age>12) – 12,000 (age ≤12) mg/m^2 IV	weeks 0, 1, 4, 5
(with Leucovorin)		

BCD		
Bleomycin*	15 mg/m^2 IV	days 1 + 2
Cyclophosphamide	600 mg/m^2 IV	days 1 + 2
Dactinomycin	0.6 mg/m^2 IV	days 1 + 2
*not in patients with significant decreases in pulmonary function week 6 followed by surgery at week 6		

Postoperative		
If Grade III/IV necrosis (good histologic response)		
Doxorubicin	25 mg/m^2 civi days 1–3	weeks 8, 15, 22, 29
Methotrexate	8,000 (age >12)–12,000 (age >12) mg/m^2 IV	weeks 11, 14, 18, 21, 25, 28, 32, 35
(with Leucovorin)		
BCD		
Bleomycin*	15 mg/m^2 IV	days 1, 2
Cyclophosphamide	600 mg/m^2 IV	days 1, 2
Dactinomycin	0.6 mg/m^2 IV	days 1, 2
Weeks 12, 19, 26, 33		
*not in patients with significant decreases in pulmonary function		
If Grade I/II necrosis (standard histologic response)		
Cisplatin	120 mg/m^2 IV (20 min infusion)	day 1
Doxorubicin	25 mg/m^2 IV civi	days 1–3
Weeks 8, 15, 22, 27, 32		
Methotrexate	8,000 (age >12)–12,000 (age ≤12) mg/m^2 IV	
Weeks 11, 14, 18, 21		
with Leucovorin rescue)		
BCD		
Bleomycin*	15 mg/m^2 IV	days 1, 2
Cyclophosphamide	600 mg/m^2 IV	days 1, 2
Dactinomycin	0.6 mg/m^2 IV	days 1, 2
Weeks 12, 19, 25, 30		
*not in patients with significant decreases in pulmonary function)		

Reference: MEYERS et al. J.Clin Oncol. 10(1998):2452-2458

Protocol OS-4

Preoperative		
Methotrexate	12,000 mg/m^2 IV (6 hours infusion)	weeks 0, 4
Leucovorin	15 mg every 6 h x 11 starting 24 h after beginning of methotrexate	
Cisplatin	120 mg/m^2 IV civi days 1–3	weeks 1, 5
Doxorubicin	60 mg/m^2 IV (6 h infusion)	week 1
in association with		
Cisplatin	30 mg/m^2 IV (4 hour infusion) days 1, 2	
in association with		
Ifosfamide	3,000 mg/m^2 IV (1 h infusion) days 1 + 2	weeks 5, 8
(with mesna)		
Surgery		week 10

Postoperative		
Therapy is started within 5 days after surgery. All drugs are given as single agents per course.		
Methotrexate	12,000 mg/m^2 IV (6 hour infusion)	weeks 3, 12, 21, 30
Leucovorin	5 mg every 6 h x 11 starting 24 h after beginning of methotrexate	
Cisplatin	120 mg/m^2 IV civi day 1–3	weeks 4, 13, 22
Doxorubicin	45 mg/m^2 IV (6 h infusion) days 1+2	weeks 0, 9, 18, 27
Ifosfamide	2,000 mg/m^2 IV (1 h infusion) days 1–5	weeks 7, 16, 25
(with mesna)		

Note: when necrosis is total, the last 3 cycles are omitted.
Reference: BACCI et al. Acta Oncologia 37(1998);41-48

Carboplatin-Etoposide (High Dose Chemotherapy)

(For relapsed Osteosarcoma)		
Cyclophosphamide	4 g/m^2 IV	day 1
Etoposide	100 mg/m^2/hr IV every 12 hours	day 2, 3, 4
G-CSF	10 mg/kg/d 48 hrs after Chemotherapy	
High dose Chemotherapy (HDCT)		
Carboplatin	375 mg/m^2/d IV for 4 days (2 hour infusion)	
Etoposide	450 mg/m^2/d IV for 4 days (continuous infusion)	
Peripheral blood stem cell	48 hrs after end of High dose Chemotherapy	
1st cycle HDCT	1–2 weeks after mobilization	
2nd cycle HDCT	4–6 weeks after 1st cycle	

Reference: Fagoli F et al. J Clin Oncol 20(8):2150-2156, (2002)

Etoposide-High Dose Ifosfamide

Etoposide	100 mg/m^2/hr IV	for 5 days
Ifosfamide	3.5 g/m^2 IV (4 hrs infusion)	for 5 days
Mesna	700 mg/m^2 IV (3 hrs infusion)	
Additional Mesna	3, 6, 9 hr after Ifosfamide treatment	
G-CSF	5 mg/Kg/d S.C. day 6 onwards	
Repeat every 3 weeks for 2 courses		
Followed by Surgery		

Continuation Therapy 1–2 weeks after surgery

Methotrexate	12 g/m^2/course IV	10 course
Leucovorin	15 mg/dose IV	10 dose
Doxorubicin	75 mg/m^2/course IV	10 course
Methotrexate	120 mg/m^2/course IV	4 course
Doxorubicin	75 mg/m^2/course IV	1 course
Etoposide	500 mg/m^2/Course IV	3 course
Ifosfamide	12 g/m^2/course IV	3 course
Maintenance Chemotherapy to last 34 weeks		

Reference: Goorin AM et al. J Clin Oncol 20(2):426-433, (2002)

OS-91 Protocol

Ifosfamide	2.65 g/m^2 daily for 3 days	wk 0, 3, 6, 20, 29
Carboplatin	560 mg/m^2 on day1	wk 0, 3, 6, 20, 29
Surgery on week 9		
Doxorubicin	25 mg/m^2 daily for 3 days	wk 11, 17, 26, 35, 38
Methotrexate	12 g/m^2	wk 14, 15, 1, 23, 24, 25, 32, 33, 34

Reference: Najat CD et al. Cancer, 2006;106(2):403-412

OS-86 Protocol

Ifosfamide	1.6 g/m^2 daily for 5 days	wk 0, 3, 6, 18, 25
Methotrexate	12 g/m^2	wk 7, 8, 9, 19, 20, 21, 26, 27, 28
Doxorubicin	30 mg/m^2 daily for 3 days	wk 10
Surgery on week 13		
Cisplatin	100 mg/m^2 on day 1	wk 15, 22, 29, 32
Doxorubicin	37.5 mg/m^2 daily on days 2 & 3	wk 15, 22, 29, 32

Reference: Najat CD et al. Cancer, 2006;106(2):403-412

Cisplatin-Doxorubicin

Cisplatin	120 mg/m^2 IA	day 1
Doxorubicin.	75 mg/m^2 IV CI 72 hrs	day 1-3
To Repeat cycle every 3 weeks		

Reference: Rha SY et al. Oncol Rep.1999 6(3):631-7

Etoposide-Ifosfamide

Induction Therapy	
Etoposide/Ifosfamide + GCSF q 3 weeks x 2	
(6 weeks)	
Radiologic and Pathologic Assessment + Surgery	

Continuation Therapy	
Etoposide	100 mg/m^2/d x 5 days 2 courses
Ifosfamide	3.5 g/m^2/d x 5 days 2 courses
G-CSF	5μg/kg/d, begin day 6

Reference: Goorin AM et al. J Clin Oncol, Vol 20, No 2, 2002: pp. 426-433

SECOND LINE THERAPY

Docetaxel + Gemcitabine

Docetaxel	75-100 mg/m^2/d IV	d8
Dacarbazine	250 mg/m^2/d civi	d1-4
Q3w		

Reference: Antman, K et al. J Clin Oncol 1993;11:1276.

Cyclophosphamide + Etoposide

1st course		
Cyclophosphamide	4 g/m^2/d	d1
Etoposide	200 mg/m^2/d	d2-4
2nd course: planned at 21-28 d after 1st course		

Reference: Berger M et al. Cancer. 2009 Jul 1;115(13):2980-7.

Cyclophosphamide + Topotecan

Cyclophosphamide	250 mg/m^2/dose
Topotecan	0.75 mg/m^2/dose
Each given as 30 min infusion daily x 5 d	

Reference: Saylors RL et al. J Clin Oncol. 2001 Aug 1;19(15):3463-9.

Gemcitabine

Gemcitabine	1000 mg/m^2/week x 7 consecutive weeks followed by 1 week rest followed by
Maintenance Gemcitabine q4w	1000 mg/m^2/week x 3 consecutive weeks

Reference: Merimsky O et al. Cancer Chemother Pharmacol. 2000;45(2):177-81.

High-dose samarium-153 ethylene diamine tetramethylene phosphonate (153Sm-EDTMP) for relapsed or refractory disease beyond 2nd line therapy

153Sm-EDTMP	1, 3, 4.5, 6, 12, 19, or 30 mCi/kg

Reference: Anderson PM et al. J Clin Oncol. 2002 Jan 1;20(1):189-96.

PART - I
Solid Tumor

Ovarian Cancer

OVARIAN CANCER

Ovarian Cancer is classified as Epithelial Cancer, Germ Cell Tumor & Low Malignant Potential Tumor. As per the NCI data 22,280 new cases and 15,500 deaths are estimated in the US in year 2012.

OVARIAN EPITHELIAL CANCER

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies and the fifth most frequent cause of cancer death in women, with 50% of all cases occurring in women over age 65. The most important risk factor is a family history of a first-degree relative with the disease. The highest risk appears in women with two or more first-degree relatives with ovarian cancer. In most families affected with the breast and ovarian cancer syndrome or site-specific ovarian cancer, genetic linkage has been found to the BRCA1 locus on chromosome 17q21. BRCA2, also responsible for some instances of inherited ovarian and breast cancer and has been mapped by genetic linkage to chromosome 13q12. Prognosis in ovarian cancer is influenced by several factors, but multivariate analyses suggest that the most important favorable factors include: Younger age, Good performance status, Cell type other than mucinous and clear cell, Lower stage, Well-differentiated tumor, Smaller disease volume prior to any surgical debulking, Absence of ascites, Smaller residual tumor following primary cytoreductive surgery.

OVARIAN GERM CELL TUMOR

Germ cell tumors of the ovary are uncommon but aggressive tumors in young women or adolescent girls, are frequently unilateral and curable if found and treated early.

OVARIAN LOW MALIGNANT POTENTIAL TUMOR

Tumors of low malignant potential (i.e., borderline tumors) account for 15% of all epithelial ovarian cancers. Nearly 75% of these tumors are stage I at the time of diagnosis.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Yancik R: Cancer 71 (2 Suppl):517-23, (1993).
Piver MS et al. Eur J Gynaecol Oncol 17(3):169-76, (1996).
Miki Y et al. Science 266(5182):66-71, (1994).
Easton DF et al. Am J Hum Genet 52(4):678-701, (1993).
Steichen-Gersdorf E et al. Am J Hum Genet 55(5):870-5, (1994).
Wooster R et al. Science 265(5181):2088-90, (1994).
Omura GA et al. J Clin Oncol 9(7):1138-50, (1991).
van Houwelingen JC et al. J Clin Oncol 7(6):769-73, (1989).
Neijt JP et al. Eur J Cancer 27(11):1367-72, (1991).
Hoskins WJ et al. Gynecol Oncol 47(2):159-66, (1992).
Thigpen T et al. Cancer 71 (2 Suppl):606-14, (1993).

PRIMARY TUMOR (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to ovaries (one or both)
T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1b	IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1c	IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
T2	II	Tumor involves one or both ovaries with pelvic extension and/or implants
T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
T2b	IIB	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
T2c	IIC	Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings
T3	III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c	IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis

Note: Liver capsule metastasis T3/Stage III; liver parenchymal metastasis M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.

REGIONAL LYMPH NODES (N)

TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

DISTANT METASTASIS (M)

TNM	FIGO	
M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	IV	Distant metastasis (excludes peritoneal metastasis)

STAGE GROUPING

GROUP	T	N	M
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
II	T2	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIC	T2c	N0	M0
III	T3	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T3c	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Adjuvant chemotherapy
- Maintenance chemotherapy
- Chemotherapy for advanced or recurrent or metastatic cancer
- Endocrine therapy for recurrent cancer

ADJUVANT CHEMOTHERAPY

Carboplatin + Paclitaxel

Carboplatin	AUC 5–7.5 IV over 1 hr	d1
Paclitaxel	175 mg/m^2 IV over 3 hrs	d1
Q3w x 6 cycles		

Reference:
Pignata S et al. J Clin Oncol. 2011 Sep 20;29(27):3628-35.
Bell J et al. Gynecol Oncol. 2006 Sep;102(3):432-9.
Ozols, RF et al. J Clin Oncol 2003;21:3194.
Du Bois, A et al. J Natl Cancer Inst 2003;95:1320.
Neijt, JP et al. J Clin Oncol 2000;18:3084.

Carboplatin + dose-dense/weekly Paclitaxel

Carboplatin	AUC 6 IV	d1
Paclitaxel	80 mg/m^2 IV	d1, 8, 15
Q3w x 6–9 cycles		

Reference:
Katsunata N et al. Lancet 2009 Oct 17;374(9698):1331-8.
Isonishi S et al. 2008 ASCO annual meeting. Abstract 5506.

Carboplatin-Docetaxel (Chemotherapy-naive ovarian cancer)

Carboplatin	AUC-5 IV	day 1
Docetaxel	75 mg/m^2 IV over 1 hour	day 1
Repeat every 3 weeks for 6 cycles.		

Reference: Vasey PA et al. J Natl Cancer Inst. 2004 Nov 17;96(22):1682-91.

Cisplatin + Paclitaxel

Cisplatin	75 mg/m^2 IV over 30 min	d1
Paclitaxel	135–175 mg/m^2 IV over 3 hrs	d1
Q3w x 6 cycles		

Reference:
Ozols, RF et al. J Clin Oncol 2003;21:3194.
Du Bois, A et al. J Natl Cancer Inst 2003;95:1320.
Neijt, JP et al. J Clin Oncol 2000;18:3084.
McGuire WP et al. J N Engl J Med. 1996 Jan 4;334(1):1-6.

Paclitaxel IV + Cisplatin IP + Paclitaxel IP

Paclitaxel	135 mg/m^2 IV over 24 hrs	d1
Cisplatin	100 mg/m^2 in 2 L normal saline ip	d2
Paclitaxel	60 mg/m^2 in 2 L normal saline ip	d8
Q3w x 6 cycles		

Reference: Armstrong DK et al. N Eng J Med 2006;354:34.

Paclitaxel IV + Cisplatin IP + Paclitaxel IP

Paclitaxel	135 mg/m^2 IV over 3 hrs	d1
Cisplatin	50 mg/m^2 IP	
d1		
Paclitaxel	50 mg/m^2 IP	d8
Q3w x 6 cycles		

Reference: Landrum LM et al. Gynecol Oncol. 2011 Sep;122(3):527-31.

Carboplatin + Paclitaxel + Bevacizumab

Carboplatin	AUC 6 IV over 1 hr	d1
Paclitaxel	175 mg/m^2 IV over 3 hrs	d1
Q3w x 6 cycles		
plus		
Concurrent Bevacizumab	15 mg/kg IV C2-6	
or		
Concurrent Bevacizumab C2-6	15 mg/kg IV C2-6	
Plus Maintenance Bevacizumab C7-22		

Reference:
Burger RA et al. J Clin Oncol 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 28, No 18_suppl (June 20 Supplement), 2010: LBA1

Carboplatin + Paclitaxel + Bevacizumab

Carboplatin	AUC 5-6 IV over 1 hr	d1
Paclitaxel	175 mg/m^2 IV over 3 hrs	d1
Q3w x 6 cycles		
plus		
Concurrent Bevacizumab	7.5 mg/kg IV q3w x 5-6 cycles	
Followed by		
Continued/maintenance Bevacizumab 7.5 mg/kg IV q3w x 12 additional cycles or until progression		

Reference:
Burger RA et al. J Clin Oncol 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 29, No 18_suppl (June 20 Supplement), 2011: LBA5006

MAINTENANCE CHEMOTHERAPY

Paclitaxel

Paclitaxel	135-175 mg/m^2 IV
Q4w x 12 cycles	

Reference: Markman, M et al. J Clin Oncol 2003;21:2460.

CHEMOTHERAPY FOR RECURRENT OR METASTATIC CANCER

PLATINUM-SENSITIVE DISEASE

Carboplatin + Paclitaxel

Carboplatin	AUC 5 - 6 IV	d1
Paclitaxel	175 mg/m^2 IV over 3 hrs	d1
Q3w		

Reference:
The ICON and AGO collaborators. Lancet 2003;361:2099.
ParmarMK et al. Lancet 2003 Jun 21;361(9375):2099-106.

Carboplatin + dose-dense/weekly Paclitaxel

Carboplatin	AUC 6 IV	d1
Paclitaxel	80 mg/m^2 IV	d1, 8, 15
Q3w x 6 - 9 cycles		

Reference: Katsunata N et al. Lancet 2009 Oct 17;374(9698):1331-8.

Carboplatin-Docetaxel

Carboplatin	AUC-5 IV	day 1
Docetaxel	75 mg/m^2 IV over 30 min	day 1
Repeat every 3 weeks for 6 cycles.		

Reference: Strauss HG et al. Gynecol Oncol. 2007 Mar;104(3):612-6.

Carboplatin+Weekly Docetaxel

Carboplatin	AUC-2 IV	day 1, 8, 15
Docetaxel	35 mg/m^2 IV	day 1 qw
Repeat every 4 weeks		

Reference: Kushner DM et al. Gynecol Oncol. 2007 May;105(2):358-64.

Carboplatin + Gemcitabine

Carboplatin	AUC 4 IV	d1
Gemcitabine	1000 mg/m^2 IV	d1 and 8
Q3w x 6 cycles		

Reference:
Pfisterer J et al. Int J Gynecol Cancer 2005;15:36.
Rose PG et al. Int J Gynecol Cancer. 2005 May-Jun;15 Suppl 1:18-22.

Carboplatin + Liposomal pegylated Doxorubicin (PLD)

Carboplatin	AUC 5 IV	d1
PLD	30 mg/m^2 IV	d1
Q4w x 6 cycles		

Reference: Pujade-Lauraine E et al. J Clin Oncol. 2010 Jul 10;28(20):3323-9

Cisplatin + Paclitaxel

Cisplatin	50 mg/m^2 IV	d1
Paclitaxel	175 mg/m^2 IV over 3 hrs	d1
Q3w		

Reference: The ICON and AGO collaborators. Lancet 2003;361:2099.

Gemcitabine + Pegylated liposomal doxorubicin alternating with Cisplatin + Cyclophosphamide

Gemcitabine	800 mg/m^2 IV	d1, 8
Pegylated liposomal doxorubicin	30 mg/m^2 IV	d1
Alternating with		
Cisplatin	60 mg/m^2 IV	d1
Cyclophosphamide	600 mg/m^2 IV	d1
Q3w x 8 cycles		

Reference: Pectasides D et al. Gyn Oncol 2008;108:47.

Carboplatin

Carboplatin	AUC 5 IV	d1
Q3w		

Reference: Pfisterer J et al. J Clin Oncol. 2006 Oct 10;24(29):4699-707.

Docetaxel-Oxaliplatin

Docetaxel	75 mg/m^2 IV over 1 hr	day 1
Oxaliplatin	100 mg/m^2 IV over 2 hr	day 1
Repeat every 3 weeks		

Reference: Ferrandina G et al. Ann Oncol. 2007 Aug;18(8):1348-53.

PLATINUM-RESISTANT DISEASE

Pegylated liposomal doxorubicin (PLD)

PLD	40 – 50 mg/m^2 IV over 1 h	q4w

Reference:
Gordon, AN et al. Gynecol Oncol. 2004 Oct;95(1):1-8.
Ferrandina G et al. J Clin Oncol 2008;26:890.
Mutch DG et al. J Clin Oncol 2007;25:2811.
Gordon, AN et al. J Clin Oncol 2000;18:3093.

Gemcitabine

Gemcitabine	800–1000 mg/m^2 IV over 1 h	qw x 3 wks every 4 wks

Note: Approved by FDA on 7/14/2006
Reference:
Ferrandina G et al. J Clin Oncol 2008;26:890.
Mutch DG et al. J Clin Oncol 2007;25:2811.
Markman, M et al. Gynecol Oncol 2003;90:593.

Vinorelbine

Vinorelbine	30 mg/m^2 IV bolus	d1 and 8
Q3w		

Reference: Rothenberg ML et al. Gynecol Oncol. 2004 Dec;95(3):506-12.
Sorensen, P et al. Gynecol Oncol 2001;81:58.

Etoposide

Etoposide	50–60 mg/m^2 P.O.	qd x 3 wks every 4 wks

Reference: Rose, PG et al. J Clin Oncol 1998;16:405.

Topotecan IV

Regimen 1

Weekly Topotecan		
Topotecan	4 mg/m^2/wk	d1, 8, 15

Reference: Sehouli J et al. J Clin Oncol. 2011 Jan 10;29(2):242-8.

Regimen 2

Topotecan	1–1.5 mg/m^2/d IV over 30 min	d1–5 q3w

Reference:
Gronlund, B et al. Cancer 2002;95:1656.
Bookman, MA et al. J Clin Oncol 1998;16:3345.

Regimen 3

Topotecan	3.75–4 mg/m^2 IV over 30 min	d1, 8, 15 q4w

Reference:
Abushahin F et al. Gyn Oncol 2008;108:53.
Safra T et al. Gyn Oncol 2007;105:205.
Levy T et al. Gyn Oncol 2004;95:686.

Topotecan P.O.

Topotecan	2.3 mg/m^2/d P.O.	d1–5 q3w

Reference: Clarke-Pearson, DL et al. J Clin Oncol 2001;19:3967.

Albumin-bound Paclitaxel

nab-Paclitaxel	260 mg/m^2 IV over 30 min	d1
Q3w x 6 cycles		

Reference: Teneriello MG et al. J Clin Oncol. 2009 Mar 20;27(9):1426-31.

Oral Altretamine

Oral Altretamine	260 mg/m^2 P.O. x 14d	
Q4w		

Reference: Alberts DS et al. Int J Gynecol Cancer. 2004 Mar-Apr;14(2):224-8.

Ifosfamide

Ifosfamide	1-1.2 gram/m^2/d IV	d1-5
Q4w		

Reference: Markman, M et al. J Clin Oncol 1992;10:243.

Pemetrexed

Pemetrexed	900 mg/m^2/d IV over 10 min
Q3w	

Reference: Miller DS et al. J Clin Oncol. 2009 Jun 1;27(16):2686-91

Bevacizumab

Bevacizumab	15 mg/kg IV	q3w until progression

Reference:
Burger RA et al. J Clin Oncol 2007;25:5165.
Cannistra SA et al. J Clin Oncol 2007;25:5180.

Oral Capecitabine

Oral Capecitabine	2000 mg/m^2 P.O. in 2 divided doses with meals x 14d followed by 7d rest period
Q3w	

Reference: Wolf JK et al. Gynecol Oncol. 2006 Sep;102(3):468-74.

5-FU + LV

Leucovorin	200 mg/m^2/d IV bolus	d1-5
	followed by	
5-FU	370 mg/m^2/d IV bolus	d1-5
Q4w		

Reference: Look, KY et al. Am J Clin Oncol 1995;18:19.

Cyclophosphamide + Bevacizumab

Cyclophosphamide	50 mg P.O.	qd
Bevacizumab	10 mg/kg IV	qw x 3 followed by q2w
Continue until disease progression or limiting toxicity		

Reference: Garcia AA et al. J Clin Oncol 2008;26:76.

Tamoxifen

Tamoxifen	20 mg P.O.	b.i.d.

Reference:
Kristensen G et al. 2008 ASCO annual meeting. Abstract 5508.
Ahlgren JD et al. J Clin Oncol 2003;11:1957.
Markman M et al. Gynecol Oncol 1996;62:4.
Hatch KD et al. Cancer 1991;68:269.

Oxaliplatin (In cisplatin-/carboplatin-pretreated advanced ovarian cancer)

Oxaliplatin	130 mg/m^2 IV over 2 hours	day 1
To be repeated every 3 weeks.		

Reference: Piccart MJ et al. J Clin Oncol. 2000 Mar;18(6):1193-202.

Docetaxel-Carboplatin (Chemotherapy-naive ovarian cancer)

Docetaxel	70 mg/m^2 IV over 1 hour	day 1
Carboplatin	AUC-5 IV	day 1
Repeat every 3 weeks for 5 cycles.		

Reference: Aoki Y et al. IntJ Gynecol Cancer 12(6):704-9, (2002).

CAP

Cyclophosphamide	500 mg/m^2 IV	day I
Doxorubicin	50 mg/m^2 IV	day I
Cisplatin	50 mg/m^2 IV	day 1
Repeat every 3 weeks.		

Reference: CantuMG etal. J Clin OncoI 20(5):1232-1237, (2002).

CEP

Cyclophosphamide	500 mg/m^2 IV	day I
Epirubicin	75 mg/m^2 IV	day I
Cisplatin	50 mg/m^2 IV	day I
Repeat every 4 weeks.		

Reference: Wils J et al. Anticancer Drugs 10(3):257-61, (1999).

Ifosfamide-Paclitaxel

Ifosfamide	1,500 mg/m^2 IV over 1 hour	day 2 – 5
(with mesna)		
Paclitaxel	175 mg/m^2 IV over 3 hour	day 1
Repeat every 3 weeks.		

Reference: Klaassen et al. Anti-Cancer Drugs (9):359-361, (1998).

Ifosfamide-Oral Etoposide

Ifosfamide	2.25 g/m^2 IV	day 1-2
Oral Etoposide	100 mg daily P.O.	day 1-10
Repeat every 4 weeks.		

Reference: Aravantinos G et al. Ann Oncol ll(5):607-12, (2000).

Oral Etoposde-Cisplatin

Oral Etoposide	50 mg daily
Cisplatin	50-70 mg/m^2 IV
Repeat every week for 6 cycles.	

Reference: Van der Burg ME et al. Br J Cancer 86(1):19-25, (2002).

Cisplatin-Cyclophosphamide

Cisplatin	100 mg/m^2 IP	day 1
Cyclophosphamide	600 mg/m^2 IV over 60-90 min	day 1
Repeat every 3 weeks.		

Reference: Albert DS, N Engl J Med 1996;335:1950-5.

Paclitaxel

(For microscopic residual disease)

Paclitaxel	60 mg/m^2 IP	Weekly for 16 weeks

Reference: Markman B et al. J Clin Oncol 16:2620-2624, (1998)

PVB

(In advanced or recurrent, pure granulosa (-theca) cell tumours)

Cisplatin	20 mg/m^2 IV	day 1-5
Vinblastine	0.15 mg/kg IV	day 1-2
Bleomycin	30 units IV	day 2
	15 units	day 15
Repeat every 4 weeks for 4 cycles.		

Reference: Pecorelli S et al. Eur J Cancer 35(9):1331-7, (1999).

Olaparib

Olaparib	400 mg BD

Reference: Gelomn KA et al. Lancet Oncol. 2011 Sep;12(9):852-61.

ENDOCRINE THERAPY FOR RECURRENT CANCER

Oral Tamoxifen-Goserelin

Tamoxifen	20 mg P.O. twice daily	
Goserelin	3.6 mg S.C.	Once a month

Reference: Hasan J et al. Br J Cancer. 2005 Sep 19;93(6):647-51

Letrozole

Letrozole	2.5 mg P.O. OD

Reference:
Ramirez PT et al. Gynecol Oncol. 2008 Jul;110(1):56-9.
Papadimitriou CA et al. Oncology. 2004;66(2):112-7.

Anastrozole

Anastrozole	1 mg P.O. OD

Reference: Del Carmen MG et al. Gynecol Oncol. 2003 Dec;91(3):596-602.

PART - I
Solid Tumor

Pancreatic Cancer

PANCREATIC CANCER

As per the NCI 43,920 new cases and 37,390 deaths from pancreatic cancer are estimated in the US in year 2012. Despite the high mortality rate associated with pancreatic cancer, its etiology is poorly understood. Symptoms caused by pancreatic cancer may depend on the site of tumour within the pancreas and the degree of involvement. Cancer of the exocrine pancreas is rarely curable and has an overall survival rate of $<4\%$. The highest cure rate occurs if the tumor is truly localized to the pancreas however this stage accounts for $<20\%$ of cases.

For patients with advanced cancers, the overall survival rate of all stages is $<1\%$ at 5 years with most patients dying within 1 year. No tumor-specific markers exist for pancreatic cancer. The markers such as serum CA 19–9 have low specificity. Most patients have an elevated CA 19–9 at diagnosis. Following or during definitive therapy, the increase of CA 19–9 levels may identify patients with progressive tumor growth.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Silverman DT et al. Br J Cancer 80(11):1830-7, (1999).
Greenlee RT et al. CA Cancer J Clin 50(1):7-33, (2000)
Lillemoe KD: Ann Surg 221(2):133-48, (1995).
Yeo CJ: J Am Coll Surg 187(4):429-42, (1998).
Nitecki SS et al. Ann Surg 221(1):59-66, (1995).
Conlon KC et al. Ann Surg 223(3):273-9, (1996).
Willett CG et al. Am J Surg 172(4):350-2, (1996).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ *
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

**Note: This also includes the "PanInIII" classification*

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Adjuvant chemotherapy
- Adjuvant chemoradiation
- Adjuvant chemotherapy and chemoradiation for pancreatic head cancer
- Chemoradiation for locally advanced unresectable cancer
- Chemotherapy for locally advanced unresectable cancer
- Chemotherapy for stage IV (metastatic) cancer

ADJUVANT CHEMOTHERAPY

Gemcitabine

Gemcitabine	1000 mg/m^2 IV over 30 min	qw x 3 weeks
Q4w x 6 cycles		

Reference:
Neuhaus P et al. 2008 ASCO annual meeting. LBA4504.
Oettle H et al. JAMA 2007;297:267.

5-FU + LV

5-FU	425 mg/m^2/d IV bolus	d1–5
Leucovorin	20 mg/m^2/d IV bolus	d1–5
Q4w x 6 cycles		

Reference: Neoptolemos, JP et al. N Engl J Med 2004;350:1200

ADJUVANT CHEMORADIATION

5-FU + RT

5-FU	500 mg/m^2/d IV bolus	d1–3 repeat once after 2 wks
Concurrent radiotherapy	2 Gy/d to 20 Gy	repeat once after 2 wks

Reference: Neoptolemos, JP et al. N Engl J Med 2004;350:1200.

ADJUVANT CHEMOTHERAPY AND CHEMORADIATION FOR PANCREATIC HEAD CANCER

Before chemoradiation:		
Gemcitabine	1000 mg/m^2 IV over 30 min	qw x 3 weeks
Concurrent chemoradiaton	starting 1–2 weeks after gemcitabine	
5-FU	250 mg/m^2/d civi	during radiation
Radiotherapy	1.8 Gy/d to a total of 50.4 Gy	
3–5 weeks after chemoradiation:		
Gemcitabine	1000 mg/m^2 IV over 30 min	qw x 3 weeks q4w x 3

Reference: Regine WF et al. JAMA 2008;299:1019.

CHEMORADIATION FOR LOCALLY ADVANCED UNRESECTABLE CANCER

Gemcitabine + RT

Gemcitabine	600 mg/m^2 IV	qw x 6
Concurrent radiotherapy	1.8 Gy/d x 28 fractions to a total of 50.4 Gy	
4 weeks later		
Consolidation gemcitabine	1000 mg/m^2 IV qw x 3 every 4 weeks (1 cycle) for 5 cycles	

Reference: Loehrer PJ et al. 2008 ASCO annual meeting. Abstract 4506.

5-FU + RT

5-FU	500 mg/m^2/d IV bolus	d1–3 and 29–31
Concurrent radiotherapy to 40 Gy		
Beginning on day 71:		
5-FU	500 mg/m^2 IV bolus	qw till disease progression

Reference: Moertel, CG et al. Cancer 1981;48:1705.

Capecitabine + RT

Capecitabine	800 mg/m^2 P.O.	b.i.d. 5 days/week
Concurrent radiotherapy to 50.4 Gy		
Then		
Capecitabine progression	1000 mg/m^2 P.O.	b.i.d. x 14 days q3w till

Reference: Saif MW et al. J Clin Oncol 2005;23:8679.

CHEMOTHERAPY FOR LOCALLY ADVANCED UNRESECTABLE CANCER

5-FU + LV + Mitomycin + Dipyridamole

5-FU	200 mg/m^2/d civi x 4 weeks	q5w
Leucovorin	30 mg/m^2 IV bolus qw x 4 weeks	q5w
Mitomycin	10 mg/m^2 (max 15 mg) IV bolus	q6w x 4 doses
Dipyridamole	75 mg P.O. tid during FU administration	
Surgical resection if tumor becomes resectable		

Reference: Isacoff WH et al. J Clin Oncol 2007;25:1665.

Gemcitabine

Gemcitabine	1000 mg/m^2 as 30 min IV infusion	days 1, 8 & 15
To be repeated every 4 weeks		

Reference: Heinemann V et al. J Clin Oncol 24:3946-3952, (2006)

CHEMOTHERAPY FOR STAGE IV (METASTATIC) CANCER

Gemcitabine

Gemcitabine	1000 mg/m^2 IV over 30 min	qw x 7 wks
	followed by 1 w break, then	
	weekly x 3 wks every 4 wks.	

Reference: Burris, HA 3rd et al. J Clin Oncol 1997;15:2403.

Fixed-dose-rate Gemcitabine

Gemcitabine	1500 mg/m^2 IV over 150 min	qw x 3 wks every 4 wks

Reference:
Poplin E et al. 2006 ASCO annual meeting. Abstract LBA4004.
Tempero M et al. J Clin Oncol. 2003 Sep 15;21(18):3402-8.

Gemcitabine + Erlotinib

Gemcitabine	1000 mg/m^2 IV	qw x 7 wks
followed by 1 w break, then weekly x 3 wks every 4 wks.		
Erlotinib	100 mg P.O.	qd

Note: Approved by FDA on 11/2/2005
Reference: Moore MJ et al. J Clin Oncol 2007;25:1960.

FOLFIRINOX

Leucovorin	400 mg/m^2 IV bolus	d1
5-FU	400 mg/m^2 IV bolus d1 and 2400 mg/m^2 IV 46 h continuous infusion biweekly	
Oxaliplatin	85 mg/m^2 IV	d1
Irinotecan	180 mg/m^2 IV	d1
Q6w		

Reference: Conroy T et al. J Clin Oncol 28:15s, 2010 (suppl; abstr 4010)

Gemcitabine + Capecitabine

Regimen 1		
Gemcitabine	1000 mg/m^2 IV over 30 min	d1 and 8
Capecitabine	650 mg/m^2 P.O. b.i.d.	d1–14
Q3w		

Reference:
Bernhard J et al. J Clin Oncol 2008;26:3695.
Herrmann R et al. J Clin Oncol 2007;25:2212.

Regimen 2		
Gemcitabine	1000 mg/m^2 IV	qw for 3 wks every 4 wks
Capecitabine	830 mg/m^2 P.O. b.i.d.	for 3 wks every 4 wks

Reference: Cunningham D et al. J Clin Oncol. 2009 Nov 20;27(33):5513-8.

Gemcitabine + Cisplatin

Gemcitabine	1000 mg/m^2 IV over 30 min	d1 and 15
Cisplatin	50 mg/m^2 IV over 1 hour	d1 and 15
Q4w		

Reference: Heinemann V et al. J Clin Oncol 2006;24:3946.

Fixed-dose rate Gemcitabine + Docetaxel + Capecitabine (GTX)

Gemcitabine	750 mg/m^2 IV over 75 min	
Docetaxel	30 mg/m^2 IV	d4 and 11
Capecitabine	750 mg/m^2 P.O. b.i.d.	d1–14
Q3w		

Reference: Fine RL et al. Cancer Chemother Pharmacol. 2008 Jan;61(1):167-75.

Gemcitabine + nab-Paclitaxel

Gemcitabine	1000 mg/m^2 IV	d1, 8, 15
nab-Paclitaxel	100–150 mg/m^2 IV	d1, 8, 15
Q4w		

Reference: Von Hoff DD et al. J Clin Oncol 27:15s, 2009 (suppl; abstr 4525)

Capecitabine + Oxaliplatin

Oxaliplatin	130 mg/m^2 IV	d1
Capecitabine	1000 mg/m^2 P.O. b.i.d.	d1–14
Q2w		

Reference: Xiong HQ et al. Cancer. 2008 Oct 15;113(8):2046-52.

Gemcitabine + Oxaliplatin

Gemcitabine	1000 mg/m^2 IV over 100 min	d1
Oxaliplatin	100 mg/m^2 IV over 2 hrs	d2
Q2w		

Reference:
Louvet, C et al. J Clin Oncol 2005;23:3509.
Poplin E et al. J Clin Oncol. 2009 Aug 10;27(23):3778-85.
Colluci G et al. J Clin Oncol. 2010 Apr 1;28(10):1645-51.

Capecitabine + Erlotinib

Capecitabine	1000 mg/m^2 P.O.	b.i.d. x 14 days q3w
Erlotinib	150 mg P.O.	qd

Reference: Kulke MH et al. J Clin Oncol 2007;25:4787.

Oxaliplatin + 5-FU + Leucovorin (OFF)

5-FU	2000 mg/m^2 IV over 24 hours	d1, 8, 15, 22
Leucovorin	200 mg/m^2 IV over 30 min	d1, 8, 15, 22
Oxaliplatin	85 mg/m^2 IV	d8, 22
Q6w		

Reference: Pelzer U et al. Eur J Cancer. 2011 Jul;47(11):1676-81.

(PEF-G) Gemcitabine-Cisplatin-Epirubicin-5-FU

Gemcitabine	600 mg/m^2	day 1, 8
Cisplatin	40 mg/m^2	day 1
Epirubicin	40 mg/m^2	day 1
5-fluorouracil	200 mg/m^2	day 1, 28
Repeat cycle every 28 days		

Reference: Reni et al. J. Clin. Oncol. 19(2001):2679-2686

Gemcitabine-Irinotecan

Gemcitabine	900 mg/m^2	day 1, 8
Irinitecan	300 mg/m^2	day 8
Repeat cycle every 3 weeks		

Reference: Stathopoulos GP et al. Br J Cancer. 2006 Sep 4;95(5):587-92. Epub 2006 Aug 8

Oxaliplatin-5-FU-FA

Oxaliplatin	100 mg/m^2	day 1
Folinic acid	400 mg/m^2	day 1
5-fluorouracil	400 mg/m^2 bolus	day 1
	followed by 3000 mg/m^2 CI 46 hr	
Repeat cycle every 2 weeks		

Reference: Louvet et al. J. Clin. Oncol. 20:23, (2002):4543-4548

Raltitrexed-Irinotecan

(In gemcitabine-pretreated advanced pancreatic adenocarcinoma)

Irinotecan	200 mg/m^2	day 1
Raltitrexed	3 mg/m^2	day 2
Repeat cycle every 3 weeks		

Reference: Ulrich-Pur H et al. Br J Cancer. 2003 Apr 22;88(8):1180-4.

FAM

5-Fluorouracil.	600 mg/m^2 IV	days 1, 8, 29 and 36
Doxorubicin.	30 mg/m^2 IV	days 1 and 29
Mitomycin.	10 mg/m^2	day 1
Repeat the cycle every 56 days.		

Reference: Glimelius B et al. Ann Oncol 1996;7:593-600

PART - I
Solid Tumor

Penile Cancer

PENILE CANCER

As per the NCI data 1.570 new cases and 310 deaths from penile (and other male genital) cancer are estimated in the US in year 2012. Penile cancer is rare in most developed nations. Some studies suggest an association between human papillomavirus (HPV) infection and penile cancer. When diagnosed early (stage 0, stage I, and stage II), penile cancer is highly curable. Curability decreases sharply for stage III and stage IV. The selection of treatment depends on the size, location, invasiveness, and stage of the tumor.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Del Mistro A, Chieco Bianchi L: Eur J Cancer 37(10):1227-35, (2001).
Griffiths TR, Mellon JK: BJU Int 84(5):579-86, (1999).
Poblet E et al. Am J Surg Pathol 23(9):1119-23, (1999).
Frisch M et al. Scand J Infect Dis 28(6):629-32, (1996).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma*
T1a	Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3–4)
T1b	Tumor invades subepithelial connective tissue with LVI or is poorly differentiated
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures

**Note: Broad pushing penetration (invasion) is permitted – destructive invasion is against this diagnosis*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed*
pNX	Regional lymph nodes cannot be assessed**
N0	No palpable or visibly enlarged inguinal lymph nodes*
pN0	No regional lymph node metastasis**
N1	Palpable mobile unilateral inguinal lymph node*
pN1	Metastasis in a single inguinal lymph node**
N2	Palpable mobile multiple or bilateral inguinal lymph nodes *
pN2	Metastasis in multiple or bilateral inguinal lymph nodes**
N3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral*
pN3	Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral**

**Based upon palpation, imaging*
***Based upon biopsy, or surgical excision*

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis*

**Note: Lymph node metastasis outside of the true pelvis in addition to visceral or bone sites.*

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
	Ta	N0	M0
I	T1a	N0	M0
II	T1b	N0	M0
	T2	N0	M0
	T3	N0	M0
IIIa	T1–3	N1	M0
IIIb	T1–3	N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Neoadjuvant Paclitaxel + Ifosfamide + Cisplatin (TIP) Regimen

Paclitaxel	175 mg/m^2 IV over 3 hrs	day 1
Ifosfamide	1200 mg/m^2 IV over 2 hrs	day 1–3
Cisplatin	25 mg/m^2 IV over 2 hrs	day 1–3
To be repeated after every 3 week		

Reference: Haas GP et al. J Clin Oncol. 2010 Aug 20;28(24):3851-7.

5-FU + Cisplatin

Continuous infusion 5-FU	1000 mg/m^2 IV	day 1–5
Cisplatin	100 mg/m^2 IV	day 1
To be repeated after every 3–4 week		

Reference: Shammas FV et al. J Urol. 1992 Mar;147(3):630-2.

CMB Regimen

Cisplatin	75 mg/m^2 IV	day 1
Methotrexate	25 mg/m^2 IV bolus	day 1, 8
Bleomycin	10 units/m^2 IV bolus	day 1, 8
To be repeated after every 3 week		

Note: Bleomycin-containing regimens were associated with unacceptable toxicity and are no longer recommended
Reference: Haas GP et al. J Urol161(6):1823-5, (1999).105

Cisplatin-Interferon alpha

Cisplatin	20 mg/m^2 IV	day 1
Interferon α-2B	5 MIU/m^2 S.C.	day 1–5
To be repeated after every 4 week		

Reference: Mitropoulos D et al. J Urol 152(4):1124-6, (1994).

PALLIATIVE THERAPY

Irinotecan + Cisplatin

Irinotecan	60 mg/m^2 IV	day 1, 8, 15
Cisplatin	80 mg/m^2 IV	day 1
To be repeated after every 4 week		

Reference: Theodore C et al. Ann Oncol. 2008 Jul;19(7):1304-7.

Paclitaxel

Paclitaxel	175 mg/m^2 IV	day 1
Q3w		

Reference: Di Lorenzo G et al. Eur Urol. 2011 Dec;60(6):1280-4.

PART - I
Solid Tumor

Prostate Cancer

PROSTATE CANCER

Carcinoma of the prostate is predominantly a tumor of older men, which frequently responds to treatment when widespread and may be cured when localized. The rate of tumor growth varies from very slow to moderately rapid, and some patients may have prolonged survival even after the cancer has metastasized to distant sites such as bone. As per the NCI data, 241,740 new cases and 28,170 deaths are estimated in U S in year 2012. The approach to treatment is influenced by age and coexisting medical problems. Side effects of various forms of treatment should be considered in selecting appropriate management. Survival of the patient with prostatic carcinoma is related to the extent of the tumor. When the cancer is confined to the prostate gland, median survival in excess of 5 years can be anticipated. Patients with locally advanced cancer are not usually curable, and a substantial fraction will eventually die of their tumor, though median survival may be as long as 5 years. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually 1 to 3 years, and most such patients will die of prostate cancer. Other factors affecting the prognosis of patients may include histologic grade of the tumor, patient's age, other medical illnesses, and level of PSA. Poorly differentiated tumors are more likely to have already metastasized by the time of diagnosis and are associated with a poorer prognosis.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Gittes RF: N Engl J Med 324(4):236-45, (1991).
Paulson DF, Moul JW, Walther PJ: J Urol 144(5):1180-4, (1990).
Matzkin H et al. Cancer 70(9):2302-9, (1992).
Pisansky TM et al. J Clin Oncol 11(11):2158-66, (1993).
Chodak GW et al. N Engl J Med 330(4):242-8, (1994).
Prostate Cancer Treatment (PDQ®): National Cancer Institute, available at: http://www.cancer.gov/cancertopics/pdq/treatment/prostate/healthprofessional/allpages#Reference2.14

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected

T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate*
pT2	Organ confined
T2a	Tumor involves one-half of one lobe or less
pT2a	Unilateral, one-half of one side or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
pT2b	Unilateral, involving more than one-half of side but not both sides
T2c	Tumor involves both lobes
pT2c	Bilateral disease
T3	Tumor extends through the prostate capsule**
pT3	Extraprostatic extension
T3a	Extracapsular extension (unilateral or bilateral)
pT3a	Extraprostatic extension or microscopic invasion of bladder neck***
T3b	Tumor invades seminal vesicle(s)
pT3b	Seminal vesicle invasion
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
pT4	Invasion of rectum, levator muscles and/or pelvic wall

Note: There is no pathologic T1 classification.
**Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.*
***Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.*
****Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes were not assessed
pNX	Regional nodes not sampled
N0	No regional lymph node metastasis
pN0	No positive regional nodes
N1	Metastasis in regional lymph node(s)
pN1	Metastases in regional node(s)

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

**Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced*

STAGE GROUPING

GROUP	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA <10	Gleason ≤ 6
	T2a	N0	M0	PSA <10	Gleason ≤ 6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA $\geq 10 < 20$	Gleason ≤ 6
	T2a	N0	M0	PSA <20	Gleason ≤ 7
	T2b	N0	M0	PSA <20	Gleason ≤ 7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥ 20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥ 8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

**When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Hormonal and radiation therapy for localized cancer
- Chemotherapy and hormonal therapy for PSA recurrence
- Hormonal therapy for metastatic cancer
- Chemotherapy for metastatic cancer

HORMONAL AND RADIATION THERAPY FOR LOCALIZED CANCER

Goserelin + Flutamide + RT

Goserelin	3.6 mg S.C.	q4w 2 months before radiotherapy and then during radiotherapy
Flutamide	250 mg P.O.	tid 2 months before radiotherapy and then during radiotherapy
Radiotherapy	70 Gy	

Reference:
Roach III M et al. J Clin Oncol 2008;26:585.
Pilepich, MV et al. Int J Radiat Oncol Biol Phys 2001;50:1243.

Goserelin + Flutamide + RT-Goserolin

Goserelin	3.6 mg S.C.	q4w 2 months before radiotherapy and then during radiotherapy
Flutamide	250 mg P.O.	tid 2 months before radiotherapy and then during radiotherapy
Radiotherapy	70 Gy	
After radiotherapy, continue		
Goserelin	3.6 mg S.C.	q4w x 2 years

Reference:
Horwitz EM et al. J Clin Oncol 2008;26:2497.
Hanks GE et al. J Clin Oncol 2003;21:3972.

CHEMOTHERAPY AND HOMONAL THERAPY FOR PSA RECURRENCE

Docetaxel + Estramustine-Goserelin + Bicalutamide

Docetaxel	70 mg/m^2 IV over 1 h	d2
Estramustine	280 mg P.O. tid	d1–5
Warfarin	1 mg P.O. qd for prophylaxis of thrombosis	
Q3w x 4 cycles		
Followed by hormonal therapy starting on week 13:		
Goserelin	10.8 mg S.C.	q3m x 15 months
Bicalutamide	50 mg P.O.	qd x 15 months

Reference: Taplin ME et al. J Clin Oncol 2006;24:5408.

HORMONAL THERAPY FOR METASTATIC CANCER

Degarelix

Degarelix	240 mg S.C. x 1 month, followed by	
	80 or 160 mg monthly x 12 months	

Approved by US FDA in 2008 for treatment of men with advanced prostate cancer.
Reference: Klotz L et al. BJU Int. 2008 Dec;102(11):1531-8.

Abiraterone acetate + Prednisone

Abiraterone acetate	1 g P.O. qd at least 1 hr before or 2 hrs after meals	
Prednisone	5 mg P.O. b.i.d.	
Q4w		

Approved by US FDA in 2011 for treatment of men withmetastatic castratio-recurrent prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.
Reference: Klotz L et al. BJU Int. 2008 Dec;102(11):1531-8.

Luprolide

Luprolide	7.5 mg I.M.	qm
	or	
	22.5 mg I.M.	q3m

Reference: Loblaw DA et al. J Clin Oncol 2007;25:1596.

Goserelin

Goserelin	3.6 mg S.C.	qm
	or	
	10.8 mg S.C.	q3m

Reference: Loblaw DA et al. J Clin Oncol 2007;25:1596.

Bicalutamide

Bicalutamide	50 mg P.O.	qd

Reference: Loblaw DA et al. J Clin Oncol 2007;25:1596.

Bicalutamide	150 mg P.O.	qd

Reference: McLeod DG et al. BJU Int. 2006 Feb;97(2):247-54.

Flutamide

Flutamide	250 mg P.O.	tid

Reference: Loblaw DA et al. J Clin Oncol 2007;25:1596.

Ketoconazole + Hydrocortisone

Ketoconazole	400 mg P.O.	tid
Hydrocortisone	30 mg P.O. qam, 10 mg P.O. qpm	

Reference:
Small EJ et al. J Clin Oncol 2004;22:1025.
Small EJ et al. J Urol 1984;132:61.

Prednisone

Prednisone	5 mg P.O.	b.i.d.

Reference: Tannock, I et al. J Clin Oncol 1989;7:590.

Dexamethosone

Dexamethasone	0.5–2 mg P.O.	qd

Reference: Nishimura, K et al. Cancer 2000;89:2570.

CHEMOTHERAPY FOR METASTATIC CANCER

Docetaxel q3w + Prednisone

Docetaxel	75 mg/m^2 IV over 1 h	q3w x 10 cycles
Prednisone	5 mg P.O.	b.i.d.

Reference:
Berthold DR et al. J Clin Oncol 2008;26:242.
Tannock IF et al. N Eng J Med 2004;351:1502.

Docetaxel qw + Prednisone

Docetaxel	30 mg/m^2 IV over 30 min	qw x 5 weeks every 6 weeks for 5 cycles
Prednisone	5 mg P.O.	b.i.d.

Reference:
Berthold DR et al. J Clin Oncol 2008;26:242.
Tannock IF et al. N Eng J Med 2004;351:1502.

Docetaxel + Estramustine

Estramustine	280 mg P.O.	tid d1–5
Docetaxel	60 mg/m^2 IV	d2
Warfarin	2 mg P.O.	qd
Aspirin	325 mg P.O.	qd
Q3w x 12 cycles		

Reference: Petrylak DP et al. N Eng J Med 2004;351:1513.

Mitoxantrone + Prednisone

Mitoxantrone	12 mg/m^2 IV over 30 min	q3w x 10 cycles
Prednisone	5 mg P.O.	b.i.d.

Reference:
Tannock IF et al. N Eng J Med 2004;351:1502.
Petrylak DP et al. N Eng J Med 2004;351:1513.

Estramustine + Vinblastine

Estramustine	600 mg/m^2 P.O.	qd x 6 weeks every 8 weeks
Vinblastine	4 mg/m^2 IV	qw x 6 weeks every 8 weeks

Reference: Hudes G et al. J Clin Oncol 1999;17:3160.

Satraplatin + Prednisone

Satraplatin	80 mg/m^2 P.O.	qd d1–5 q5w
Prednisone	5 mg P.O.	b.i.d.

Reference: Sternberg CN et al. 2007 ASCO annual meeting. Abstract 5019.

Estramustine + Cyclophosphamide

Estramustine	10 mg/kg P.O.	qd
Cyclophosphamide	2 mg/kg P.O.	qd
for 2 weeks every 4 weeks		

Reference: Bracarda S et al. Cancer 2000;88:1438.

Cyclophosphamide

Regimen 1

Cyclophosphamide	50 mg/m^2 P.O.	qd

Reference: Lord R et al. J Urol 2007;177:2136.

Regimen 2

Cyclophosphamide	100 mg/m^2 P.O.	qd x 2 weeks every 4 weeks

Reference: Raghavan D et al. Br J Urol 1993;72:625.

Vinblastine

Vinblastine	4 mg/m^2 IV	qw x 6 weeks every 8 weeks

Reference: Hudes G et al. J Clin Oncol 1999;17:3160.

Vinorelbine

Vinorelbine	30 mg/m^2 IV	d1 and 8 q3w

Reference: Morant R et al. Eur J Cancer 2002;38:1626.

Thalidomide

Thalidomide	200 mg/day (with dose increment of 200 mg/day every 2 weeks, until maximum dose of 1200 mg/day)
To be administered every evening	

Reference: Figg WD et al. Clinical Cancer Research Vol. 7, 1888-1893, July 2001

Docetaxel-Estramustine (Hormone-refractory prostate cancer)

Docetaxel	70 mg/m^2	day 2 every 21 days
Estramustine	10 mg/m^2/day P.O. t.i.d	day 1–5
24 hour before docetaxel dose		
Dexamethasone	8 mg b.i.d.	day 1–3 starting

Reference: Savatese et al. J Clin Oncol 19:2509-2515, (2001).

Docetaxel-Vinorelbine (Hormone-refractory prostate cancer)

Docetaxel	70 mg/m^2 IV	day 1 & 8
Vinorelbine	20 mg/m^2	day 1 & 8
Repeat every 21 days		

Reference: Koletsky AJ et al. Cancer J. 2003 Jul-Aug;9(4):286-92.

Estramustine-Suramin-Docetaxel (Hormone-refractory prostate cancer)

Estramustine	10 mg/kg P.O. daily	day 1–21
Docetaxel	70 mg/m^2 IV	day 2
Suramin	Total dose of 2150 mg in the cycle.	
Repeat the cycle every 28 days.		

Reftrence: Safarinejad MR et al. Urol Oncol. 2005 Mar-Apr;23(2):93-101.

DEP (Metastatic hormone-refractory prostate cancer)

Docetaxel	70 mg/m^2 IV	day 2
	OR	
	35 mg/m^2 IV	day 2 & 9
Estramustine	280 mg P.O. tid	day 1–5 & 8–12
Prednisolone	10 mg P.O.	Daily
Repeat the cycle every 21 days.		

Reftrence: Oudard S et al. J Clin Oncol. 2005 May 20;23(15):3343-51.

Sipuleucel-T

Sipuleucel-T	40 million large cells minimum (expressing the costimulatory molecule CD54) IV infusion at weeks 0, 2, 4, approximately 3 days after each leukapheresis procedure.

Approved by the USFDA in Apr, (2010)
Reference: Kantoff PW et al. N Engl J Med. 2010 Jul 29;363(5):411-22.

Cabazitaxel

Cabazitaxel	25 mg/m^2 IV	over 1 hr
Q3 weeks		

Approved by the USFDA in 2010
Reftrence: deBono JS et al. Lancet 2010 Oct 2;376(9747):1147-54.

MANAGEMENT OF OSTEOPOROSIS

Zoledronic acid

Zoledronic acid	4 mg IV every 3 months x 1 year

Reftrence:
Saad F et al. J Natl Cancer Inst. 2004 Jun 2;96(11):879-82.
Smith MR et al. J Urol. 2003 Jun;169(6):2008-12.
Saad F et al. J Natl Cancer Inst. 2002 Oct 2;94(19):1458-68.

Zoledronic acid	4 mg IV annually

Reftrence: Michaelson MD et al. J Clin Oncol. 2007 Mar 20;25(9):1038-42.

Alendronate

Alendronate	70 mg P.O. once weekly

Reftrence: Greenspan SL et al. Ann Intern Med. 2007 Mar 20;146(6):416-24.

Denosumab

Denosumab	60 mg S.C. every 6 months

Reftrence: Smith MR et al. N Engl J Med. 2009 Aug 20;361(8):745-55.

Denosumab	120 mg S.C. every 4 weeks

Reftrence: Fizazi K et al. Lancet 2011 Mar 5;377(9768):813-22. Epub 2011 Feb 25.

PART - I
Solid Tumor

Retinoblastoma

RETINOBLASTOMA

Retinoblastoma is a relatively uncommon tumor of childhood that arises in the retina and accounts for about 3% of the cancers occurring in children younger than 15 years. The estimated annual incidence in the United States is approximately 10 to 14 per million children aged 0 to 4 years. Although retinoblastoma may occur at any age, it most often occurs in younger children, usually before the age of 2 years. Ninety-five percent of cases are diagnosed before the age of 5 years. Retinoblastoma is a tumor that occurs in heritable (40%) and nonheritable (60%) forms. Heritable disease includes those patients with a positive family history (10%) and who have sustained a new germline mutation at the time of conception (30%). Retinoblastoma is usually confined to the eye, and as a result, more than 90% of children with retinoblastoma will be cured. Patients with the heritable type of retinoblastoma have a markedly increased frequency of second malignant neoplasms (SMN). Most of the SMN are osteosarcomas, soft tissue sarcomas, or melanomas. A markedly increased mortality from lung, bladder, and other epithelial cancers occurs in patients with heritable retinoblastoma who were spared radiation. The type of treatment required depends on both the extent of the disease within the eye and whether the disease has spread beyond the eye, either to the brain or to the rest of the body. It is not uncommon for patients with retinoblastoma to have extensive disease within one eye at diagnosis, with either massive tumors involving more than one half of the retina, multiple tumors diffusely involving the retina, or obvious seeding of the vitreous. The goals of therapy are 3-fold: eradicate the disease, preserve as much vision as possible, and decrease risk of late sequelae from treatment, particularly SMN. Patients with retinoblastoma demonstrate a variety of long-term visual field defects after treatment for their intraocular disease. These defects are related to tumor size, location, and treatment method.

Reference:
Kopelman JE, McLean IW, Rosenberg SH: Ophthalmology 94(4):371-7, (1987).
Abramson DH et al. Arch Ophthalmol 122(9):1324-30, (2004).
Retinoblastoma Treatment (PDQ®): National Cancer Institute, available at: http://www.cancer.gov/cancertopics/pdq/treatment/retinoblastoma/healthprofessional/allpages#Reference2.40
Gallie BL et al. Pediatr Clin North Am 38(2):299-315, (1991).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumors no more than 2/3 the volume of the eye with no vitreous or subretinal seeding
pT1	Tumor confined to eye with no optic nerve or choroidal invasion
T1a	No tumor in either eye is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea.
T1b	At least one tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea. No retinal detachment or subretinal fluid beyond 5 mm from the base of the tumor.
T1c	At least one tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea. With retinal detachment or subretinal fluid beyond 5 mm from the base of the tumor.
T2	Tumors no more than 2/3 the volume of the eye with vitreous or subretinal seeding. Can have retinal detachment.
pT2	Tumor with minimal optic nerve and/or choroidal invasion
T2a	Focal vitreous and/or subretinal seeding of fine aggregates of tumor cells is present, but no large clumps or "snowballs" of tumor cells.
pT2a	Tumor superficially invades optic nerve head but does not extend past lamina cribrosa or tumor exhibits focal choroidal invasion.
T2b	Massive vitreous and/or subretinal seeding is present, defined as diffuse clumps or "snowballs" of tumor cells.
pT2b	Tumor superficially invades optic nerve head but does not extend past lamina cribrosa and exhibits focal choroidal invasion.
T3	Severe intraocular disease
pT3	Tumor with significant optic nerve and/or choroidal invasion
T3a	Tumor fills more than 2/3 of the eye.

pT3a	Tumor invades optic nerve past lamina cribrosa but not to surgical resection line or tumor exhibits massive choroidal invasion.
T3b	One or more complications present, which may include tumor-associated neovascular or angle closure glaucoma, tumor extension into the anterior segment, hyphema, vitreous hemorrhage, or orbital cellulitis.
pT3b	Tumor invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion.
T4	Extraocular disease detected by imaging studies.
pT4	Tumor invades optic nerve to resection line or exhibits extraocular extension elsewhere.
T4a	Invasion of optic nerve.
pT4a	Tumor invades optic nerve to resection line but no extraocular extension identified
T4b	Invasion into the orbit.
pT4b	Tumor invades optic nerve to resection line and extraocular extension identified
T4c	Intracranial extension not past chiasm.
T4d	Intracranial extension past chiasm.

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement (preauricular, cervical, submandibular)
N2	Distant lymph node involvement

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Systemic metastasis.
M1a	Single lesion to sites other than CNS
M1b	Multiple lesions to sites other than CNS.
M1c	Prechiasmatic CNS lesion(s).
M1d	Postchiasmatic CNS lesion(s).
M1e	Leptomeningeal and/or CSF involvement.

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Idarubicin

(Extraocular retinoblastoma)

Idarubicin	10 mg/m^2 IV over 30 min	day 1, 2
In Weeks 0 and 3		

Reference: Guillermo L. Chantada et al. J. Clin. Oncol. 1999, 17(6):1847-1850

Etoposide + Carboplatin

Regimen # 1 (Extraocular retinoblastoma)

Etoposide	150 mg/m^2/d	day 1–3
Carboplatin	200 mg/m^2/d	day 1–3

In children younger than 1yr or weighing <10kg	
Etoposide	5 mg/kg
Carboplatin	6.7 mg/kg
Followed by intensive Sequential Local Therapy (Local Cryotherapy)	

Reference: M. Nenadov Beck et al. J Clin Oncol. 2000, 18(15):2881-2887

Regimen # 2 (Intraocular Retinoblastoma)		
Carboplatin	600 mg/m^2/dose	day 1
or		
18 mg/kg/dose for infants <12 months		day 1
Etoposide	150 mg/m^2/dose	days 1, 2
or		
5 mg/kg/dose for infants <12 months		days 1, 2
To be repeated every 28 days for six cycles		
Cycles 3-6 were administered with focal retinal therapy.		

Reference: Zage PE et al. Pediatric Blood & Cancer. Volume 50, Issue 3, Pages 567-572

CARBOPEC

(High risk retinoblastoma)		
Carboplatin	350 mg/m^2/day	day 1-5
Etoposide	350 mg/m^2/day	day 1-5
Cyclophosphamide	1.6 g/m^2/day	day 2-5
Followed by autologus haematopoietic stem cell rescue		

Reference: Namouni F et al. Eur J Cancer 1997;33(14):2368

Carboplatin + Thiotepa + Etoposide

(Metstatic Retinoblastoma)		
Carboplatin	500 mg/m^2/day	day 1-3
Thiotepa	300 mg/m^2/day	day 1-3
Etoposide	250 mg/m^2/day	day 1-3
With autologous stem cell rescue		

Reference: Dunkel IJ, Cancer 2000, 89(10):2117-21

CDO

Cyclophosphamide	20-40 mg/kg* IV over 1 hour	day 1
Doxorubicin	0.67 mg/kg IV over 1 hour	day 1-3*
Vincristine	0.05 mg/kg IV	day 1
*Week 9: 40 mg/kg, weeks 3, 6, 9, 12, 15, 18, 21: 20 mg/kg and weeks 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57: 30 mg/kg		
**stopped after week 21.		
Plus radiotherapy.		

Note: For patients with orbital disease (state II).
Reference: Schvartzman et al. J Clin Oncol 14:1532-1536, (1996).

VEC

Carboplatin	560 mg/m^2 IV over 60 minutes	day 0
(18.6 mg/kg for patients #36 months of age)		
Etoposide	150 mg/m^2 IV 60 minutes	days 0, 1
(5 mg/kg for patients #36 months of age)		
Vincristine	1.5 mg/m^2 IV	day 0
(Maximum dose not to exceed 2 mg (0.05 mg/kg for patients #36 months of age)		
Given every 28 days for total of six cycles		

Supportive care		
Antiemetics		
Ondansetron	0.45 mg/kg IV (max dose 24 mg)	prior to day 0, 1
Dexamethasone	0.25 mg/kg IV	prior to day 0, 1
Phenergan	0.5 mg/kg P.O.	day 0 then q 6 h pm
Diphenhydramine	1 mg/kg hs	day 0 then q 6 h prn
Pneumocystis carinii prophylaxis		
Trimethoprim sulfa	5 mg/kg/day divided into two doses, every monday & tuesday	

Reference: Debra L. J Clin Oncol 18:12-17. 2000

Carboplatin

Carboplatin	18.7 mg/kg IV for children under 12 kg in weight and
Carboplatin	560 mg/m^2 IV for children 12 kg or more

Note: administered within days to weeks of diagnosis
Reference:
Abramson DH et al. Br J Ophthalmol 2005;89:1616-1619.
Dunkel IJ et al. Pediatr Blood Cancer. 2007 Oct 15;49(5):643-8.

Vincristine-Carboplatin

Vincristine	0.05 mg/kg
Carboplatin	560 mg/m^2 (GFR $>$ 50 mL/min/m^2)
	or
	AUC 6.5 mg/mL/min (GFR $<$ 50 mL/min/m^2)
To be repeated every 3 weeks for 8 courses.	

Reference: Rodriguez-GC et al. J Clin Oncol. 2003 May 15;21(10):2019-25.

PART - I
Solid Tumor

Soft Tissue Sarcoma

SOFT TISSUE SARCOMA

Soft tissue sarcomas are malignant tumors that may arise in any of the mesodermal tissues of the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%). As per the NCI data, 10,660 new cases and 3,820 deaths from soft tissue sarcoma are estimated in the US in year 2009. Rarely, these tumors arise in the gastrointestinal tract or gastrointestinal stroma, and a small percentage of these are called gastrointestinal stromal tumors (GISTs). Malignant GISTs can occur from the esophagus to the rectum but occur most commonly in the stomach and small intestine. Soft tissue sarcomas usually occurs with greater frequency in patients with von Recklinghausen's disease (neurofibromatosis), Gardner's syndrome, Werner's syndrome, Tuberous sclerosis, Basal cell nevus syndrome & Li-Fraumeni syndrome (p53 mutations).

Soft tissue sarcomas may be heterogeneous, so adequate tissue should be obtained via either core-needle or incisional biopsy for microscopic examination to determine histologic type and tumor grade. The prognosis for patients with adult soft tissue sarcomas depends on several factors, including the patient's age and the size, histologic grade, and stage of the tumor. Factors associated with a poorer prognosis include age older than 60 years, tumors >5 cm, or high-grade histology.

Pediatric soft tissue sarcomas are a group of malignant tumors that originate from primitive mesenchymal tissue and account for 7% of all childhood tumors. Rhabdomyosarcomas, tumors of striated muscle, and undifferentiated sarcomas account for more than one half of all cases of soft tissue sarcomas in children. The remaining non-rhabdomyosarcomatous STS accounts for approximately 3% of all childhood tumors. This heterogeneous group of tumors includes neoplasms of smooth muscle (leiomyosarcoma), connective tissue (fibrous and adipose), vascular tissue (blood and lymphatic vessels), and the peripheral nervous system. Synovial sarcomas, fibrosarcomas, and neurofibrosarcomas predominate in pediatric patients.

These neoplasms can present initially as an asymptomatic solid mass, or they may be symptomatic because of local invasion of adjacent anatomical structures. Systemic symptoms (e.g., fever, weight loss, and night sweats) are rare. The prognosis and biology of NRSTS tumors vary greatly depending upon the age, the primary site, tumor size, tumor invasiveness, histologic grade, depth of invasion, and extent of disease at diagnosis.

Reference:
American Cancer Society.: Cancer Facts and Figures 2009.
Le Doussal V et al. Cancer 77(9):1823-30, (1996).
Le QT et al. Int J Radiat Oncol Biol Phys 37(5):975-84, (1997).
Coindre JM et al. Cancer 91(10):1914-26, (2001).
Vraa S et al. Eur J Cancer 34(12):1876-82, (1998).
Pappo AS, Pratt CB: Cancer Treat Res 91:205-22, (1997).
Dillon P et al. J Pediatr Surg 27(2):241-4; discussion 244-5, (1992).
Rao BN: Semin Surg Oncol 9(6):524-31, (1993 Nov-Dec).
Fletcher CD et al. Am J Pathol 154(6):1841-7, (1999).
Skytting BT et al. Acta Orthop Scand 70(6):536-42, (1999).
Herzog CE: J Pediatr Hematol Oncol 27(4):215-8, (2005).

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T1a	Superficial tumor
T1b	Deep tumor
T2	Tumor more than 5 cm in greatest dimension
T2a	Superficial tumor
T2b	Deep tumor

Note: Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1*	Regional lymph node metastasis

**Note: Presence of positive nodes (N1) in M0 tumors is considered Stage III*

DISTANT METASTASIS (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

STAGE GROUPING

GROUP	T	N	M	
IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
IIB	T2a	N0	M0	G2
III	T2a, T2b	N0	M0	G3
	T2b	N0	M0	G2
	Any T	N1	M0	Any G
IV	Any T	Any N	M1	Any G

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Soft tissue sarcoma (adults)
  - Single agent
  - Combination chemotherapy
- Soft tissue sarcoma (pediatrics)

SOFT TISSUE SARCOMA (ADULTS)

EXTREMITY/TRUNK, HEAD/NECK, RETROPERITONEAL, INTRA-ABDOMINAL

COMBINATION CHEMOTHERAPY

AD

Doxorubicin	15 mg/m^2/d civi	d1–4
Dacarbazine	250 mg/m^2/d civi	d1–4
Q3w		

Reference: Antman, K et al. J Clin Oncol 1993;11:1276.

AI

Regimen 1		
Doxorubicin	50 mg/m^2 IV bolus	d1
Ifosfamide	5 g/m^2 IV over 24 hrs	d1
Mesna	600 mg/m^2 IV bolus before ifosfamide	
Mesna	2.5 g/m^2 mixed with ifosfamide IV over 24 hrs	
Mesna	1.25 g/m^2 IV over 12 hrs after ifosfamide	
Q3w		

Reference: Le Cesne, A et al. J Clin Oncol 2000;18:2676.

Regimen 2		
Doxorubicin	60 mg/m^2 civi over 72 hrs	d1
Ifosfamide	1.5 g/m^2/d IV over 2 hrs	d1–4
Mesna	225 mg/m^2 IV over 1 h before ifosfamide,	
4 hrs and 8 hrs after ifosfamide		
Filgrastim	5 mcg/kg S.C.	qd x 10 days starting on day 5
Q3w		

Reference:
Worden, FP et al. J Clin Oncol 2005;23:105.
Grobmyer SR et al. Ann Oncol. 2004 Nov;15(11):1667-72.

MAID (Mesna + Doxorubicin + Ifosfamide + Dacarbazine)

Doxorubicin	15 mg/m^2/d civi	d1–4
Ifosfamide	2 g/m^2/d civi	d1–3
Dacarbazine	250 mg/m^2/d civi	d1–4
Mesna	2.5 g/m^2/d civi	d1–4
Q3w		

Reference:
Antman, K et al. J Clin Oncol 1993;11:1276.
Antman, K et al. Cancer 1998;82:1288.

Ifosfamide + Epirubicin + Mesna

Epirubicin	60 mg/m^2/d civi	d1–2
Ifosfamide	1.8 g/m^2/d civi	d1–5
Mesna	2.5 g/m^2/d civi	d1–4
Mesna	2.5 g/m^2/d civi	d1–4
Q3w		

Reference: Frustaci S et al. J Clin Oncol. 2001 Mar 1;19(5):1238-47.

Gemcitabine + Docetaxel

Gemcitabine	675–900 mg/m^2 IV over 90 min	d1, 8
Docetaxel	100 mg/m^2 IV over 1 h	d8
Filgrastim	5 mcg/kg S.C. qd	d9–15
Q3w		

Reference:
Maki RG et al. J Clin Oncol 2007;25:2755.
Hensley, ML et al. J Clin Oncol 2002;20:2824.
Leu, KM et al. J Clin Oncol 2004;22:1706.

Gemcitabine + Vinorelbine

Gemcitabine	800 mg/m^2 IV over 90 min	d1, 8
Vinorelbine	25 mg/m^2 IV	
Q3w		

Reference: Dileo P et al. Cancer. 2007 May 1;109(9):1863-9.

Mitomycin-Doxorubicin-Cisplatin

Mitomycin	8 mg/m^2 IV	day 1–4
Doxorubicin	40 mg/m^2 IV	day 1
Cisplatin	60 mg/m^2 IV	day 1–3
To be repeated evety 3 weeks.		

Reference: Edmonson et al. J Clin Oncol 11:1269-1275, (1993).

Adjuvant Chemotherapy

(Adult soft tissue sarcomas of the extremities)		
Epirubicin	60 mg/m^2 IV	day 1, 2
Ifosfamide	1.8 mg/m^2 IV	day 1–5
(with mesna)		
To be repeated every 3 weeks for for 5 cycles.		
G-CSF support.		

Reference: Frustaci S et al. J Clin Oncol 19:1238-1247, (2001).

SINGLE AGENT

Doxorubicin

Doxorubicin	75 mg/m^2 IV bolus	q3w

Reference: Santoro, A et al. J Clin Oncol 1995;13:1537.

Pegylated liposomal doxorubicin

Pegylated liposomal doxorubicin	50 mg/m^2 IV over 1 h	q4w

Reference: Judson, I et al. Eur J Cancer 2001;37:870.

Ifosfamide

Ifosfamide	1.8 g/m^2/d civi	d1-5
Mesna	2.5 g/m^2/d civi	d1-4
Q3w		

Reference: Frustaci S et al. J Clin Oncol. 2001 Mar 1;19(5):1238-47.

Ifosfamide

Regimen # 1

Ifosfamide	3 g/m^2/d IV over 4 hrs	d1-3 q3w

Reference: van Oosterom, AT et al. Eur J Cancer 2002;38:2397.

Regimen # 2 (High dose ifosfamide)

Ifosfamide	2 g/m^2 IV over 2 hrs	q12 hrs x 7 doses (total 14 g)
Mesna	500 mg/m^2 mixed with first dose of ifosfamide IV over 2 hrs,	
	followed by 2.4 g/m^2/d civi x 4 days	
Filgrastim	5 mcg/kg S.C.	qd starting on d4

Reference: Patel, SR et al. J Clin Oncol 1997;15:2378.

Regimen # 3

Ifosfamide	5 g/m^2 IV over 24 hours (max 8,000 mg)	day I
With mesna		
To be repeat every 3 weeks		

Reference: Bramwell et al. Eur J Cancer Clin Oncol 23:311-321, (1987).

Regimen # 4

Ifosfamide	12,000 mg/m^2/course IV	over 3-6 days
2,000 mg/m^2 IV over 2-4 hours day I		
Then		
12,000 mg/m^2 IV civi		over 3 to 6 days
To be repeated every 4 weeks (with growth factor support)		
(Also as salvage therapy after doxorubicin or "standard dose" ifosfamide).		

Reference: Buesa et al. Ann Oncol 9:871-876, (1998).

Gemcitabine

Regimen # 1

Gemcitabine	1200 mg/m^2 IV over 120 min	d1, 8
q3w		

Reference: Maki RG et al. J Clin Oncol 2007;25:2755.

Regimen # 2		
Gemcitabine	200 mg/m^2 IV over 6 hours	day 1, 8 & 15
Q4w		

Reference: Spath Schwalbe E et al. Anticancer Drugs. 2000 Jun;11(5):325-9.

Paclitaxel

Regimen # 1		
Paclitaxel	175 mg/m^2 IV over 3 hours	day 1
Repeat every 3 weeks, for 6 cycles.		

Reference: Fata F et al. Cancer 1999;86:2034-7.

Regimen # 2		
Paclitaxel	250 mg/m^2 IV over 24 hours	day 1
Repeat every 3 weeks, for 8–12 cycles.		

Reference: Fata F et al. Cancer 1999;86:2034-7.

Temozolomide

Temozolomide	200 mg/m^2/d b.i.d. x 5 days
followed by 90 mg/m^2 (9 doses) q4w.	

Reference: Talbot SM et al. Cancer. 2003 Nov 1;98(9):1942-6.

Vinorelbine

Vinorelbine	30 mg/m^2/week IV x 6 weeks
Q3w	

Reference: Kuttesch JF Jr et al. Pediatr Blood Cancer. 2009 Oct;53(4):590-3.

Pazopanib

Pazopanib	800 mg od x 5 days
followed by 90 mg/m^2 (9 doses) q4w.	

Reference: Van der Graaf WT et al. J Clin Oncol 29:2011 (suppl; abstr LBA10002)

SOFT TISSUE SARCOMA (PEDIATRICS)

VAC

Vincristine	2 mg/m^2 weekly IV	for 12 weeks
(max 2 mg)		
Actinomycin-D	0.015 mg/kg/d IV	for 5 days
(max 0.5 fig/day) every 3 months for 5 or 6 courses		
Cyclophosphamide	2.5 fig/kg/day P.O.	for 2 years

Reference:
Maurer HM et al. Cancer 40(5):2015-2026, (1977).
Carola AS et al. J Clin Oncol, Vol 27, No 31 (November 1), 2009: pp. 5182-5188

Cyclophosphamide-Topotecan

Cyclophosphamide	250 mg/m^2/dose IV	day 1–5
Topotecan	0.75 mg/m^2/dose IV	day 1–5
Q3w		

Note: Both drugs to be administered as 30 min infusion with Filgrastim support.
Reference:
Saylors RL et al. J Clin Oncol 19:3463-3469. 2001
Walterhouse DO et al. J Clin Oncol. 2004 Apr 15;22(8):1398-403.

Irinotecan-Vincristine

Vincristine	1.5 mg/m^2	weeks 0, 1, 3, 4
Irinotecan	2 cycles of 20 mg/m^2 daily for 5 days, repeated for 2 weeks	

Reference: Pappo AS et al. J of Clin Oncol, Vol 25, No 4), 2007: pp. 362-369

Vincristine	1.5 mg/m^2 d1	weeks 1, 2, 4, 5
Irinotecan	20 mg/m^2 daily for 5 days, repeated for 2 weeks @ Week 1, 2, 4, 5	
x 44 w		

Vincristine	1.5 mg/m^2 d1	weeks 1, 2, 4, 5
Irinotecan	50 mg/m^2 daily for 5 days, @ Week 1, 4	
x 44 w		

Reference: Mascarenhas L et al. J Clin Oncol. 2010 Oct 20;28(30):4658-63.

Irinotecan

Irinotecan	600 mg/m^2 IV over 60 minute every 3 weeks

Reference: Vassal G et al. J Clin Oncol. 2007 Feb 1;25(4):356-61.

IVA

Ifosfamide	3,000 mg/m^2 IV	day 1, 2
(with mesna)		
Dactinomycin	1.5 mg/m^2 IV (max 2 mg)	day 1
Vincristine	1.5 mg/m^2 IV (max 2 mg)	day 1

Note: Doses were reduced in infants <1 year (50% in children <6 months and 33% in children between 6 and 12 months). Patients with completely resected primary tumour received 3 courses of IVA Patients with incompletely resected tumour received 6-10 courses of IVA (and/or doxorubicin + cisplatin with or without radiotherapy) according to stage.

Doxorubicin	60 mg/m^2 IV	day 1
Cisplatin	100 mg/m^2 IV	day 1

Reference: Flamant F et al. Eur J Cancer 34(7):1050-1062, (1998).

CEV

Carboplatin	500 mg/m^2 IV	day 1
Epirubicin	150 mg/m^2 IV	day 1
Vincristine	1.5 mg/m^2 IV	day 1, 7

Reference: Frascella E et al. Eur J Cancer 32A(5):821-5, (1996).

Ifosfamide-Doxorubicin-VAC

Ifosfamide	1.8 g/m^2/day IV	for 5 days
Doxorubicin	30 mg/m^2/day IV	for 2 days
Repeat every 3 weeks for 12 weeks.		
Followed by VAC		
Vincristine	2 mg/m^2 weekly IV (max 2 mg)	for 12 weeks
Actinomycin-D	0.015 mg/kg/d IV	for 5 days
(max 0.5 mg/day) every 3 months for 5 or 6 courses		
Cyclophosphamide	2.5 mg/kg/day P.O.	for 2 years
Repeat every 3 weeks for 36 weeks.		

Reference: SandIer E et al. Me,d Paed OncoI 37(5):442-8, (2001).

Vincristine + Actinomycin + Cyclophosphamide

Age	Vincristine	Dactinomycin	Cyclophosphamide + Actinomycin	Topotecan (mg/m^2/d x 5)	Cyclophosphamide + Topotecan (mg/m^2/d x 5)
<1	0.025 mg/kg	0.025	36 mg/kg	0.75	250
1-3	0.05 mg/kg	0.045	73 mg/kg	0.75	250
>3	1.5 mg/m^2	0.045	2,200 mg/m^2	0.75	250

Reference: Arndt CA et al. J Clin Oncol. 2009 Nov 1;27(31):5182-8.

Vincristine + Dactinomycin + Cyclophosphamide

Age (yrs)	Vincristine	Dactinomycin	Cyclophosphamide	G-CSF/	GM-CSF
<1	0.75 mg/m^2	0.025 mg/kg	1.1 g/m^2	5 µg/kg S.C. qd	250 µg/m^2/day
>1	1.5 mg/m^2	0.045 mg/kg (>1 yr and and ≤30 kg)	2.2 g/m^2	5 µg/kg S.C. qd	250 µg/m^2/day
>3	1.5 mg/m^2	1.5 mg/m^2 (>1 yr and and >30 kg)	2.2 g/m^2	5 µg/kg S.C. qd	250 µg/m^2/day

Reference: Raney RB et al. J Clin Oncol. 2011 April 1;29(10):1312-1318.

Cyclophosphamide-Vinorelbine

Cyclophosphamide	25 mg/m^2	x 4w
Vinorelbine	15 mg/m^2 (with dose escalation in steps of 5 mg/m^2) d1, 8, 15	

Reference: Casanova M et al. Cancer 2001:101,(7),:1664-1671,

Vincristine-Irinotecan-Temozolomide

Vincristine	1.5 mg/m^2 (max 2 mg) IV d1, 8	x 4w
Irinotecan	15 mg/m^2/d d1-5, 8-12	
Temozolomide	100 mg/m^2 P.O. od d1-5	

Reference: Mcnall Knapp RY et al. Pediatr Blood Cancer. 2010 Jul 1;54(7):909-15.

SINGLE AGENTS

Doxorubicin

Doxorubicin	60 mg/m^2 IV over 48 hrs x 2 courses	q3w

Reference: Bergeron C et al. Eur J Cancer. 2008 Feb;44(3):427-31.

Topotecan (followed by VAC/VTC)

Topotecan	2–2.4 mg/m^2 IV x 5 d	q3w

Reference: Pappo AS et al. J Clin Oncol. 2001 Jan 1;19(1):213-9.

High-dose Methotrexate (HDMTX) (followed by VACI-Mesna)

Methotrexate	12 g/m^2 IV x 1–4 courses

Reference: Pappo AS et al. J Pediatr Hematol Oncol. 1997 Sep-Oct;19(5):438-42.

GIST

Imatinib

Imatinib	400 or 600 mg P.O. od

Reference: Demetri GD et al. N Engl J Med. 2002 Aug 15;347(7):472-80.

Imatinib	400 mg P.O. od or b.i.d

Reference: Verweil J et al. Lancet 2004 Sep 25-Oct 1;364(9440):1127-34.

Sunitinib

Sunitinib	50 mg P.O. od x 4w
Q6w	

Reference: Demetri GD et al. Lancet 2006 Oct 14;368(9544):1329-38.

DISEASE PROGRESSION AFTER IMATINIB AND SUNITINIB

Sorefenib

Sorefenib	400 mg P.O. b.i.d

Reference: Kindler HL et al. J Clin Oncol 29:2011 (suppl; abstr 10009)

Sorefenib	400 mg P.O. b.i.d. until disease progression or development of intolerance.

Reference: Park SH et al. Invest New Drugs. 2012 Jan 25.

Nilotinib

Nilotinib	400 mg P.O. b.i.d. x 4w

Reference: Montemurro M et al. Eur J Cancer. 2009 Sep;45(13):2293-7.

Dasatinib

Dasatinib	70 mg P.O. b.i.d.

Reference: Trent JC et al. J Clin Oncol 29:2011 (suppl; abstr 10006)

DESMOID TUMORS (AGGRESSIVE FIBROMATOSIS)

Tamoxifen + Sulindac

Tamoxifen	120 mg P.O. od
Sulindac	300 mg P.O. od

Reference: Hansmann A et al. Cancer. 2004 Feb 1;100(3):612-20.

Methotrexate + Vinblastine

Methotrexate	30 mg/m^2 IV
Vinblastine	6 mg/m^2 IV
for 1 year	

Reference: Azzarelli A et al. Cancer. 2001 Sep 1;92(5):1259-64.

Doxorubicin + Dacarbazine

Doxorubicin	60–90 mg/m^2 IV
Dacarbazine	750–1000 mg/m^2 IV
for a median of 5 cycles (2–10 cycles)	

Reference: Patel SR et al. Cancer. 1993 Dec 1;72(11):3244-7.

Imatinib

Imatinib	300 mg P.O. b.i.d. [body surface area (BSA) $\geq$ 1.5 m^2),
	200 mg P.O. b.i.d. (BSA = 1.0–1.49 m^2),
	100 mg P.O. b.i.d. (BSA $<$ 1.0 m^2).

Reference: Chugh R et al. Clin Cancer Res. 2010 Oct 1;16(19):4884-91.

Imatinib

Imatinib	400 mg/d P.O. od x 1 year

Reference: Penel N et al. Ann Oncol. 2011 Feb;22(2):452-7.

Sorafenib

Sorafenib	400 mg/d P.O. od

Reference: Grounder MM et al. Clin Cancer Res. 2011 Jun 15;17(12):4082-90.

PIGMENTED VILLONODULAR SYNOVITIS/ TENOSYNOVIAL GIANT CELL TUMOR (PVNS/TGCT)

Imatinib

Imatinib	400 mg/d P.O. od	

Reference: Cassier PA et al. Cancer. 2012 Mar 15;118(6):1649-55.

ANGIOSARCOMA

Paclitaxel

Paclitaxel	80 mg/m^2 IV over 1 hours	day 1, 8, 15
Q4w		

Reference: Penel M et al. J Clin Oncol. 2008 Nov 10;26(32):5269-74.

Bevacizumab

Bevacizumab	15 mg/kg IV q3w

Reference: Agulnik M et al. J Clin Oncol 27:15s, 2009 (suppl; abstr 10522)

SOLITARY FIBROUS TUMOR/ HEMANGIOPERICYTOMA

Temozolomide-Bevacizumab

Temozolomide	150 mg/m^2 P.O. d1–7, 15–21
Bevacizumab	5 mg/kg IV d8, 22
q4w	

Reference: Park MS et al. Cancer. 2011 Nov 1;117(21):4939-47.

Sunitinib

Sunitinib	37.5 mg/d

Reference:
Casali PG et al. J Clin Oncol, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 15S (May 20 Supplement), 2009:10571
Stacchioti S et al. Clin Cancer Res. 2009 Feb 1;15(3):1096-104.
George S et al. J Clin Oncol. 2009 Jul 1;27(19):3154-60.

ALVEOLAR SOFT PART SARCOMA

Sunitinib

Sunitinib	37.5 mg/d

Reference:
Stacchioti S et al. Mol Cancer Ther. 2010 May;9(5):1286-97.
Stacchioti S et al. Clin Cancer Res. 2009 Feb 1;15(3):1096-104.

PECOMA, RECURRENT ANGIOMYOLIPOMA, LYMPHANGIOLEIOMYOMATOSIS

Sirolimus

Sirolimus	2 mg/d

Reference: McCormack FX et al. N Engl J Med. 2011 April 28;364(17):1595-1606.

Sirolimus	0.25 mg/m^2 (to achieve steady state levels between 1–5 mg/ml)

Reference: Bissler JJ et al. N Engl J Med. 2008 Jan 10;358(2):140-51.

Sirolimus	0. 5 mg/m^2 (to achieve steady state levels between 3–6 mg/ml)

Reference: Davies DM et al. Clin Cancer Res. 2011 Jun 15;17(12):4071-81.

CHORDOMA

Imatinib + low dose Cisplatin

Imatinib	400 mg/d
Cisplatin	25 mg/m^2/wk

Reference:
Casali PG et al. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007:10038

Imatinib + Sirolimus

Imatinib	400 mg/d
Cisplatin	2 mg/d

Reference: Stacchiotti S et al. Ann Oncol. 2009 Nov;20(11):1886-94.

Imatinib

Imatinib	800 mg/d until progression

Reference: Stacchiotti S et al. J Clin Oncol. 2012 Mar 20;30(9):914-20.

INFLAMMATORY MYOFIBROBLASTIC TUMOR (IMT) WITH ALK TRANSLOCATION

Crizotinib

Crizotinib	250 mg P.O. b.i.d

Reference: Butrynski JE et al. N Engl J Med. 2010 October 28;363(18):1727-1733.

PART - I
Solid Tumor

Testicular Cancer

TESTICULAR CANCER

Testicular cancer is a highly treatable, often curable cancer that usually develops in young and middle-aged men. As per the NCI data 8,590 new cases and 360 deaths are estimated in the US in year 2012. It is broadly divided into seminoma and nonseminoma types for treatment planning because seminomas are more sensitive to radition therapy. Tumors that have a mixture of seminoma and nonseminoma components should be managed as nonseminoma type. Nonseminomas include embryonal carcinomas, teratomas, yolk sac carcinomas and choriocarcinomas, and various combinations of these cell types. Tumors that appear to have a seminoma histology but that have elevated serum levels of alpha fetoprotein (AFP) should be treated as nonseminomas. Risk of metastases is lowest for teratoma and highest for choriocarcinoma, with the other cell types being intermediate. Prognostic factors like presence of liver, bone, or brain metastases, very high serum markers, primary mediastinal nonseminoma, large number of lung metastases, independently predict worse prognosis.

Serum markers (AFP, hCG and lactate dehydrogenase) are an important aspect of the diagnosis and follow-up of testicular cancer. Evaluation of the retroperitoneal lymph nodes is an important aspect of treatment planning in adults with testicular cancer. Patients who have been cured of testicular cancer have approximately a 2% to 5% cumulative risk of developing a cancer in the opposite testicle during the 25 years after initial diagnosis. Within this range, men with nonseminomatous primary tumors appear to have a lower risk of subsequent contralateral testis tumors than men with seminomas. HIV-infected men are at increased risk for developing testicular germ cell cancer.

Reference:
1. *American Cancer Society.: Cancer Facts and Figures 2012.*
2. *Socinski MA, Stomper PC: Semin Urol 6(3):203-15, (1988).*
3. *Consensus conference. JAxMA 259(14):2132-8, (1988).*
4. *Osterlind A et al. J Natl Cancer Inst 83(19):1391-5, (1991).*
5. *Colls BM et al. J Clin Oncol 14(7):2061-5, (1996).*
6. *Fosså SD et al. J Natl Cancer Inst 97(14):1056-66, (2005).*
7. *van Leeuwen FE et al. J Clin Oncol 11(3):415-24, (1993).*
8. *Foster RS, Donohue JP: Semin Oncol 19(2):166-70, (1992).*

PRIMARY TUMOR (T)

The extent of primary tumor is usually classified after radical orchiectomy and, for this reason, a pathologic stage is assigned.

pTX Primary tumor cannot be assessed

pT0 No evidence of primary tumor (e.g., histologic scar in testis)

pTis Intratubular germ cell neoplasia (carcinoma in situ)

pT1 Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis

pT2 Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis

pT3 Tumor invades the spermatic cord with or without vascular/lymphatic invasion

pT4 Tumor invades the scrotum with or without vascular/lymphatic invasion

**Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.*

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension

pN1 Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to 5 nodes positive, none more than 2 cm in greatest dimension

N2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension

pN2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor

N3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

pN3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	No regional nodal or pulmonary metastasis
M1b	Distant metastasis other than to non-regional lymph nodes and lung

SERUM TUMOR MARKERS (S)

SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 x N* AND hCG (mIu/ml) <5000 AND AFP (mg/ml) <1000
S2	LDH 1.5–10 x N OR hCG (mIu/ml) 5000–50,000 OR AFP (mg/ml) 1000–10,000
S3	LDH >10 x N OR hCG (mIu/ml) >50,000 OR AFP (mg/ml) >10,000

**N indicates the upper limit of normal for the LDH assay.*

STAGE GROUPING

GROUP	T	N	M	S (serum tumor markers)
0	pTis	N0	M0	S0
I	pT1–4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any pT/Tx	N0	M0	S1–3 (post orchiectomy)
II	Any pT/Tx	N1–3	M0	SX
IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
III	Any pT/Tx	Any N	M1	SX
IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

- Initial chemotherapy
- Salvage chemotherapy

INITIAL CHEMOTHERAPY

Carboplatin (for stage I seminoma)

Carboplatin	AUC 7 x 1 dose

Reference:
Oliver RT et al. 2008 ASCO annual meeting. Abstract 1.
Oliver RT et al. Lancet 2005;366:293.

BEP

Regimen 1 (5 day schedule)		
Bleomycin	30 U or 30 mg IV bolus	d1, 8, 15 or d2, 9, 16
Etoposide	100 mg/m^2/d IV over 1 h	d1–5
Cisplatin	20 mg/m^2/d IV over 1 h	d1–5
Q3w x 3–4 cycles		

Reference:
Culine S et al. J Clin Oncol 2008;26:421.
de Wit R et al. J Clin Oncol 2001;19:1629.
Nichols CR et al. J Clin Oncol 1998;16:1287.
Williams, SD et al. N Engl J Med 1987;316:1435.
Saxman et al. J. Clin Oncol 16(1998):702-706

Regimen 2 (3 day schedule)		
Bleomycin	30 U or 30 mg IV bolus	d1, 8, 15
Etoposide	165 mg/m^2/d IV	d1–3
Cisplatin	50 mg/m^2/d IV	d1–2
Q3w x 3–4 cycles		

Reference: de Wit R et al. J Clin Oncol 2001;19:1629.

EP

Etoposide	100 mg/m^2/d IV over 1 h	d1–5
Cisplatin	20 mg/m^2/d IV over 1 h	d1–5
Q3w x 4 cycles		

Reference: Kondagunta, GV et al. J Clin Oncol 2005;23:9290.

VIP (for patients with underlying lung disease)

Etoposide	75 mg/m^2/d IV over 1 h	d1–5
Ifosfamide	1.2 g/m^2/d IV	d1–5
Cisplatin	20 mg/m^2/d IV over 1 h	d1–5
Mesna	120 mg/m^2 IV bolus d1 before ifosfamide,	
	followed by 1.2 g/m^2/d civi	d1–5
Filgrastim	5 mcg/kg S.C. qd	d7–16
Q3w x 4 cycles		

Reference:
Nichols, CR et al. J Clin Oncol 1998;16:1287.
Hinton, S et al. Cancer 2003;97:1869.

PVB

(Good-prognosis germ cell carcinoma)

Cisplatin	100 mg/m^2 IV	day I
Vinblastine	6 mg/m^2 IV	day 1, 2
Bleomycin	30 units I.M.	weekly
To be repeated every 3 weeks for maximum of 4 courses.		

Note: Greater toxicities as compared to the regimen without bleomycin
Reference: Levi JA et al. J Clin Oncol11 (7):1300-5, (1993).

BOP

(Adjuvant for high-risk stage I non-seminomatous germ cell tumour)

Cisplatin	50 mg/m^2 IV	days 1 & 2
Vincristine	1.4 mg/m^2 IV	days 2 & 8
Bleomycin	30000 IU mg IV	days 2 & 8
To be repeated every 2 weeks.		

Reference: Dearnaley DP et al. Br J Cancer. 2005 Jun 20;92(12):2107-13

POMB/ACE

Vincristine	1 mg/m^2 (max 2 mg) IV bolus	day 1
Methotrexate	300 mg/m^2 IV (12 h infusion)	day 1
Folinic acid	15 mg x 4 every 12 h	day 2 + 3
Bleomycin	15 mg IV (24 h infusion)	day 2
Cisplatin	120 mg/m^2 IV (12 h infusion)	day 4
After 2 weeks interval		
Dactinomycin	0.5 mg IV bolus	day 1–3
Cyclophosphamide	500 mg/m^2 IV (30 min infusion)	day 3
Etoposide	100 mg/m^2 IV (infusion)	days 1–3

Note: POMB and ACE given alternatingly after the first two cycles which are both POMB
Reference: BOWER et al. Ann. Oncol. 8(1997):477-483

BEP/EP

Cisplatin	20 mg/m^2 IV	days 1–5
Etoposide	100 mg/m^2 IV	days 1–5
Bleomycin	30 mg IV	days 1, 8, 15
To be repeated every 3 weeks (4 cycles), followed by 2 cycles of EP (using the same doses of cisplatin and etoposide, but omitting bleomycin).		

Reference: KAYE et al. J. Clin Oncol 16(1998):692-701

SALVAGE CHEMOTHERAPY

VIP

Etoposide	75 mg/m^2/d IV over 1 h	d1–5
Ifosfamide	1.2 g/m^2/d IV	d1–5
Cisplatin	20 mg/m^2/d IV over 1 h	d1–5
Mesna	120 mg/m^2 IV bolus d1 before	
	ifosfamide, followed by 1.2 g/m^2/d civi	d1–5
Filgrastim	5 mcg/kg S.C. qd	d7–16
Q3w x 4 cycles		

Reference:
Loehrer, PJ Sr et al. Ann Intern Med 1988;109:540.
McCaffrey, JA et al. J Clin Oncol 1997;15:2559.

VeIP (for patients who received prior etoposide)

Vinblastine	0.11 mg/kg/d IV over 1 h	d1–2
Ifosfamide	1.2 g/m^2/d IV	d1–5
Cisplatin	20 mg/m^2/d IV over 1 h	d1–5
Mesna	400 mg/m^2 IV 15 min before	
	first ifosfamide dose, followed by 1.2 g/m^2/d civi	d1–5
Q3w x 4 cycles		

Reference:
Loehrer, PJ Sr et al. Ann Intern Med 1988;109:540.
Loehrer PJ, Sr et al. J Clin Oncol 1998;16:2500.

TIP

Regimen # 1		
Paclitaxel	250 mg/m^2 IV over 24 hrs	d1
Ifosfamide	1.5 g/m^2/d IV over 1 h	d2–5
Cisplatin	25 mg/m^2/d IV over 30 min	d2–5
Mesna	500 mg/m^2 IV before ifosfamide, and	
at 4 and 8 hrs after ifosfamide daily		d2–5
Filgrastim	5 μg/kg S.C. qd	d7–18
Q3w x 4 cycles		

Reference: Kondagunta, GV et al. J Clin Oncol 2005;23:6549.

Regimen # 2		
Paclitaxel	250 mg/m^2 IV over 24 hours	day 1
Ifosfamide	1.2 g/m^2 IV over 4 hours	day 2 - 6
(with mesna)		
Cisplatin	20 mg/m^2 IV over 20 min	day 2 - 6
Mesna	400 mg/m^2 IV before ifosfamide and at every 4 hours thereafter, for a total of three doses per day	
G-CSF	5 µg/kg S.C. daily	day 7 - 18
Q3w x 4 cycles		

Reference: Motzer RJ et al. J Clin Oncol18(12):2413-8, (2000).

Cisplatin + Epirubicin

Cisplatin	20 mg/m^2/d IV	d1 - 5
Epirubicin	90 mg/m^2 IV over 15 - 30 min	d1
Filgrastim	5 mcg/kg S.C. qd	d7 - 16,
	or	
pegfilgrastim	6 mg S.C.	d7
Q3w x 4 cycles		

Reference: Bedano P et al. J Clin Oncol 2006;24:5403.

Gemcitabine + Paclitaxel (for platinum-refractory disease)

Paclitaxel	100 - 110 mg/m^2 IV over 1 h	d1, 8, 15
Gemcitabine	1000 mg/m^2 IV over 30 min	d1, 8, 15
Q4w x 6 cycles		

Reference:
Mulherin BP et al. J Clin Oncol 29:2011 (suppl; abstr 4562)
Einhorn LH et al. J Clin Oncol 2007;25:513.
Hinton, S et al. J Clin Oncol 2002;20:1859.

Gemcitabine + Oxaliplatin

Gemcitabine	1000 mg/m^2 IV over 30 min	d1, 8
Oxaliplatin	130 mg/m^2 IV	d1
Q3w x 6 cycles		

Reference:
Pectasides D et al. Ann Oncol. 2004 Mar;15(3):493-7
Kollmannsberger C et al. J Clin Oncol. 2004 Jan 1;22(1):108-14.

Gemcitabine + Oxaliplatin

Gemcitabine	1250 mg/m^2 IV over 30 min	d1, 8
Oxaliplatin	130 mg/m^2 IV	d1
Q3w		

Reference: De Giorgi U et al. Eur Urol. 2006 Nov;50(5):1032-8; discussion 1038-9.

Gemcitabine +Paclitaxel + Oxaliplatin

Gemcitabine	800 mg/m^2 IV	d1, 8
Paclitaxel	80 mg/m^2 IV over 1 h	d1, 8
Oxaliplatin	130 mg/m^2 IV	d1
Q3w x min 2 cycles		

Reference: Bokemeyer C et al. Ann Oncol. 2008 Mar;19(3):448-53.

PART - I
Solid Tumor

Thymoma

THYMOMA

Thymomas are epithelial tumors of the thymus, which may or may not be extensively infiltrated by non-neoplastic lymphocytes. A thymic epithelial tumor that exhibits clear-cut cytologic atypia and histologic features no longer specific to the thymus is known as a thymic carcinoma (also known as type C thymoma). Invasive thymomas and thymic carcinomas are relatively rare tumors, which together represent about 0.2% to 1.5% of all malignancies. In general, thymomas are indolent tumors with a tendency toward local recurrence rather than metastasis. Thymic carcinomas, however, are typically invasive, with a high risk of relapse and death. Most patients with thymoma or thymic carcinoma are aged 40 through 60 years. Thymoma has been associated with an increased risk for second malignancies, which appears to be unrelated to thymectomy, radiation therapy, or a clinical history of myasthenia gravis. The measurement of interferon-alpha and interleukin-2 antibodies is helpful to identify patients with a thymoma recurrence.

Reference:
Fornasiero A et al. J Clin Oncol 8(8):1419-23, (1990).
Ogawa K et al. Cancer 94(12):3115-9, (2002).
Blumberg D et al. J Thorac Cardiovasc Surg 115(2):303-8; discussion 308-9, (1998).
Schmidt-Wolf IG et al. Ann Hematol 82(2):69-76, (2003).
Evoli A et al. Neurology 59(12):1844-50, (2002).
Pan CC et al. Cancer 92(9):2406-11, (2001).
Engels EA, Pfeiffer RM: Int J Cancer 105(4):546-51, (2003).
Buckley C et al. Neurology 57(9):1579-82, (2001).

STAGING

Modified Masaoka clinical staging of thymoma*

Masaoka stage	Diagnostic criteria
Stage	I Macroscopically and microscopically completely encapsulated
Stage II	(A) Microscopic transcapsular invasion. (B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, lung).
Stage IV	(A) Pleural or pericardial dissemination. (B) Lymphogenous or hematogenous metastasis

Reference: NCCN Clinical Practice Guidelines in Oncology: Thymic Malignancies. V.2. 2009

FIRST-LINE COMBINAITON CHEMOTHERAPY REGIMENS

CAP (preferred for thymoma)

Cisplatin	50 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Cyclophosphamide	500 mg/m^2 IV	d1
Q3w		

Reference: Loehrer, PJ et al. J Clin Oncol 1994;12:1164.

CAP with Prednisone

Cisplatin	30 mg/m^2 IV	d1-3
Doxorubicin	20 mg/m^2/d IV	d1-3
Cyclophosphamide	500 mg/m^2 IV	d1
Prednisone	100 mg/d	d1-5
Q3w		

Reference: Kim ES et al. Lung Cancer 2004;44:369.

ADOC

Cisplatin	50 mg/m^2 IV	d1
Doxorubicin	40 mg/m^2 IV	d1
Vincristine	0.6 mg/m^2 IV	d3
Cyclophosphamide	700 mg/m^2 IV	d4
Q4w		

Reference: Fornasiero, A et al. Cancer 1991;68:30.

PE

Cisplatin	60 mg/m^2 IV	d1
Etoposide	120 mg/m^2/d IV	d1-3
Q3w		

Reference: Giaccone, G et al. J Clin Oncol 1996;14:814.

VIP

Etoposide	75 mg/m^2/d IV	d1-4
Ifosfamide	1.2 g/m^2 IV	d1-4
Cisplatin	20 mg/m^2 IV	d1-4
Q3w		

Reference: Loehrer PJ et al. Cancer 2001;91:2010.

Carboplatin-Paclitaxel (preferred for thymic carcinoma)

Carboplatin	AUC 6
Paclitaxel	225 mg/m^2/d IV
Q3w	

Reference: Lemma GL et al. J Clin Oncol 2011;29:2060.

PART - I
Solid Tumor

Thyroid Cancer

THYROID CANCER

Carcinoma of the thyroid gland is an uncommon cancer but is the most common malignancy of the endocrine system. As per the NCI data, estimated 56,460 new cases and 1,780 deaths from thyroid cancer are reported in the US in year 2012. The overall incidence of cancer in a cold nodule is 12% to 15%, but it is higher in people younger than 40 years and in people with calcifications present on preoperative ultrasonography. It usually occurs in people between the ages of 25 and 65 years.

Differentiated tumors (papillary or follicular) are highly treatable and curable. Poorly differentiated tumors (medullary or anaplastic) are much less common, are aggressive, metastasize early, and have a much poorer prognosis.

Patients with a history of radiation administered in infancy and childhood for benign conditions of the head and neck, such as enlarged thymus, acne, or tonsillar or adenoidal enlargement, have an increased risk of cancer as well as other abnormalities of the thyroid gland. The prognosis for differentiated carcinoma is better for patients younger than 40 years without extracapsular extension or vascular invasion. Age appears to be the single most important prognostic factor. Patients considered to be low risk by the age, metastases, extent, and size (AMES) risk criteria include women younger than 50 years and men younger than 40 years without evidence of distant metastases.

Reference:
1. *American Cancer Society.: Cancer Facts and Figures 2012.*
2. *Hundahl SA et al. Cancer 83(12):2638-48, (1998).*
3. *Tennvall J et al. Cancer 57(7):1405-14, (1986).*
4. *Khoo ML et al. Head Neck 24(7):651-5, (2002).*
5. *Grant CS et al. Surgery 104(6):954-62, (1988).*
6. *Sanders LE, Cady B: Arch Surg 133(4):419-25, (1998).*
7. *Mazzaferri EL: Mayo Clin Proc 66(1):105-11, (1991).*
8. *Staunton MD: Eur J Surg Oncol 20(6):613-21, (1994).*
9. *Mazzaferri EL, Jhiang SM: Am J Med 97(5):418-28, (1994).*

PRIMARY TUMOR (T)

All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification).

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension limited to the thyroid

T1a Tumor 1 cm or less, limited to the thyroid

T1b Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid

T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid

T3 Tumor more than 4 cm in greatest dimension limited to the thyroid, or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)

T4a Moderately advanced disease. Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve

T4b Very advanced disease. Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

All anaplastic carcinomas are considered T4 tumors

T4a Intrathyroidal anaplastic carcinoma

T4b Anaplastic carcinoma with gross extrathyroid extension

REGIONAL LYMPH NODES (N)

Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

N1a Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)

N1b Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma.

Papillary or Follicular (Differentiated) Under 45 Years

GROUP	T	N	M
I	Any T	Any N	M0
II	Any T	Any N	M1

Papillary or Follicular (Differentiated) 45 Years and Older

GROUP	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

Medullary Carcinoma (All age groups)

GROUP	T	N	M
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
III	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

Anaplastic Carcinoma – All anaplastic carcinomas are considered Stage IV

GROUP	T	N	M
IVA	T4a	Any N	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS FOR METASTATIC DIFFERENTIATED THYROID CARCINOMA

Iodophilic Tumours

Radioiodine	-3.0 GBq	

Reference: Vini L et al. The Lancet Oncology3:407-14, (2002)

Doxorubicin-Cisplatin

Doxorubicin.	60 mg/m^2 IV	day 1
Cisplatin.	40 mg/m^2 IV	day 1

Note: The dose of doxorubicin is to be adjusted for hematologic or hepatic dysfunction. Treatment is to be repeated every 3 weeks to a total dose of 550 mg/m^2 of doxorubicin or until evidence of failure of therapy.
Reference: Shimaoka K, Schoenfeld DA, DeWys WD, et al. Cancer 56:2155-2160, (1985).

BAP

Bleomycin	30 units/m^2 IV	day 1 – 3
Doxorubicin.	60 mg/m^2 IV	day 5
Cisplatin.	60 mg/m^2 IV	day 5

Reference: De Besi P et al. J Endocrinol Invest 14(6):457-480, (1991)

Carboplatin-Epirubicin

Carboplatin	300 mg/m^2 IV over 30 mins	day 1
Epirubicin	75 mg/m^2 IV bolus (4 hrs after carboplatin administration) Repeat cycle after 4 – 6 weeks.	

Reference: Santini F, et al. J Clin Endocrinol Metab 87:4160-4165, (2002)

Motesanib

(Progressive, advanced or metastatic, radioiodine-resistant differentiated cancer)

Motesanib diphosphate	125 mg P.O./daily

Reference: Sherman SI et al. N Engl J Med 2008;359:31-42.

Motesanib diphosphate	50-75 mg P.O. od or 25 mg P.O. b.i.d. daily x 3w
Q4w	

Reference: Rosen LS et al. J Clin Oncol. 2007 Jun 10;25(17):2369-76.

CVD

(Advanced medullary thyroid carcinoma)

Cyclophosphamide	750 mg/m^2	day 1
Vincristine	1.4 mg/m^2	day 1
Dacarbazine	600 mg/m^2	day 1, 2
To b repeated every 3 or 4 weeks depending on the tolerance		

Reference: Wu et al. Cancer January 15, (1994) Volume 73, No. 2 Pages 432-436

Dacarbazine-5-FU

(Advanced medullary thyroid cancer)

Dacarbazine	250 mg/sqm (5 day intravenous courses)
5-Fluorouracil	450 mg/sqm over 12 hour infusion
To be repeated every 4 weeks.	

Reference: Orlandi F et al. Annals of Oncology 5:763-765, (1994).

Sorafenib

(Metastatic, iodine-refractory thyroid carcinoma)

Sorafenib	400 mg P.O. twice daily

Reference:
Gupta AV et al. J Clin Oncol. 2008 Oct 10;26(29):4714-9.
Hoftjizer H et al. Eur J Endocrinol. 2009 Dec;161(6):923-31.

Sorafenib/Sunitinib

{Progressive, radioactive iodine-refractory differentiated thyroid carcinoma (DTC)}

Sorafenib	400 mg P.O. b.i.d
Sunitinib	50 mg P.O. od x 4w q6w or
	50 mg P.O. od x 2w q3w

Reference: Cabanillas ME et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2588-95.

Sunitinib

{Metastatic WTC and MTC}

Sunitinib	37.5 mg P.O. od on a continuous basis

Reference:
Carr L et al. J Clin Oncol, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 15S (May 20 Supplement), 2009:6056
Goulart B et al. J Clin Oncol, 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 26, No 15S (May 20 Supplement), 2008:6062

Sunitinib	50 mg P.O. od x 4w q6w or

Reference:
Cohen EE et al. J Clin Oncol,, 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 26, No 15S (May 20 Supplement), 2008:6025

Axitinib

Axitinib	5 mg P.O. b.i.d

Reference: Cohen EE et al. Journal J Clin Oncol. 2008 Oct 10;26(29):4708-13.

Desipeptide

Desipeptide	13 mg/m^2 IV d1, 8, 15
Q4w	

Reference:
Sherman EJ et al. J Clin Oncol. 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 27, No 15S (May 20 Supplement), 2009:6059

Sunitinib-Bortezomib

Sunitinib	37.5 mg or 50 mg P.O. od x 4w
Bortezomib	1-1.6 mg/m^2 weekly x 4w
Q6w	

Reference:
Harvey RD et al. J Clin Oncol, 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition).Vol 28, No 15_suppl (May 20 Supplement), 2010:5589

Celecoxib

Celecoxib	400 mg P.O. b.i.d. x 1 yr

Reference: Mrozek E et al. J Clin Endocrinol Metab. 2006 Jun;91(6):2201-4.

Lenalidomide

Lenalidomide	25 mg P.O. od

Reference:
Ain KB et al. J Clin Oncol, 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition).Vol 26, No 15S (May 20 Supplement), 2008:6027

Pazopanib

Pazopanib	800 mg P.O. od q4w
until disease progression, drug intolerance, or both	

Reference:
Bible KC et al. Lancet Oncol. 2010 Oct;11(10):962-72.

CHEMOTHERAPY REGIMENS FOR METASTATIC PAPILLARY THYROID CARCINOMA

Vandetanib (locally advanced/metastatic medullary thyroid cancer)

Vandetanib	300 mg P.O. od

Reference:
Wells SA et al. J Clin Oncol. 2012 Jan 10;30(2):134-41.
Wells SA et al. J Clin Oncol, 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition).Vol 28, No 15_suppl (May 20 Supplement), 2010:5503
Wells SA et al. J Clin Oncol. 2010 Feb 10;28(5):767-72.

Vandetanib	100 mg P.O. od

Reference: Robinson BG et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2664-71.

Sorafenib

Sorafenib	400 mg P.O. b.i.d

Reference: Lam Et et al. J Clin Oncol. 2010 May 10;28(14):2323-30.

Sunitinib

Sunitinib	50 mg P.O. od x 4w
Q6w	

Reference:
De Souza JA et al. J Clin Oncol, 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition).Vol 28, No 15_suppl (May 20 Supplement), 2010:5504

Doxorubicin-Streptozocin-Dacarbazine-5-FU

(Advanced medullary thyroid cancer)

Doxorubicin.	60 mg/m^2 IV in 5 min	day 1
Streptozocin	500 mg/m^2 IV in 4 hrs	day 1-5
After 4 weeks		
5-Fluorouracil	400 mg/m^2 IV d1-5	
Dacarbazine	200 mg/m^2 IV d1-5	
Q8w		

Reference: Nocera M et al. Br J Cancer. 2000 Sep;83(6):715-8.

Motesanib diphosphate

Motesanib diphosphate	125 mg P.O. od x upto 48w

Reference: Schlumberger MJ et al. J Clin Oncol. 2009 Aug 10;27(23):3794-801.

PART - I
Solid Tumor

Urethral Cancer

URETHRAL CANCER

The prognosis of urethral cancer depends on its anatomical location and the depth of invasion. Superficial tumors located in the anterior urethra of both the female and male are generally curable; deeply invasive lesions or those lesions located in the posterior urethra, because they are almost always deeply invasive, are rarely curable by any combinations of therapy.

Female urethral cancer is more common than male urethral cancer, but both tumors are quite rare. The majority of information comes from cases accumulated over many decades at major cancer centers. Rarely, melanomas or periurethral sarcomas can occur.

Reference:
Urethral Cancer Treatment (PDQ®): National Cancer Institute, available at: http://www.cancer.gov/cancertopics/pdq/treatment/urethral/healthprofessional/allpages

PRIMARY TUMOR (T)

Primary Tumor (T) (male and female)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4	Tumor invades other adjacent organs

Urothelial (Transitional Cell) Carcinoma of the Prostate

Tis pu	Carcinoma in situ, involvement of the prostatic urethra
Tis pd	Carcinoma in situ, involvement of the prostatic ducts
T1	Tumor invades urethral subepithelial connective tissue
T2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle

T3 Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)

T4 Tumor invades other adjacent organs (invasion of the bladder)

REGIONAL LYMPH NODES (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single lymph node 2 cm or less in greatest dimension

N2 Metastasis in a single node more than 2 cm in greatest dimension, or in multiple nodes

DISTANT METASTASIS (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0a	Ta	N0	M0
0is	Tis	N0	M0
	Tis pu	N0	M0
	Tis pd	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Docetaxel-Oxaliplatin

Docetaxel	75 mg/m^2
Oxaliplatin	85 mg/m^2
To be repeated every 3 weeks	

Reference: Sandy S et al. Chemotherapy 2009;55:321-326

Pemetrexed

Pemetrexed	500 mg/m^2
Every 21 days along with folic acid and vitamin B12 supplementation	

Reference: Galsky MD et al. Invest New Drugs. 2007 Jun;25(3):265-70. Epub 2006 Dec 5.

5-FU-Mitomycin-RT

5-fluorouracil	1,000 mg/m^2	days 1 to 4
Repeat after 4 weeks for total 2 cycles of 5-FU		
Mitomycin-C	10 mg/m^2	days 1 and 29
with		
Concurrent external beam radiation therapy 45 to 55 Gy in 25 fractions during 5 weeks to the genitalia, perineum, and inguinal and external iliac lymph nodes		

Reference: Cohen MS et al. J Urol. Feb 2008;179(2):536-41

PART - I
Solid Tumor

Vaginal Cancer

VAGINAL CANCER

Carcinomas of the vagina are uncommon tumors comprising 1% to 2% of gynecologic malignancies and are often curable in early stages. As per the NCI 2,420 new cases and 820 deaths from vaginal (and other female genital) cancer are estimated in the US in year 2009. It is histologically differentiated in squamous cell carcinoma and adenocarcinoma. The histologic distinction between these two types is important because the two types represent distinct diseases, each with a different pathogenesis and natural history. Squamous cell vaginal cancer (in approximately 85% of cases) initially spreads superficially within the vaginal wall and later invades the paravaginal tissues and the parametria. Distant metastases occur in the lungs and liver. Adenocarcinoma (approximately 15% of cases) has a peak incidence between 17 and 21 years of age and differs from squamous cell carcinoma by an increase in pulmonary metastases and supraclavicular and pelvic node involvement. Adenosquamous carcinoma is a rare and aggressive mixed epithelial tumor comprised of approximately 1% to 2% of cases.

Prognosis depends primarily on the stage of disease, but survival is reduced in patients more than 60 years of age, are symptomatic at the time of diagnosis, have lesions of the middle and lower third of the vagina, or have poorly differentiated tumors. Therapeutic alternative depend on the stage; surgery or radiation therapy is highly effective in early stages, while radiation therapy is the primary treatment of more advanced stages.

Reference:
American Cancer Society.: Cancer Facts and Figures 2009.
Gallup DG et al. Obstet Gynecol 69(5):782-5, (1987).
Herbst AL et al. Am J Obstet Gynecol 119(5):713-24, (1974).
Kucera H, Vavra N: Gynecol Oncol 40(1):12-6, (1991).
Eddy GL et al. Am J Obstet Gynecol 165(2):292-6; discussion 296-8, (1991).
Perez CA et al. Int J Radiat Oncol Biol Phys 15(6):1283-90, (1988).
Pride GL et al. Obstet Gynecol 53(2):218-25, (1979).

PRIMARY TUMOR (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	*	Carcinoma in situ

T1	I	Tumor confined to vagina
T2	II	Tumor invades paravaginal tissues but not to pelvic wall
T3	III	Tumor extends to pelvic wall**
T4	IVA	Tumor invades mucosa of the bladder or rectum and/or extends beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

**FIGO staging no longer includes Stage 0 (Tis).*
***Pelvic wall is defined as muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis.*

REGIONAL LYMPH NODES (N)

TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	III	Pelvic or inguinal lymph node metastasis

DISTANT METASTASIS (M)

TNM	FIGO	
M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	IVB	Distant metastasis

STAGE GROUPING

GROUP	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1–T3	N1	M0
	T3	N0	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

**FIGO no longer includes Stage 0 (Tis).*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Cisplatin-Epirubicin

Cisplatin	50 mg/m^2 IV	Weekly for 9 wks
Epirubicin	70 mg/m^2 IV	Week 1, 4 & 7
Chemotherapy will be followed by radical hysterctomy		
Repeat the cycles every 9 weeks.		

Reference: Zanetta G, et al. Gynecol Oncol. 1997 Mar;64(3):431-5

MVAC

Methotrexate	30 mg/m^2 IV	day 1
Vinblastin	3 mg/m^2 IV	days 2, 15 & 22
Doxorubicin	30 mg/m^2 IV	day 2
Cisplatin.	70 mg/m^2 IV	day 2
Repeat the cycles every 4 weeks		

Reference: Long HJ 3rd, et al. Gynecol Oncol. 1995 May;57(2):235-9

BOMP

Bleomycin.	10 units I.M.	day 1 and weekly
Vincristine.	1.0 mg/m^2 IV	days 1, 8, 22 and 29
Mitomycin.	10 mg/m^2 IV	day 1
Cisplatin.	50 mg/m^2 IV	days 1 and 22
Repeat the cycles every 6 weeks		

Reference: Vogl SE, et al. Cancer Treat Rep 64:1005-1007, (1980).

Paclitaxel-Cisplatin

(Neoadjuvant therapy)	
Paclitaxel	175 mg/m^2
Cisplatin	75 mg/m^2
Every 21days for three courses followed by radical surgery	

Reference: Pierluigi BP, Gynecologic Oncology, 2008, 111(2): Pages 307-311

PART - I
Solid Tumor

Vulvar Cancer

VULVAR CANCER

Vulvar cancer is primarily a disease of elderly women but can occur in premenopausal women as well. Vulvar cancer is highly curable when diagnosed in an early stage. As per the NCI 3,580 new cases and 900 deaths are estimated in the US in year 2009. Survival is most dependent on the pathologic status of the inguinal nodes. Risk factors for node metastasis are clinical node status, age, degree of differentiation, tumor stage, tumor thickness, depth of stromal invasion, and the presence of capillary-lymphatic space invasion.

The prevailing evidence favors human papillomavirus (HPV) as a causative factor in genital tract carcinomas. The labia majora is most common site of involvement and accounts for about 50% of cases whereas labia minora accounts for 15% to 20% of cases. Well-differentiated lesions tend to spread along the surface with minimal invasion, while anaplastic lesions are more likely to be deeply invasive. Spread beyond the vulva is either to adjacent organs such as the vagina, urethra, and anus, or via the lymphatics to the inguinal and femoral lymph nodes, followed by the deep pelvic nodes.

Reference:
American Cancer Society.: Cancer Facts and Figures 2009.
Homesley HD et al. Am J Obstet Gynecol 164(4):997-1003; discussion 1003-4, (1991).
Boyce J et al. Gynecol Oncol 20(3):364-77, (1985).
Sedlis A et al. Am J Obstet Gynecol 156(5):1159-64, (1987).
Binder SW et al. Gynecol Oncol 37(1):9-16, (1990).
Homesley HD et al. Gynecol Oncol 49(3):279-83, (1993).

PRIMARY TUMOR (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis *		Carcinoma in situ (preinvasive carcinoma)
T1a	IA	Lesions $\leq$2 cm in size, confined to the vulva or perineum and with stromal invasion $\leq$1.0 mm**
T1b	IB	Lesions $>$2 cm in size or any size with stromal invasion $>$1.0 mm, confined to the vulva or perineum
T2***	II	Tumor of any size with extension to adjacent perineal structures (Lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)

T3****	IVA	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone.

**FIGO staging no longer includes Stage 0 (Tis).*
***The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.*
****FIGO uses the classification T2/T3. This is defined as T2 in TNM.*
*****FIGO uses the classification T4. This is defined as T3 in TNM.*

REGIONAL LYMPH NODES (N)

TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		One or two regional lymph node with the following features
N1a	IIIA	One or two lymph node metastasis each 5 mm or less
N1b	IIIA	One lymph node metastases 5 mm or greater
N2	IIIB	Regional lymph node metastasis with the following features:
N2a	IIIB	Three or more lymph node metastases each less than 5 mm
N2b	IIIB	Two or more lymph node metastases 5 mm or greater
N2c	IIIC	Lymph node metastasis with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastasis

An effort should be made to describe the site and laterality of lymph node metastases.

DISTANT METASTASIS (M)

TNM	FIGO	
M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

STAGE GROUPING

GROUP	T	N	M
0*	Tis	N0	M0
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T1, T2	N1a, N1b	M0
IIIB	T1, T2	N2a, N2b	M0
IIIC	T1, T2	N2c	M0
IVA	T1, T2	N3	M0
	T3	Any N	M0
IVB	Any T	Any N	M1

**FIGO no longer includes Stage 0 (Tis).*
Reference: AJCC, 2010, 7th edition

CHEMOTHERAPY REGIMENS

Cisplatin

In surgically resected valvular cancer patients		
Cisplatin	100 mg/m^2 IV	day 1
Repeat every 3 weeks		

Reference: Bellati. F et al. Gynecol Oncol. 2005 Jan;96(1):227-31

Cisplatin and 5-FU

Cisplatin	50 mg/m^2 IV	day 1
5 FU	1000 mg/m^2/day IV	day 1-4

Reference: Berg J et al. Gynaecol Oncol 1991:42;197

Mitomycin and 5FU

Mitomycin	10 mg/m^2	day 1
5 FU	1000 mg/m^2/day IV	day 1-4

Reference: Podratz KC et al. Obstet Gynaecol, 1983;61:63

Bleomycin-Methotrexate-CCNU (BMC)

1st week:		
Bleomycin	5 mg I.M.	day 1-5
Methotrexate	15 mg P.O.	day 1 & 4
CCNU	40 mg P.O.	day 5-7

2^{nd}–6^{th} week:		
Bleomycin	5 mg I.M.	day 1 & 4
(of every week)		
Methotrexate	15 mg P.O.	day 1
(of every week)		
Repeat every 7 weeks.		

Reference: Wagener HC et al. Gynecol Oncol. 2001 Jun;81(3):348-54

Topical Imiquimod

Imiquimod 5% cream-patients applied a thin layer of study medication to the lesions and let it remain overnight without a cover twice a week for a period of 16 weeks.

Reference:
Van Seters M et al. N Engl J Med. 2008 Apr 3;358(14):1465-73.
Le T et al. Gynecol Oncol. 2007 Sep;106(3):579-84. Epub 2007 Jun 19.

Paclitaxel

(Vulvar cancer not amenable to surgery or radiotherapy)	
Paclitaxel	175 mg/m^2 IV
Q3w	
With standard premedication	

Reference: Witteveen P.O. et al. Annals of Oncology 20:1511-1516, (2009)

Cisplatin and 5-FU

(Neoadjuvant for anal & urethral sphincter preservation)		
Regimen # 1		
Ondansetron	32 mg	day 1
Dexamethasone	20 mg	day 1
Cisplatin	50 mg/m^2 IV over 1 mg/min	day 1
Followed by		
5-fluorouracil	1000 mg/m^2 IV over 24 h	day 1
Dexamethasone	8 mg qAM	day 2–5
Metoclopramide	20 mg q8 h	day 2–5
5-fluorouracil	1000 mg/m^2 IV over 24 h	day 2–5

Regimen # 2		
Ondansetron	32 mg	day 1
Dexamethasone	20 mg	day 1
Cisplatin	50 mg/m^2 IV over 1 mg/min	day 1
Dexamethasone	8 mg qAM	day 2–5
Metoclopramide	20 mg q8 h	day 2–5

Reference: Geisler JP et al. Gynecologic Oncology 100(2006)53-57

LEUKEMIA

PART – II
Hematological Malignancies

Acute Lymphoblastic Leukemia (all)

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

As per the NCI data, 6,050 new cases and 1,440 deaths from acute lymphoblastic leukemia (ALL; also called acute lymphocytic leukemia) are estimated in the US in year 2012. As in childhood ALL, adult patients with ALL are at risk of developing central nervous system (CNS) involvement during the course of their disease. This is particularly true for patients with L3 histology. L3 AL is associated with a variety of translocations which involve translocation of the c-myc proto-oncogene to the immunoglobulin gene locus: t(2;8), t(8;12), and t(8;22). Both treatment and prognosis are influenced by this complication. Diagnostic confusion with acute myelocytic leukemia (AML), hairy-cell leukemia, and malignant lymphoma is not uncommon. Proper diagnosis is crucial because of the difference in prognosis and treatment of ALL and AML. Immunophenotypic analysis is essential because leukemias that do not express myeloperoxidase include M0 and M7 AML as well as ALL.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Kantarjian HM et al. Blood 72(5):1784-9, (1988).
Adult Acute Lymphoblastic Leukemia Treatment (PDQ®): National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/adultALL/healthprofessional/allpages#Reference2.6

CHEMOTHERAPY REGIMENS

- Induction regimens for Ph-positive ALL
- Linker regimen
- CALGB 8811 regimen
- Hyper-CVAD/MTX-Ara-C
- Refractory and recurrent ALL

INDUCTION REGIMENS FOR PH-POSITIVE ALL

ADULTS PATIENTS AGED >= 40 YEARS:

Dasatinib + hyper-CVAD

Dasatinib	50 mg P.O. b.i.d. or 100 md P.O. od
d1–14 of each of 8 cycles of alternating hyper-CVAD, and high-dose cytarabine and methotrexate.	
Complete remission:	
Dasatinib	50 mg P.O. b.i.d. or 100 md P.O. od
Monthly vincristine and prednisone for 2 years, followed by dasatinib indefinitely.	

Reference: Ravandi F et al. Blood. 2010 Sep 23;116(12):2070-7.

Imatinib + hyper-CVAD

Imatinib	600 mg P.O. od d1–14 of induction
Imatinib 600 mg continuously courses 2–8, 800 mg during 24 mos of maintenance therapy with monthly VCR-prednisone interrupted by 2 intensifications (hyper-CVAD + I.M.), then I.M. indefinitely.	

Reference: Thomas DA et al. J Clin Oncol 28:15s, 2010 (suppl; abstr 6506)

JALSG* regimen

Drug	Measurement	Day No.
For remission induction		
Cyclophosphamide	1,200 mg/m^2** IV (3 hrs)	1
Daunorubicin	60 mg/m^2† IV (1 hr)	1–3
Vincristine	1.3 mg/m^2‡ IV (bolus)	1, 8, 15, 22
Prednisolone	60 mg/m^2 P.O.	1–21§
Imatinib	600 mg P.O.	8–63
Methotrexate, Cytarabine, Dexamethasone	15, 40, 4 mg§§ IT	29
For C1		
Methotrexate	1 g/m^2 IV (24 hrs)	1
Cytarabine	2 g/m^2 IV (3 hrs) x 2	2, 3
Methylprednisolone	50 mg IV (1 hr) x 2	1–3
Methotrexate, Cytarabine, Dexamethasone	15, 40, 4 mg IT§§§	1
For C2		
Imatinib	600 mg P.O.	1–28
Methotrexate, Cytarabine, Dexamethasone	15, 40, 4 mg IT	1

**Japan Adult Leukemia Study Group*
***Cyclophosphamide 800 mg/m^2*
†Daunorubicin 30 mg/m^2
‡Vincristine max 2.0 mg
§Prednisolone for days 1-7 in case of patients 60 years or older
§§ Cytarabine 1 g/m^2
§§§ IT = Intrathecally

For maintenance		
Vincristine	1.3 mg/m^2‡ IV (bolus)	1
Prednisolone	60 mg/m^2 P.O.	1–5
Imatinib	600 mg P.O.	1–28

Note: C1 and C2 are alternated for four cycles each. Maintenance treatment was administered every 4 weeks up to 2 years from the date of complete remission.
Reference: Yanada M et al. J Clin Oncol. 2006 Jan 20;24(3):460-6.

‡*Vincristine max 2.0 mg*

Imatinib-Prednisone (for Ph-positive ALL)

Prednisone (Pretreatment)	10–40 mg/m^2/d	
Imatinib (Induction)	800 mg P.O.	qd
Prednisone (Induction)	40 mg/m^2/d	d1–45

Reference: Vignetti M et al. Blood. 2007 May 1;109(9):3676-8.

Dasatinib-Prednisone (for Ph-positive ALL)

Prednisone (Pretreatment)	10–60 mg/m^2/d x 7d	
Dasatinib (Induction)	70 mg P.O. b.i.d.	x 84d
Prednisone (Induction)	60 mg/m^2/d (120 mg/d max)	uptil d24,
Then tapered and stopped at d32		
Intrathecal Methotrexate		d22, 43

Reference: Foa R et al. Blood. 2011 Dec 15;118(25):6521-8.

MAINTENANCE REGIMENS

- Weekly methotrexate + daily 6-mercaptopurine (6-MP) + monthly vincristine/prednisone pulses (for 2–3 years)
- Add TKIs (imatinib/dasatinib) to the above maintenance regimen

INDUCTION REGIMENS FOR PH-NEGATIVE ALL

ADULT PATIENTS AGED > = 40 YEARS:

CALGB 8811LARSON REGIMEN

Course I: Induction (4 wks)

Cyclophosphamide	1200 mg/m^2 (800 mg/m^2 if pts older than 60) IV	d1
Daunorubicin	45 mg/m^2/d (30 mg/m^2/d if pts older than 60) IV	d1–3
Vincristine	2 mg IV	d1, 8, 15, 22
Prednisone	60 mg/m^2/d P.O. d1–21	(d1–7 if pts older than 60)
L-Asparaginase	6000 U/m^2 S.C.	d5, 8, 11, 15, 18, 22

Course II: Early intensification (4 wks/cycle x 2 cycles)

Intrathecal methotraxate	15 mg	d1
Cyclophosphamide	1000 mg/m^2 IV	d1
6-Mercaptopurine	60 mg/m^2/d P.O.	d1–14
Cytarabine	75 mg/m^2/d S.C.	d1–4, 8–11
Vincristine	2 mg IV	d15, 22
L-Asparaginase	6000 IU/m^2 S.C.	d15, 18, 22, 25

Course III: CNS prophylaxis and interim maintenance (12 wks)

Cranial radiation	2,400 cGy	d1–12
Intrathecal methotraxate	15 mg	d1, 8, 15, 22, 29
6-Mercaptopurine (6-MP)	60 mg/m^2/d P.O.	d1–70
Methotraxate	20 mg/m^2 P.O.	d36, 43, 50, 57, 64

Course IV: Late intensification (8 wks)

Daunorubicin	30 mg/m^2 IV	d1, 8, 15
Vincristine	2 mg IV	d1, 8, 15
Dexamethasone	10 mg/m^2/d P.O.	d1–14
Cyclophosphamide	1000 mg/m^2 IV	d29
6-Thioguanine	60 mg/m^2/d P.O.	d29–42
Cytarabine	75 mg/m^2/d S.C.	d29–32, 36–39

Course V: Prolonged maintenance (until 24 months from diagnosis)

Vincristine	2 mg IV	d1
Prednisone	60 mg/m^2/d P.O.	d1–5
Methotraxate	20 mg/m^2 P.O.	d1, 8, 15, 22
6-Mercaptopurine (6-MP)	80 mg/m^2/d P.O.	d1–28
Q4w		

Reference: Larson R et al. Blood 1995;85:2025.

LINKER 4-DRUG REGIMEN

Induction chemotherapy

Daunorubicin	60 mg/m^2/d IV	d1–3
Vincristine	1.4 mg/m^2 (max 2 mg for >40 yrs) IV	d 1, 8, 15 and 22
Prednisone	60 mg/m^2/d P.O.	d1–28
L-Asparaginase	6000 U/m^2/d S.C.	d17–28
If bone marrow on d14 has residual leukemia		
Daunorubicin	50 mg/m^2 IV	d15
If bone marrow on d28 has residual leukemia		
Daunorubicin	50 mg/m^2 IV	d29 and 30

Vincristine	2 mg IV	d29 and 36
Prednisone	60 mg/m^2/d P.O.	d29–42
L-Asparaginase	6000 U/m^2/d I.M.	d29–35

Consolidation chemotherap

Treatment A (cycle 2, 4, 6, 8) (HDAC/Etoposide)		
Etoposide	500 mg/m^2 IV	d1, 4, 8, 11
Cytarabine	2000 mg/m^2 IV	d1, 4, 8, 11
Treatment B (cycle 1, 3, 5, 7) (DVPAsp)		
Daunorubicin	60 mg/m^2/d IV	d1–2
Vincristine	1.4 mg/m^2 (max 2 mg for $>$40 yrs)	d 1, 8, 15
Prednisone	60 mg/m^2/d P.O.	d1–21
L-Asparaginase	12000 U/m^2 S.C.	d2, 4, 7, 9, 11, 14
Treatment C (cycle 9) (HDMTX/6-MP)		
Methotraxate	220 mg/m^2 IV bolus, then 60 mg/m^2 x 36 h on d1–2, 15–16	
Leucovorin	15 mg/m^2 IV q6 h x 12 doses beginning at 42 hrs	
6-MP	75 mg/m^2 P.O.	d1–28

Maintenance chemotherapy

Methotrexate	20 mg/m^2 P.O.	qw x 30 months
6-Mercaptopurine	75 mg/m^2 P.O.	qd x 30 months
CNS prophylaxis		
Begin within 1 wk of CR		
Cranial radiation	1.8 Gy/d to 18 Gy	
Intrathecal Methotrexate	12 mg qw x 6 wks	
CNS treatment		
In patients with CNS involvement, start intrathecal chemotherapy during induction chemotherapy.		
Intrathecal Methotrexate	12 mg qw x 10 wks, then qm x 9 months	
Cranial radiation	1.8 Gy/d to 28 Gy	

Reference:
Linker C et al. J Clin Oncol. 2002 May 15;20(10):2464.
Linker CA et al. Blood 1987;69:1242.
Linker CA et al. Blood 1991;78:2814.

HYPER-CVAD+/-RITUXIMAB

Induction

Hyper-CVAD	
Laminar air flow rooms if age $\geq$ 60 years	
Rituximab	375 mg/m^2 IV days 1, 11 if CD20 $\geq$ 20%

Consolidation

Cycle 2-4-6-8 or cycles 3, 5, 7, 9 (3-4 wks/cycle)

Methotrexate	200 mg/m^2 IV over 2 hrs followed by 800 mg/m^2 civi over 22 hrs	
d1		
Cytarabine	3 g/m^2 (1 g/m^2 for age >60 years) IV over 2 hrs q12 hrs	
	x 4 doses d2-3	
Solu-Medrol	50 mg IV q12 h x 6 doses d1-3	
Leucovorin	50 mg IV q6 hrs starting 12 hrs after completion of MTX till MTX	
level <0.05 uM		
Acetazolamide	if urine pH <7	

Cycle 1-3-5-7 or cycle 1, 4, 6, 8 (3-4 wks/cycle)

Cyclophosphamide	300 mg/m^2 IV over 2 hrs q12 hrs x 6 doses	d1-3
Mesna	600 mg/m^2/d civi d1-3 to start 1 h before cyclophosphamide till 12 hrs after completion of cyclophosphamide	
Vincristine	2 mg IV	d4, 11
Doxorubicin	50 mg/m^2 IV over 24 hrs	d4 (48 h if EF <50%)
Dexamethasone	40 mg IV or P.O. qd	d1-4 and d11-14

Cycles 1-4

If CD20 ≥20%: 8 doses rituximab 375 mg/m^2 IV
Days 1, 11 (hyper-CVAD)
Days 1, 8 (LDNR- or MTX-cytarabine)

Intrathecal chemotherapy

Prophylaxis

Methotrexate	12 mg d2 of each cycle for a total of 3-4 treatments
Cytarabine	100 mg d7 or 8 of each cycle for a total of 3-4 treatments

Therapeutic

Intrathecal chemotherapy twice a week		
Methotrexate	12 mg and	
Cytarabine	100 mg respectively	
till no more cancer cells in CSF		
then decrease intrathecal chemotherapy to once a week x 4, followed by		
Methotrexate	12 mg	d2
Cytarabine	100 mg	d8
for the remaining chemotherapy cycles		

Maintenance

Oral POMP (6-mercaptopurine, VCR, MTX, prednisone) Months 1–5, 8–17, 20–30

Intensification

Hyper-CVAD (plus rituximab 375 mg/m^2 IV days 1, 11 if CD20 $\geq$ 20%) Months 6, 18

Intensification

MTX 100 mg/m^2 IV day 1 weekly x 4
L-asparaginase 20,000 units IV day 2 weekly x 4
Months 7, 19

Support care

IV/oral alkalinzation all courses; rasburicase/allopurinol for induction		
Cipro	500 mg P.O.	b.i.d.
Fluconazole	200 mg P.O.	qd
Acyclovir	200 mg P.O.	b.i.d.
Filgrastim	10 mcg/kg S.C. qd to start on d5 of hyperCVAD and d4 of high dose	
methotraxate and cytarabine or		
Pegfilgastrim 6 mg subcutaneously		
Leucovorin rescue: 50–100 mg IV every 4–6 h if MTX levels were elevated at the end of infusion [0 h, confirmed on repeat sample] to greater than 20 μmol/L, >1 μmol/L at 24 h, or >0.1 μmol/L at 48 h		
Duration of doxorubicin infusions increased for modified hyper-CVAD regimens for cardioprotection		

Reference: Thomas DA et al. J Clin Oncol. 2010 Aug 20;28(24):3880-9.

HYPER-CVAD/MTX-ARA-C

Cycle 1–3–5–7 (3–4 wks/cycle)

Cyclophosphamide	300 mg/m^2 IV over 2 hrs q12 hrs x 6 doses	d1–3
Mesna	600 mg/m^2/d civi d1–3 to start 1 h before	
cyclophosphamide till 12 hrs after completion of cyclophosphamide		
Vincristine	2 mg IV	d4, 11
Doxorubicin	50 mg/m^2 IV over 24 hrs	d4
Dexamethasone	40 mg P.O. qd	d1–4 and d11–14

Cycle 2–4–6–8 (3–4 wks/cycle)

Methotrexate	200 mg/m^2 IV over 2 hrs followed by 800 mg/m^2 civi over 22 hrs
	d1
Cytarabine	3 g/m^2 (1 g/m^2 for patients over 60 years old) IV over 2 hrs q12 hrs
	x 4 doses d2–3
Leucovorin	50 mg IV q6 hrs starting 12 hrs after completion of MTX till MTX
	level <0.05 uM

Intrathecal chemotherapy

Prophylaxis

Methotrexate	12 mg d2 of each cycle for a total of 3–4 treatments
Cytarabine	100 mg d8 of each cycle for a total of 3–4 treatments

Therapeutic

Intrathecal chemotherapy twice a week		
Methotrexate	12 mg and	
Cytarabine	100 mg respectively	
till no more cancer cells in CSF		
then decrease intrathecal chemotherapy to once a week x 4, followed by		
Methotrexate	12 mg	d2
Cytarabine	100 mg	d8
for the remaining chemotherapy cycles		

Support care

Cipro	500 mg P.O.	b.i.d.
Fluconazole	200 mg P.O.	qd
Acyclovir	200 mg P.O.	b.i.d.
Filgrastim	10 mcg/kg S.C. qd to start on d5 of hyperCVAD and d4 of high dose methotraxate and cytarabine	

Reference:
Kantarjian H et al. Cancer. 2004 Dec 15;101(12):2788.
Kantarjian H et al. J Clin Oncol 2000;18:547.
Thomas DA et al. Blood 2004;104:1624.

MRC UKALL XII/ECOG E2993 REGIMEN (INDUCTION THERAPY)

Phase 1, weeks 1–4		
Daunorubicin	60 mg/m^2 IV	d1, 8, 15, 22
Vincristine	1.4 mg/m^2 IV	d1, 8, 15, 22
L-Asparaginase	10,000 U IV or I.M.	d17, 28
Prednisone	60 mg/m^2 P.O.	d1–28
Methotrexate	12.5 mg it	d15

Phase 2, weeks 5–8		
Cyclophosphamide	650 mg/m^2 IV	d1, 15, 29
Cytarabine	75 mg/m^2 IV	d1–4, 8–11, 15–18, 22–25
6-Mercaptopurine	6 mg/m^2 P.O.	d1–28
Methotrexate	12.5 mg it	d1, 8, 15, 22

Reference: Rowe JM et al. Blood. 2005 Dec 1;106(12):3760-7.

PEDIATRIC-INSPIRED PROTOCOLS FOR AYA PATIENTS AGED 15–39 YEARS:

GRAALL 2003 REGIMEN

Remission induction	
Corticosteroid prephase	
Prednisone	60 mg/m^2/d on days –7 to –1
Methotrexate IT	15 mg between days –7 and –4
Induction course	
Prednisone	60 mg/m^2/d on days 1–14
Daunorubicin	50 mg/m^2/d on days 1, 2, and 3; 30 mg/m^2/d on days 15 and 16
Vincristine	2 mg on days 1, 8, 15, and 22
L-asparaginase*	6,000 U/m^2/d on days 8, 10, 12, 20, 22, 24, 26, and 28
Cyclophosphamide	750 mg/m^2/d on day 1; 750 mg/m^2/d on day 15 in good early responders; 500 mg/m^2/12 h on days 15 and 16 in poor early responders
Lenograstim	150 μg/m^2/d from day 17 to myeloid recovery
Salvage course	
Idarubicin	12 mg/m^2/d on days 1–3
Cytarabine	2 g/m^2/12 h on days 1–4
Lenograstim	150 μg/m^2/d from day 9 to myeloid recovery
Consolidation blocks	
Blocks 1, 4, and 7	
Cytarabine	2 g/m^2/12 h on days 1 and 2
Dexamethasone	10 mg/12 h on days 1 and 2
L-asparaginase*	10,000 U/m^2 on day 3
Lenograstim	150 μg/m^2/d on days 7–13
Blocks 2, 5, and 8	
Methotrexate	3 g/m^2 continuous infusion on day 15
Vincristine	2 mg on day 15
L-asparaginase*	10,000 U/m^2 on day 16
6-Mercaptopurine	60 mg/m^2/d on days 15–21
Lenograstim	150 μg/m^2/d on days 22–27
Blocks 3, 6, and 9	
Cyclophosphamide	500 mg/m^2/d on days 29 and 30
Etoposide	75 mg/m^2/d on days 29 and 30
Methotrexate	25 mg/m^2 on day 29
Lenograstim	150 μg/m^2/d from day 31 to myeloid recovery

Late intensification (between consolidation blocks 6 and 7)	
For patients in CR after the first induction course	
Prednisone	60 mg/m^2/d on days 1–14
Vincristine	2 mg on days 1, 8, and 15
Daunorubicin	30 mg/m^2/d on days 1–3
L-asparaginase*	6,000 U/m^2/d on days 8, 10, 12, 18, 20, and 22
Cyclophosphamide	500 mg/m^2/12 h on day 15
Lenograstim	150 μg/m^2/d if neutrophils $<$ 0.5 G/L to myeloid recovery
For patients in CR after the salvage course	
Idarubicin	9 mg/m^2/d on days 1–3
Cytarabine	2 g/m^2/12 h on days 1–4
Lenograstim	150 μg/m^2/d from day 9 to myeloid recovery
Maintenance therapy	
Prednisone	40 mg/m^2/d on days 1–7 monthly for 12 months
Vincristine	2 mg on day 1 monthly for 12 months
Methotrexate	25 mg/m^2/wk orally for 24 months
6-Mercaptopurine	60 mg/m^2/d for 24 months
CNS therapy	
Prophylaxis	
Triple IT injections	One at days 1 and 8 of induction; one at day 29 of each series of consolidation blocks; one at day 1 of late intensification
Cranial irradiation	18 Gy before maintenance therapy initiation; 6-MP 60 mg/m^2/d during irradiation
Treatment of patients with initial CNS involvement	
Triple IT injections (MTX 15 mg, Ara-C 40 mg, and methylprednisolone 40 mg)	Eight between days –7 and 21 of induction; four during the first two consolidation blocks; one at day 29 of consolidation blocks 3 and 6
Cranial irradiation	15 Gy before SCT or 24 Gy before maintenance therapy initiation; 6-MP 60 mg/m^2/d during irradiation

Reference: Huguet F et al. J Clin Oncol 2009;27(6):911.

COG AALL-0434 REGIMEN WITH NELARABINE (FOR T-ALL)

Prephase, week 0		
IT methotrexate	Age adjusted	week 0
Prednisone	60 mg/m^2 per day P.O.	days 1–7

Induction, weeks 1–9		
Vincristine	1.5 mg/m^2 IV once per week	weeks 1–4
Prednisone	60 mg/m^2 per day P.O.	weeks 1–2
Daunorubicin	40 mg/m^2 IV once per week	weeks 1–4
E coli asparaginase	10,000 units/m^2 I.M.	days 12, 15, 18, 22, 24, 27, 30, 33
Cyclophosphamide	1 g/m^2 IV	days 36, 50
Cytarabine	75 mg/m^2 IV	days 36–39, 43–46, 50–53, 57–60
Mercaptopurine	60 mg/m^2 P.O.	days 36–63
IT methotrexate	Age adjusted	days 1, 43, 57
Consolidation, weeks 10–19		
Mercaptopurine	25 mg/m^2 P.O.	days 1–56
Methotrexate with leucovorin rescue		5 g/m^2 IV Days 8, 22, 36, 50
IT methotrexate	Age adjusted	days 8, 22, 36, 50
Reinduction, weeks 20–29		
Dexamethasone	10 mg/m^2 P.O.	days 1–21, age $<$13 years; days 1–7, 15–21, age $\geq$13 years
Vincristine	1.5 mg/m^2 IV once per week	days 1, 8, 15
Doxorubicin	25 mg/m^2 IV once per week	days 1, 8, 15
Peg aspasparaginase	2,500 units/m^2 I.M.	day 4
Cyclophosphamide	1 g/m^2 IV	day 36
Cytarabine	75 mg/m^2 IV	days 36–39, 43–46
Thioguanine	60 mg/m^2 P.O.	days 36–49
IT methotrexate	Age adjusted	days 36, 43
Maintenance, weeks 30–101		
Vincristine	1.5 mg/m^2 IV	Day 1, every 8 weeks
Dexamethasone	6 mg/m^2 P.O.	Days 15, every 8 weeks
Mercaptopurine	75 mg/m^2 P.O. once per day	Every 8 weeks
Methotrexate	20 mg/m^2 P.O. once per week	Days 1, 8, 15, 22, 36, 43, 50, every 8 weeks
Nelarabine dosing		
SER peripheral blood blast $>$1,000, day 7		
Stage one	400 mg/m^2 IV	Days 29–33 in induction, reinduction, and first four courses of maintenance
Stage two	650 mg/m^2 IV	Days 29–33 in induction, reinduction and first four courses of maintenance
SER MRD $>$1%, day 36		
Stage one	400 mg/m^2 IV	Days 29–33 in reinduction and first four courses of maintenance

Stage two	400 mg/m^2 IV	Days 29–33 in induction
Stage two	650 mg/m^2 IV	Days 29–33 in reinduction and first four courses of maintenance
RER		
Stage two	400 mg/m^2 IV	Days 29–33 in induction, reinduction and first four courses of maintenance

Reference: Dunsmore KP et al. J Clin Oncol. 2012 Aug 1;30(22):2753-9.

CCG-1961 REGIMEN

Induction		
Vincristine	1.5 mg/m^2 IV once per week	weeks 1–4
Prednisone	60 mg/m^2 per day P.O.	weeks 1–4
Daunorubicin	25 mg/m^2 IV once per week	weeks 1–4
E coli asparaginase	6,000 units/m^2 I.M.	three times a week x 9 doses
Cytarabine IT		D0
Mercaptopurine	60 mg/m^2 P.O.	days 36–63
IT methotrexate	Age adjusted	days 7, 28

Reference: Winter SS et al. J Clin Oncol 30. © 2012

Standard therapy	**Increased intensity therapy**		
Phase and treatment	**Dose**	**Phase and treatment**	**Dose**
Consolidation (5 wk)		Consolidation (9 wk)	
	1000 mg/m^2 per day		1000 mg/m^2 per day
Cyclophos-phamide	IV, days 0, 14	Cyclophos-phamide	IV, days 0, 28
	75 mg/m^2 per day		75 mg/m^2 per day SQ
	IV, days 1–4, 8–11,		IV, days 1–4, 8–11, 29–
Cytarabine	15–18, 22–25	Cytarabine	32, 36–39
	60 mg/m^2 per day		60 mg/m^2 per day
Mercaptopurine	PO, days 0–27	Mercaptopurine	PO, days 0–13, 28–41
Methotrexate*	IT, days 1, 8, 15, 22	Methotrexate	IT, days 1, 8, 15, 22
			2500 U/m^2 per day
		PEG asparaginase	IM, days 14, 42
			1.5 mg/m^2 per day
		Vincristine	days 14, 21, 42, 49

Interim maintenance (8 wk)		**Interim maintenance I (7 wk)**	
			1.5 mg/m^2 per day
	60 mg/m^2 per day		IV, days 0, 10, 20,
Mercaptopurine	PO, days 0–41	Vincristine	30, 40
Methotrexate	15 mg/m^2 per day	Methotrexate	100 mg/m^2 per day
	PO, days 0, 7, 14, 21, 28, 35		IV, days 0, 10, 20, 30, 40 (escalate by 50 mg/m^2 per dose)
			2500 U/m^2 per day
		PEG asparaginase	IM, days 1, 21
Methotrexate*	IT days 0, 28	Methotrexate*	IT days, 0. 30
Delayed intensification (7 wk)		**Delayed intensification (8 wk)**	
Reinduction (4 wk)		Reinduction (4 wk)	
	10 mg/m^2 per day		10 mg/m^2 per day
	PO, 0–7, 14–20		PO, days 0–7, 14–20
	(0–20 for patients		(0–20 for patients
Dexamethasone	treated with 1 DI)	Dexamethasone	treated with 1 DI)
	1.5 mg/m^2 per day		1.5 mg/m^2 per day
Vincristine	IV, days 0, 7, 14	Vincristine	IV, days 0, 7, 14
	25 mg/m^2 per day		25 mg/m^2 per day
Doxorubicin	IV, days 0, 7, 14	Doxorubicin	IV, days 0, 7, 14
	6000 U/m^2 per		
	day I.M., days 3, 5,		2500 IU/m^2 per day
Asparaginase	7, 10, 12, 14	PEG asparaginase	IM, day 3
Methotrexate*	IT, day 0	Methotrexate*	IT, day 0
Reconsolidation (3 wk)		Reconsolidation (4 wk)	
	1000 mg/m^2 per		1000 mg/m^2 per
Cyclophos-phamide	day IV, day 28	Cyclophos-phamide	day IV, day 28
	60 mg/m^2 per day		60 mg/m^2 per day
Thioguanine	PO, days 28–41	Thioguanine	PO, days 28–41
	75 mg/m^2 per day		75 mg/m^2 per day SQ
	SQ or IV, days 29–32,		SQ or IV, days 29–32,
Cytarabine	36–39	Cytarabine	36–39
Methotrexate*	IT, days 28, 35	Methotrexate*	IT days 28, 35

			1.5 mg/m^2 per day
		Vincristine	IV, days 42, 49
			2500 U/m^2 per day
		PEG asparaginase	IM, day 42
		Interim maintenance II (8 wk): same as Interim maintenance I–	
		Delayed intensification II (8 wk): same as Delayed intensification I	
Maintenance (12 wk)		**Maintenance (12 wk)**	
Vincristine	1.5 mg/m^2 per day IV, days 0, 28, 56	Same as standard maintenance	
	40 mg/m^2 per day		
Prednisone	PO, days 0–4, 28–32, 56–60		
	75 mg/m^2 per day		
Mercaptopurine	PO, days 0–83		
	20 mg/m^2 per day		
Methotrexate	PO, days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77		
	IT day 0 (and 28		
Methotrexate	cycles 1–4 for patients receiving 1 DI and I.M.)		

Reference: Seibel NL et al. Blood. 2008 March 1;111(5):2548-2555.

PETHEMA ALL-96 REGIMEN

Remission induction				
Vincristine	1–4	IV	2 mg	1, 8, 15, 22
Daunorubicin	1–4	IV	30 mg/m^2	1, 8, 15, 22
Prednisone	1–5	IV/PO	60 mg/m^2	1–27
	5–6	IV/PO	30 mg/m^2	28–35
Asparaginase	2–4	IV	10,000 U/m^2	10–12,17–19,24–26
Cyclophosphamide	5	IV	1,000 mg/m^2	36
IT therapy	1, 5			1, 29
Methotrexate		IT	15 mg	
Cytarabine		IT	30 mg	
Hydrocortisone		IT	20 mg	
Consolidation-1				
Mercaptopurine	1	PO	50 mg/m^2	1–7
Methotrexate	1, 4, 8	IV (24 hours)	3 g/m^2*	1, 28, 56
VM-26	2, 6	IV	150 mg/m^2/12 hours	14, 42

Cytarabine	2, 6	IV	500 mg/m^2/12 hours	14–15, 42–43
IT therapy	1, 4, 8			1, 28, 56
Methotrexate		IT	15 mg	
Cytarabine		IT	30 mg	
Hydrocortisone		IT	20 mg	
Consolidation-2/reinduction				
Dexamethasone	1–2	PO/IV	10 mg/m^2/d	1–14
	3	PO/IV	5 mg/m^2/d	15–21
Vincristine	1–3	IV	1.5 (maximum), 2 mg/m^2	1, 8, 15
Daunorubicin	1–2	IV	30 mg/m^2	1, 2, 8, 9
Cyclophosphamide	1–2	IV	600 mg/m^2/d	1, 15
Asparaginase	1–2	IM/IV	10,000 U/m^2	1–3, 15–17
IT therapy	1–2			1, 15
Methotrexate		IT	15 mg	
Cytarabine		IT	30 mg	
Hydrocortisone		IT	20 mg	
Maintenance				
Maintenance-1+ reinductions (until week 52)				
Maintenance-1				
Methotrexate		IM	20 mg/m^2/wk	
Mercaptopurine		PO	50 mg/m^2/d	
Reinductions (every 4 weeks)				
Vincristine		IV	1.5 (maximum, 2) mg/m^2	1
Prednisone		IV/PO	60 mg/m^2/d	1–7
Asparaginase		IV	20,000 U/m^2	1
IT therapy				1
Methotrexate		IT	15 mg	
Cytarabine		IT	30 mg	
Hydrocortisone		IT	20 mg	
Maintenance-2 (weeks 53–104)				
Methotrexate		IM	20 mg/m^2/wk	
Mercaptopurine		PO	50 mg/m^2/d	

Reference: Ribera JM et al. J Clin Oncol. 2008 Apr 10;26(11):1843-9.

Cytarabine + Idarubicin

Cytarabine	3 g/m^2/d IV over 3 hrs	d1–5
Idarubicin	40 mg/m^2 IV	d3

Reference: Weiss, MA et al. Cancer 2002;95:581.

Cytarabine + Idarubicin (7 + 3 regimen)

Cytarabine	100 mg/m^2/d civi	d1–7
Idarubicin	12 mg/m^2/d IV	d1–3

Reference: Karbasian-Esfahani, M et al. Cancer 2004;101:1414.

Imatinib (for Ph-positive ALL)

Imatinib	600 mg P.O.	qd

Note: Approved by FDA on 10/19/06
Reference: Ottmann OG et al. Blood 2002;100:1965.

REFRACTORY AND RECURRENT ALL

SALVAGE REGIMENS FOR RELAPSED/REFRACTORY ALL

PH-POSITIVE ALL

Dasatinib (for Ph-positive ALL)

Dasatinib	140 mg P.O.	od

Reference: Lilly MB et al. Am J Hematol. 2010 Mar;85(3):164-70.

Dasatinib	70 mg P.O.	b.i.d.

Note: Approved by FDA on 6/28/06
Reference:
Ottman O et al. Blood 2007;110:2309.
Talpaz M et al. N Eng J Med 2006;354:2531.

Nilotinib (for Ph-positive ALL)

Nilotinib	400–600 mg P.O.	b.i.d.

Reference: Kantarjian H et al. N Eng J Med 2006;354:2542.

PH-NEGATIVE ALL

Clofarabine

Clofarabine	52 mg/m^2 IV over 2 hours	day 1–5
To be repeated every 2–6 weeks		

Reference: Jeha S et al. J Clin Oncol 24:1917-1923 2006

Nelarabine (for T-cell ALL)

Nelarabine	1.5 g/m^2/d (5 mg/ml) IV over 2 hrs	d1, 3, 5
For 3 cycles		

Reference: DeAngelo DJ et al. Blood 2007;109:5136.

Cytarabine-Idarubicin

Cytarabine	3 g/m^2 IV over 3 hours	d1–5
Idarubicin	40 mg/m^2 IV	d3
G-CSF	5 mcg/kg S.C. b.i.d	d7 until ANC > 5000/microL

Reference: Weiss MA et al. Cancer. 2002 Aug 1;95(3):581-7.

Etoposide-Ifosfamide-Mitoxantrone

Etoposide	100 mg/m^2 IV qd	d1–5
Ifosfamide	1.5 g/m^2 IV qd	d1–5
Mitoxantrone	8 mg/m^2 IV qd	d1–3

Reference: Schiller G et al. Am J Hematol. 1993 Jul;43(3):195-9.

TREATMENT OPTIONS BASED ON BCR-ABL KINASE DOMAIN MUTATION STATUS

Mutation	Treatment Recommendation
T315I	HSCT or clinical trial
V299L, T315A, F317L/V/I/C	Consider Nilotinib rather than Dasatinib
Y253H, E255K/V, F359V/C/I	Consider Dasatinib rather than Nilotinib
Any other mutation	Consider high-dose Imatinib or Dasatinib or Nilotinib

Reference: NCCN Guidelines for ALL 2012.

PART – II
Hematological Malignancies

Acute Myeloid Leukemia

ACUTE MYELOID LEUKEMIA

Acute myelogenous/myeloid leukemia (AML) is a clonal disorder caused by malignant transformation of a bone marrow-derived, self-renewing stem cell or progenitor, which demonstrates a decreased rate of self-destruction and an aberrant differentiation. These events lead to an increased accumulation in bone marrow and other organs by these malignant myeloid cells. To be called acute, the bone marrow usually must include greater than 20% leukemic blasts. As per the NCI data, 13,780 new cases and 10,200 deaths are estimated in the US in 2012.

Advances in the treatment of AML (also called acute nonlymphocytic leukemia or ANLL) have resulted in substantially improved complete remission rates. More than 25% of adults with AML (about 45% of those who attain complete remission) can be expected to survive 3 or more years and may be cured. Remission rates in adult AML are inversely related to age, with an expected remission rate of $>65\%$ for those younger than 60 years. Increased morbidity and mortality during induction appear to be directly related to age. Other adverse prognostic factors include central nervous system involvement with leukemia, systemic infection at diagnosis, elevated white blood cell count ($>100{,}000/mm^3$), treatment-induced AML, and history of myelodysplastic syndrome or another antecedent hematological disorder.

Leukemias that express the progenitor cell antigen CD34 and/or the P-glycoprotein (MDR1 gene product) have an inferior outcome. Cytogenetic abnormalities that indicate a good prognosis include t(8;21), inv(16), and t(15;17). Patients with AML that is characterized by deletions of the long arms or monosomies of chromosomes 5 or 7; by translocations or inversions of chromosome 3, t(6;9), t(9;22); or by abnormalities of chromosome 11q23 have particularly poor prognoses with chemotherapy.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Myint H, Lucie NP: Leuk Lymphoma 7(5-6):425-9, (1992).
Geller RB et al. Br J Haematol 76(3):340-7, (1990).
Campos L et al. Blood 79(2):473-6, (1992).
Adult Acute Myeloid Leukemia Treatment (PDQ®): National Cancer Institute. Available at http://www.cancer.gov/cancertopics/pdq/treatment/adultAML/healthprofessional/allpages#Reference2.3

CHEMOTHERAPY REGIMENS

- Induction chemotherapy
- Consolidation chemotherapy
- Relapsed AML
- Miscellaneous

INDUCTION CHEMOTHERAPY

Cytarabine + Idarubicin (7 + 3 regimen 1)

Cytarabine	100 mg/m^2/d civi	d1–7
Idarubicin	12 mg/m^2/d IV	d1–3

Reference: Wiernik PH et al. Blood 1992;79:313.

Cytarabine + Daunorubicin (7 + 3 regimen 2)

Cytarabine	100 mg/m^2/d civi	d1–7
Daunorubicin	45–60 mg/m^2/d IV	d1–3

Reference:
Wiernik PH et al. Blood 1992;79:313.
Preisler H et al. Blood 1987;69:1441.

Cytarabine + Daunorubicin (escalated)

Cytarabine	100 mg/m^2/d civi	d1–7
Daunorubicin	90 mg/m^2/d IV	d1–3

Reference: Fernandez HF et al. N Engl J Med 2009;361:1249-1259

High dose Cytarabine + Daunorubicin (HIDAC 3–7)

Cytarabine	3 g/m^2/12 hourly	d1, 3, 5, 7 x 8 doses
Daunorubicin	50 mg/m^2/d IV	d1–3
Etoposide	75 mg/m^2/d IV	d1–7

Reference:
Bishop JF et al. Blood. 1996 Mar 1;87(5):1710-7.
Bishop JF et al. Leuk Lymphoma. 1998 Jan;28(3-4):315-27.

High dose Cytarabine + Daunorubicin (SWOG study)

Cytarabine	2 g/m^2/12 hourly	x 12 doses
Daunorubicin	45 mg/m^2/d IV	d1–3

Reference:Weick JK et al. Blood. 1996 Oct 15;88(8):2841-51.

Low dose Cytarabine

Cytarabine	20 mg b.i.d.	d1-10

Reference: Burnett AK et al. Cancer. 2007 Mar 15;109(6):1114-24.

Lestaurtinib (for elderly patients)

Lestaurtinib	60-80 mg P.O.	b.i.d.

Reference: Knapper S et al. Blood 2006;108:3262.

Decitabine + Valproic acid (for elderly patients)

Decitabine	15 mg/m^2 IV over 1 h qd	d1-10
Valproic acid	50 mg/kg P.O. qd	d1-10
Q4w		

Reference: Garcia-Manero G et al. Blood 2006;108:3271.

Clofarabine-Cytarabine

Clofarabine	40 mg/m^2 IV over 1 hour	days 2-6
Cytarabine	1 g/m^2/d IV over 2 hours	day 1-5

Reference: Faderl S. et al. Blood. Jul 1;108(1):45-51, (2006).

Clofarabine

Induction		
Clofarabine	30 mg/m^2/d IV	days 1-5
Reinduction/Consolidation		
Clofarabine	20 mg/m^2/d IV	days 1-5
(max 6 cycles)		

Reference: Kantarjian HM. et al. J Clin Oncol. 2010 Feb 1;28(4):549-55

Azacitidine (MDS)

Azacitidine	75 mg/m^2/d IV	days 1-7
Q4w		

Reference: Fenaux P. et al. Lancet Oncol. 2009 Mar;10(3):223-32.

Azacitidine (AML)

Azacitidine	75 mg/m^2/d S.C.	days 1-7

Reference: Fenaux P. et al. J Clin Oncol. 2010 Feb 1;28(4):562-9.

Decitabine

Decitabine	20 mg/m^2/d IV	days 1-5
Q4w		

Reference: Cashen AF. et al. J Clin Oncol. 2010 Feb 1;28(4):556-61

Decitabine	20 mg/m^2/d IV 1 hr infusion	days 1-5
Q4w		

Reference:
Thomas XG. et al. J Clin Oncol, 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition).Vol 29, No 15_suppl (May 20 Supplement), 2011:6504

CONSOLIDATION CHEMOTHERAPY

HDAC

Cytarabine	3 g/m^2 IV q12h x 6 doses	d1, 3 and 5 x 4 cycles

Reference: Mayer, RJ et al. N Engl J Med 1994;331:896.

IDAC

Cytarabine	400 mg/m^2/d civi	d1-5

Reference: Farag SS et al. J Clin Oncol. 2005 Jan 20;23(3):482-93.

Cytarabine + Idarubicin

Cycle 1		
Cytarabine	200 mg/m^2/d civi	d1-7
Idarubicin	12 mg/m^2/d IV	d1-3
Cycle 2		
Cytarabine	1 g/m^2 IV b.i.d.	d1-6
Amsacrine	120 mg/m^2/d IV	d1-3

Reference: Lowenberg B et al. N Engl J Med. 2011 Mar 17;364(11):1027-36.

Cytarabine + Idarubicin

Cytarabine	100 mg/m^2/d civi	d1-5 x 2 cycles
Idarubicin	13 mg/m^2/d IV	d1-2 x 2 cycles

Reference: Wiernik PH et al. Blood 1992;79:313.

Idarubicin

Idarubicin	12 mg/m^2/d IV	d1-3

Reference: Pautas C et al. J Clin Oncol. 2010 Feb 10;28(5):808-14.

Cytarabine + Daunorubicin

Cytarabine	100 mg/m^2/d civi	d1-5 x 2 cycles
Daunorubicin	45 mg/m^2/d IV	d1-2 x 2 cycles

Reference: Wiernik PH et al. Blood 1992;79:313.

Cytarabine + Idarubicin ambulatory regimen

Cytarabine	60 mg/m^2 S.C. infusion q12h x 10 doses	d1–5
Idarubicin	9 mg/m^2 IV	d1
Qm x 6 cycles		

Reference: Gardin C et al. Blood 2007;109:5129.

Cytarabine + Daunorubicin ambulatory regimen

Cytarabine	60 mg/m^2 S.C. infusion q12h x 10 doses	d1–5
Daunorubicin	45 mg/m^2 IV	d1
Qm x 6 cycles		

Reference: Gardin C et al. Blood 2007;109:5129.

RELAPSED AML

Mitoxantrone + Etoposide

Mitoxantrone	10 mg/m^2/d IV over 15 min	d1–5
Etoposide	100 mg/m^2/d IV over 30 min	d1–5
If no CR but blast reduction >50%, a second course is administered		
If CR, consolidation chemotherapy with		
Mitoxantrone	8 mg/m^2/d IV	d1–5
Etoposide	75 mg/m^2/d IV	d1–5
Cytarabine	75 mg/m^2 IV q12hrs	d1–5

Reference: Ho, AD et al. J Clin Oncol 1988;6:213.

Cytarabine + Mitoxantrone

Cytarabine	500 mg/m^2 IV q12h x 12 doses	
d1–6		
Mitoxantrone	5 mg/m^2/d IV	d1–5

Reference: Sternberg, DW et al. Cancer 2000;88:2037.

ADE

Course 1		
Cytarabine	100 mg/m^2 IV push q12h	d1–10 (20 doses)
Daunorubicin 5	0 mg/m^2 IV slow push	d1, 3, 5 (3 doses)
Etoposide	100 mg/m^2/d IV over 1 h	d1–5 (5 doses)
Course 2		
Cytarabine	100 mg/m^2 IV push q12h	d1–8 (16 doses)
Daunorubicin	50 mg/m^2 IV slow push	d1, 3, 5 (3 doses)
Etoposide	100 mg/m^2/d IV over 1 h	d1–5 (5 doses)

Reference: Milligan DW et al. Blood 2006;107:4614.

FLAG-IDA

Fludarabine	30 mg/m^2/d IV over 30 min	d1-5
Cytarabine	2 g/m^2/d IV over 4 hrs, 4 hrs after fludarabine,	d1-5
Idarubicin	10 mg/m^2/d IV	d1-3
Filgrastim	5 mcg/kg/d S.C. to begin day 6 until neutrophil recovery	

Reference:
Martin MG et al. Am J Hematol. 2009 Nov;84(11):733.
Pastore D et al. Ann Hematol 2003;82:231.

Cladribine

Cladribine	8.9 mg/m^2/d civi	d1-5

Reference: Santana VM et al. J Clin Oncol 1992;10:364.

CLAG

Cladribine	5 mg/m^2/d IV over 2 hrs	d1-5
Cytarabine	2 g/m^2/d IV over 4 hrs	d1-5
Filgrastim	300 mcg S.C.	d0-5

Reference: Robak T et al. Leuk Lymphoma 2000;39:121.

CLAG-M

Cladribine	5 mg/m^2/d iv over 2 hrs	d1-5
Cytarabine	2 g/m^2/d IV over 4 hrs starting 2 hrs after cladribine	d1-5
Mitoxantrone	10 mg/m^2/d IV	d1-3
Filgrastim	300 mcg S.C.	d0-5
If PR, a second course of CLAG-M is given		
Once CR achieved, proceed with following consolidation chemotherapy		
Course 1		
Cytarabine	1.5 g/m^2/d IV	d1-3
Mitoxantrone	10 mg/m^2/d IV	d3-5
Course 2		
Cytarabine	2 g/m^2 IV q12h x 6 doses	d1, 3, 5

Reference: Wierzbowska A et al. Eur J Haematol 2008;80:115.

Clofarabine-Cytarabine

Clofarabine	25 mg/m^2/d	d1-5
Cytarabine	2 g/m^2/d	d1-5
G-CSF	5 µg/kg	d-1 till ANC recovers

Reference: Becker PS et al. Br J Haematol. 2011 Oct;155(2):182-9.

Gemtuzumab

Gemtuzumab	9 mg/m^2 IV	q2w x 2 doses

Reference: Sievers, EL et al. J Clin Oncol 2001;19:3244.

Mito-FLAG Protocol

Mitoxantrone	7 mg/m^2 IV	day 1, 3 & 5
Fludarabine	15 mg/m^2/every 12 hrs IV	days 1-5
Cytarabine	1000 mg/m^2/over 1hr (every 12 hrs)	days 1-5

Note: To be administered with G-CSF support.
Reference: Hanel M et al. Onkologie. Aug;24(4):356-60, (2001).

Idarubicin-Cytarabine-Topotecan

Idarubicin	12 mg/m^2 IV bolus	day 1-3
Cytarabine	1 g/m^2 IV over 2 hours every 12hrs	day 1-5
Topotecan	1.25 mg/m^2 IV over 24 hours	day 1-5
To be administered as single course salvage therapy.		

Reference: Lee ST et al. Am J Hematol. Dec;68(4):237-45, (2001).

HAM

Cytarabine	3,000 mg/m^2 IV over 3 hours every 12 hours	day 1-3
Mitoxantrone	10 mg/m^2 IV over 30 min	day 3-5

Reference: Hiddemann et al. Blood 69:744-749, (1987).

MEC

Mitoxantrone	6 mg/m^2/day IV bolus	day 1-6
Etoposide	80 mg/m^2/day IV over 1 hour	day 1-6
Cytarabine	1,000 mg/m^2/day IV over 6 hours	day 1-6

Note: Etoposide was given first each day over a 1-hour period and followed immediately by the 6-hour cytarabine infusion, which was followed 3 hours later by a bolus of mitoxantrone. Complete responders were given a 4-day repeat course as consolidation and then individualized for long-term therapy.
Reference: Amardori S et al. J Clin OncoI 9:1210-1214, (1991).

Mitoxantrone-High Dose Etoposide

Mitoxantrone	7.5 mg/m^2 IV	day 1-5
Etoposide	500 mg/m^2 IV	day 1-4

Note: Mucositis is severe with this regimen. Repeat in 4 weeks or when pancytopenia or thrombocytopenia recovers.
Reference: O'Brien S et al. Cancer 68:691-694, (1991).

Mitoxantrone Etoposide Cytarabine

Mitoxantrone	12 mg/m^2 IV	day 1-3
Etoposide	200 mg/m^2/day civi	day 8-10
Cytarabine	500 mg/m^2/day civi	day 1-3, 8-10

Note: Patients who have a partial or complete remission can receive a second course for reinduction or consolidation, respectively, or may be considered for bone marrow transplantation. Only patients less than 60 years of age are treated with this regimen.
Reference: Archimbaud E et al. Blood 77:1894-1900, (1991).

MISCELLANEOUS

INTENSIVE THERAPY

Remission Induction

Daunorubicin	70 mg/m^2 IV	day 1-3
Cytarabine	100 mg/m^2 IV	every 12 hours for 7 days
6-Thioguanine	100 mg/m^2 P.O.	every 12 hours for 7 days
Prednisone	40 mg/m^2 P.O.	day 1-7
Vincristine	1 mg/m^2 IV	day 1, 7

Consolidation

Daunorubicin	70 mg/m^2 IV	day 1, 2
Cytarabine	100 mg/m^2 IV	every 12 hours for 5 days
6-Thioguanine	100 mg/m^2 P.O.	every 12 hours for 5 days
Prednisone	40 mg/m^2 P.O.	day 1-5
Vincristine	1 mg/m^2 IV	day 1

Monthly Maintenance

Cytarabine	20 to 25 mg/m^2 S.C.	every 6 hours for 5 days
6-Thioguanine	100 mg/m^2 P.O.	every 12 hours for 5 days
Prednisone	40 mg/m^2 P.O.	day 1-5
Vincristine	1 mg/m^2 N	day 1

Intensification (Course 6 and 12)

Same as remission inducrion.

Reference: Glucbberg H et al. Cancer 52:198-205, (1983).

Idarubicin Cytarabine Etoposide

Idarubicin	8 mg/m^2 IV	day 1-3
Cytarabine	2000 mg/m^2 IV/day	day 1-6
Etoposide	1600 mg/m^2 IV over 10 hours	day 7

Reference: Damon LE et al. Cancer Chemother Pharmacol Jun;53(6):468-74, (2004).

BFM 87 (Childhood AML)

Induction (ADE)

Cytarabine	100 mg/m^2/day civi	day 1, 2
	100 mg/m^2/day x 2 over 30 min every 12 hours	day 3 - 8
Daunorubicin	30 mg/m^2 over 30 min every 12 hours	day 3 - 5
Etoposide	150 mg/m^2 IV over 1 hour	day 6 - 8

Note:
This is followed by consolidation after Hematologic recovery. When on day 15 blasts in the bone marrow are ≥ 5% consolidation is started without delay, clinical condition of the patient permitting.

Consolidation (6 weeks)

Prednisone	40 mg/m^2 P.O. starting dose	day 1 - 28
Thioguanine	60 mg/m^2 P.O.	day 1 - 28
Vincristine	1.5 mg/m^2 IV (max 2 mg)	day 1, 8, 15, 22
Doxorubicin	30 mg/m^2 IV	day 1, 8, 15, 22
Cytarabine	75 mg/m^2 IV x 16	
Cyclophosphamide	500 mg/m^2 IV	day 29, 43
Cytarabine	20 - 40 mg* IT	
Brain irradiation	12 - 18 Gy**	

Note:
**age dependent «1 year 20 mg, 1-2 years 26 mg, 2-3 years 34 mg, > 3 years 40 mg*
***age dependent «1 year 12 Gy, 1-2 years 15 Gy, > 2 years 18 Gy*

Late intensification (2 blocks)

Cytarabine	3,000 mg/m^2 over 30 min every 12 hours	for 3 day
Etoposide	125 mg/m^2 over 1 hour	day 2 - 5

Maintenance

Thioguanine	40 mg/m^2 P.O. daily	
Cytarabine	40 mg/m^2 S.C.	day 1 - 4 every 4 weeks

Note:
For a total of 18 months (in children with continuous complete Remission) CNS prophylaxis with cytarabine IT; CNS irradiation in patients with initial CNS leukaemia.
Reference: Creutzig et al. J Clin Oncol ll:279-286, (1993).

BMT

Most BMT's are carried out in patients under 55 years of age, in first remission, with an HLA-identical sibling donor. The low relapse rate following BMT is the main reason for selecting allo-BMT over other post remission treatments.

Reference: Zittoun RA et al. N Engl J Med 332(4):217, (1995).

PART – II
Hematological Malignancies

Acute Promyelocytic Leukemia

ACUTE PROMYELOCYTIC LEUKEMIA

Acute promyelocytic leukemia (APL) is a rare bone marrow cancer characterized by a lack of mature blood cells and excessive amounts of immature blood cells (promyelocytes). The number of newly diagnosed cases per year in the United States is estimated to be 600 to 800. One of the most striking features of APL is its age-associated incidence rate. The disease is very uncommon in children less than 10 years of age. Its incidence increases steadily during the teen years, reaches a plateau during early adulthood, and remains constant until it decreases after age 60 years.

Among the low-risk subtypes of AML is APL. Approximately 98% of persons with APL carry a translocation of chromosomes 15 and 17, typically resulting in the fusion between RAR (retinoic acid receptor), which encodes a retinoic acid receptor, and the promyelocytic leukemia (PML) protein. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes. APL is unique from other forms of AML in its responsiveness to all trans retinoic acid (ATRA) therapy.

Reference:
Jonathan DL. The New Eng J Med. 360:928-930, (2009)
Ribeiro R, Rego R. Hematology Am Soc Hematol Educ Program. 2006;162-168.
Douer D. Best Pract Clin Hematol. 2003;16:357-367.
Vickers M, M, Jackson G, Taylor P. Leukemia. 2000;14:722-726.

CHEMOTHERAPY REGIMENS

- Newly diagnosed
- Relapsed APL

NEWLY DIAGNOSED

CALGB 9710 regimen

Induction therapy

All trans retinoic acid	45 mg/m^2 P.O. qd in 2 divided doses	d1 till hematologic CR
Cytarabine	200 mg/m^2/d civi	d3 – 9
Daunorubicin	50 mg/m^2/d IV	d3 – 6

Reference:
Fenaux, P et al. Blood 1993;82:3241.
Ades L et al. Blood. 2010 Mar 4;115(9):1690-6.
Avvisati G et al. Blood. 2011 May 5;117(18):4716-25.

Consolidation therapy

Arsenic Trioxide	0.15 mg/kg/d x 5d/week for 5 wks x 2 cycles	
(cycle 2 starts after 2 wks rest)		
followed by		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses	d1 – 7 x 2 cycles
Daunorubicin	50 mg/m^2/d IV	d1 – 3 x 2 cycles

Reference:
Powell BL et al. 2007 ASCO annual meeting. Abstract 2.
Tallman, MS et al. Blood 2002;99:759.

Maintenance therapy

All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses	d1 – 7 qow x 1 year
6-Mercaptopurine (6-MP)	60 mg/m^2 P.O.	qd x 1 year
Methotrexate	20 mg/m^2 P.O.	qw x 1 year

Reference:
Tallman, MS et al. N Engl J Med 1997;337:1021.
Tallman, MS et al. Blood 2002;100:4298.

AIDA regimen

Induction therapy

ATRA	45 mg/m^2 P.O. qd	d1 till hematologic CR
Idarubicin	12 mg/m^2/d IV	d2, 4, 6, 8

Reference: Mandelli F et al. Blood. 1997 Aug 1;90(3):1014-21.

PETHEMA LPA 99 regimen

Induction therapy

ATRA	45 mg/m^2 P.O. qd in 2 divided doses	d1 till hematologic CR
Idarubicin	12 mg/m^2/d IV	d2, 4, 6, 8

Consolidation therapy	
Course 1	
Idarubicin	5 mg/m^2/d IV x d1-4
Course 2	
Mitoxantrone	10 mg/m^2/d x d1-5
Course 3	
Idarubicin	12 mg/m^2/d IV x d1

Maintenance therapy	
6-MP	90 mg/m^2/d P.O.
Methotrexate	15 mg/m^2/wk I.M.
ATRA	45 mg/m^2 P.O. qd x d1-15
Q12w	

Reference:
Sanz MA et al. Blood. 2004 Feb 15;103(4):1237-43
Sanz MA et al. Blood. 1999 Nov 1;94(9):3015-21.

PETHEMA LPA 2005 regimen

Induction therapy		
ATRA	45 mg/m^2 P.O. qd in 2 divided doses d1 till hematologic CR	
Idarubicin	12 mg/m^2/d IV	d2, 4, 6, 8

Consolidation therapy (Low risk)	
Course 1	
Idarubicin	5 mg/m^2/d IV x d1-4
ATRA	45 mg/m^2 P.O. qd x 15d
Course 2	
Mitoxantrone	10 mg/m^2/d x d1-5
ATRA	45 mg/m^2 P.O. qd x 15d
Course 3	
Idarubicin	12 mg/m^2/d IV x d1
ATRA	45 mg/m^2 P.O. qd x 15d

Consolidation therapy (Intermediate risk)	
Course 1	
Idarubicin	5 mg/m^2/d IV x d1-4
ATRA	45 mg/m^2 P.O. qd x 15d
Course 2	
Mitoxantrone	10 mg/m^2/d x d1-5
ATRA	45 mg/m^2 P.O. qd x 15d
Course 3	
Idarubicin	12 mg/m^2/d IV x d1
ATRA	45 mg/m^2 P.O. qd x 15d

Consolidation therapy (High risk)	
Course 1	
Idarubicin	5 mg/m^2/d IV x d1–4
Cytarabine	1000 mg/m^2/d IV x d1–4
ATRA	45 mg/m^2 P.O. qd x 15d
Course 2	
Mitoxantrone	10 mg/m^2/d x d1–5
ATRA	45 mg/m^2 P.O. qd x 15d
Course 3	
Idarubicin	12 mg/m^2/d IV x d1
Cytarabine	150 mg/m^2/8h IV x d1–4
ATRA	45 mg/m^2 P.O. qd x 15d

Maintenance therapy	
6-MP	90 mg/m^2/d P.O.
Methotrexate	15 mg/m^2/wk I.M.
ATRA	45 mg/m^2 P.O. qd x d1–15
Q12w	

Reference: Sanz MA et al. Blood. 2010 Jun 24;115(25):5137-46.

EAPLG regimen (APL 2000 study)

Age < 60 and WBC < 10,000/uL

Induction therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses d1 till hematologic CR	
Cytarabine	200 mg/m^2/d civi	d3–9
Daunorubicin	60 mg/m^2/d IV	d3–5

Consolidation therapy		
Cycle 1		
Cytarabine	200 mg/m^2/d civi	d1–7
Daunorubicin	60 mg/m^2/d IV	d1–3
Cycle 2		
Cytarabine	1000 mg/m^2 IV	q12h x 8 doses
Daunorubicin	45 mg/m^2/d IV	d1–3

Maintenance therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses	d1–15 q3m x 2 year
6-Mercaptopurine	90 mg/m^2 P.O. qd x 2 year	
Methotrexate	15 mg/m^2 P.O. qw x 2 year	

Age < 60 and WBC > 10,000/uL

Induction therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses d1 till hematologic CR	
Cytarabine	200 mg/m^2/d civi	d3 - 9
Daunorubicin	60 mg/m^2/d IV	d3 - 5

Consolidation therapy		
Cycle 1		
Cytarabine	200 mg/m^2/d civi	d1 - 7
Daunorubicin	60 mg/m^2/d IV	d1 - 3
Intrathecal Cytarabine 50 mg and Methotrexate 15 mg x 3		
Cycle 2		
Cytarabine	2000 mg/m^2 IV	q12h x 10 doses
Daunorubicin	45 mg/m^2/d IV	d1 - 3
Intrathecal Cytarabine 50 mg and Methotrexate (MTX) 15 mg x 2		

Maintenance therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses	d1 - 15 q3m x 2 year
6-Mercaptopurine	90 mg/m^2 P.O. qd x 2 year	
Methotrexate	15 mg/m^2 P.O. qw x 2 year	

Age > 60 and WBC < 10,000/uL

Induction therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses d1 till hematologic CR	
Daunorubicin	60 mg/m^2/d IV	d3 - 5

Consolidation therapy		
Cycle 1		
Daunorubicin	60 mg/m^2/d IV	d1 - 3
Cycle 2		
Daunorubicin	45 mg/m^2/d IV	d1 - 3
Maintenance therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses	d1 - 15 q3m x 2 year
6-Mercaptopurine (6-MP)	90 mg/m^2 P.O. qd x 2 year	
Methotrexate	15 mg/m^2 P.O. qw x 2 year	

Age > 60 and WBC > 10,000/uL

Induction therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses d1 till hematologic CR	
Cytarabine	200 mg/m^2/d civi	d3 - 9
Daunorubicin	60 mg/m^2/d IV	d3 - 5

Consolidation therapy		
Cycle 1		
Cytarabine	200 mg/m^2/d civi	d1–7
Daunorubicin	60 mg/m^2/d IV	d1–3
Intrathecal Cytarabine 50 mg and Methotrexate 15 mg x 3		
Cycle 2		
Cytarabine	1000 mg/m^2 IV	q12h x 8 doses
Daunorubicin	45 mg/m^2/d IV	d1–3
Intrathecal Cytarabine 50 mg and Methotrexate 15 mg x 2		

Maintenance therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses	d1–15 q3m x 2 year
6-Mercaptopurine	90 mg/m^2 P.O. qd x 2 year	
Methotrexate	15 mg/m^2 P.O. qw x 2 year	

Reference: Ades L et al. J Clin Oncol 2006;24:5703.

ATRA + Arsenic Trioxide

All trans retinoic avid (ATRA)	45 mg/m^2 P.O. qd in 2 divided doses d1 till CR	
Arsenic Trioxide	0.15 mg/kg/d IV over 1 h d10 till CR	
If WBC >10 x 109/L, add		
Gemtuzumab	9 mg/m^2 IV	d1
and/or		
Idarubicin	12 mg/m^2/d IV	d1–4
Once CR obtained, change to		
All trans retinoic avid (ATRA)	45 mg/m^2 P.O. qd in 2 divided doses 2 wks on and 2	
wks off x 28 wks		
Arsenic Trioxide	0.15 mg/kg/d IV d1–5 qw 4 wks on and 4 wks off x 28 wks	

Reference:
Tsimberidou AM et al. 2006 ASCO annual meeting. Abstract 6503.
Estey E et al. Blood 2006;107:3469.

EAPLG regimen (APL 2000 study)

Age <60 and WBC <10,000/uL

Induction therapy		
All trans retinoic avid hematologic CR	45 mg/m^2 P.O. qd in 2 divided doses d1 till	
Cytarabine	200 mg/m^2/d civi	xd3–9
Idarubicin	12 mg/m^2/d IV	xd3–5

Consolidation therapy		
Cycle 1		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses d1	
Arsenic trioxide	0.15 mg/kg/d	xd1–25
Idarubicin	12 mg/m^2/d IV	xd3–5
Cycle 2		
Arsenic trioxide	0.15 mg/kg/d	xd1–25
Idarubicin	12 mg/m^2/d IV	x3d

Maintenance therapy		
All trans retinoic avid	45 mg/m^2 P.O. qd in 2 divided doses	d1–15 q3m x 2 year
6-Mercaptopurine	90 mg/m^2 P.O. qd x 2 year	
Methotrexate	15 mg/m^2 P.O. qw x 2 year	

Reference:
Ades L et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 505
Ades L et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 13

ATRA-Cytarabine-Daunorubicin-Arsenic Trioxide (C9710 study)

ATRA	45 mg/m^2 P.O. qd in 2 divided doses d1 till CR	
Cytarabine	200 mg/m^2 IV	d3–9
Daunorubicin	50 mg/m^2/d IV	d3–6
followed by		
Arsenic Trioxide	0.15 mg/kg/d	d1–5/wk x 5w (2 cycles)
Cycle 2 after 2 week rest		
Followed by		
ATRA	45 mg/m^2 P.O. qd d1–7	
Daunorubicin	50 mg/m^2/d IV	d1–3

Reference: Powell BL et al. Blood. 2010 November 11;116(19):3751.

AIDA 2000 regimen

Induction therapy		
ATRA	45 mg/m^2 P.O. qd d1 till hematologic CR	
Idarubicin	12 mg/m^2/d IV	d2, 4, 6, 8

Consolidation therapy **Low/intermediate risk**		
Course 1		
Idarubicin	5 mg/m^2/d IV x d1–4	
ATRA	45 mg/m^2 P.O. qd d1–15	
Course 2		
Mitoxantrone	10 mg/m^2/d x d1–5	
ATRA	45 mg/m^2 P.O. qd d1–15	

Course 3	
Idarubicin	12 mg/m^2/d IV x d1
ATRA	45 mg/m^2 P.O. qd d1–15

High risk	
Course 1	
Cytarabine	1000 mg/m^2/d IV x d1–4
Idarubicin	5 mg/m^2/d IV x d1–4
ATRA	45 mg/m^2 P.O. qd d1–15
Course 2	
Mitoxantrone	10 mg/m^2/d x d1–5
VP-16	100 mg/m^2/d x d1–5
ATRA	45 mg/m^2 P.O. qd d1–15
Course 3	
Idarubicin	12 mg/m^2/d IV x d1
Cytarabine	150 mg/m^2/8h IV x d1–5
6-TG	70 mg/m^2/8h IV x d1–5
ATRA	45 mg/m^2 P.O. qd d1–15

Maintenance therapy	
6-MP	50 mg/m^2/d P.O.
Methotrexate	15 mg/m^2/wk I.M.
ATRA	45 mg/m^2 P.O. qd x d1–15
Q12w	

Reference: Lo-Coco F et al. Blood. 2010 Oct 28;116(17):3171-9.

Arsenic Trioxide

Arsenic Trioxide	Induction arsenic trioxide 0.16 mg/kg IV qd till CR
3–4 wks after induction	

Reference: Zhi-Xiang Shen et al. Proc Natl Acad Sci U S A. 2004 April 13;101(15):5328–5335.

RELAPSED APL

Arsenic Trioxide

Arsenic Trioxide	Induction arsenic trioxide 0.15 mg/kg IV qd till marrow remission	
	(median 35 doses)	
3–4 wks after induction, consolidation arsenic trioxide	0.15 mg/kg IV	qd x 25 days over 5 wks

Reference:
Soignet, SL et al. J Clin Oncol 2001;19:3852.
Shen, ZX et al. Blood 1997;89:3354.
Niu, C et al. Blood 1999;94:3315.

PART – II
Hematological Malignancies

Chronic Lymphocytic Leukemia

CHRONIC LYMPHOCYTIC LEUKEMIA

CLL is a disorder of morphologically mature but immunologically less mature lymphocytes and is manifested by progressive accumulation in the blood, bone marrow, and lymphatic tissues. In this disorder, lymphocyte counts in the blood are usually greater than or equal to 5,000/mm^3 with a characteristic immunophenotype (CD5 and CD23 positive B cells). CLL occurs primarily in middle-aged and elderly adults, with increasing frequency in successive decades of life. As per the NCI data, 15,490 new cases and 4,390 deaths are estimated in the US.

The clinical course of this disease progresses from an indolent lymphocytosis without other evident disease to one of generalized lymphatic enlargement with concomitant pancytopenia. Complications of pancytopenia, includes hemorrhage and infection that is a major cause of death in these patients. Patients who develop an aggressive high-grade non-Hodgkin's lymphoma, usually diffuse large B-cell lymphoma and termed a Richter's transformation, have a poor prognosis.

Confusion with other diseases may be avoided by determination of cell surface markers. CLL lymphocytes coexpress the B-cell antigens CD19 and CD20 along with the T-cell antigen CD5. This coexpression only occurs in one other disease entity, mantle cell lymphoma. CLL B cells express relatively low levels of surface-membrane immunoglobulin (compared with normal peripheral blood B cells) and a single light chain (kappa or lambda). CLL is diagnosed by an absolute increase in lymphocytosis and/or bone marrow infiltration coupled with the characteristic features of morphology and immunophenotype, which confirm the characteristic clonal population.

CHEMOTHERAPY REGIMENS

Chlorambucil

Chlorambucil	10 mg/m^2/d P.O. x 7 days	
	or	
	40 mg/m^2 P.O.	
Q4w x 12 cycles		

Reference:
Hillmen P et al. J Clin Oncol 2007;25:5616.
Catovsky D et al. Lancet 2007;370:230.
Rai, KR et al. N Engl J Med 2000;343:1750.

Chlorambucil	0.4 mg/kg with an increase to 0.8 mg/kg,	
q2w x 1 year.		

Reference: Eichhorst BF et al. Blood. 2009 Oct 15;114(16):3382-91.

Bendamustine

Bendamustine	100 mg/m^2 IV over 30 min	d1 and 2
Q4w x 6 cycles		

Note: Approved by FDA on 3/20/08
Reference: Knauf W et al. 2007 ASH annual meeting. Abstract 2043.

Bendamustine-Rituximab

Bendamustine	70 mg/m^2 IV	d1 and 2
Rituximab	375 mg/m^2 IV	d0 of 1st course
	500 mg/m^2 IV	d1 of subsequent course x upto 6 courses
Q4w x 6 cycles		

Reference: Fischer K et al. J Clin Oncol 2011;29(26):3559.

Fludarabine

Fludarabine	25 mg/m^2/d IV x 5 days	
	or	
	40 mg/m^2/d P.O. x 5 days	
Q4w x 6–12 cycles		

Reference:
Catovsky D et al. Lancet 2007;370:230.
Rai, KR et al. N Engl J Med 2000;343:1750.

Cladribine

Regimen 1

Cladribine	0.1 mg/kg/d civi	d1–7
q4–5w		

Reference: Saven A et al. J Clin Oncol 1995;13:570.

Regimen 2		
Cladribine	0.12 mg/kg/d IV over 2 hrs	d1–5
q4w x 6 cycles		

Reference: Robak T et al. Blood 2006;108:473.

Rituximab

Rituximab	375 mg/m^2 IV	
qw x 4 wks q6m x 4 courses		

Reference: Hainsworth, JD et al. J Clin Oncol 2003;21:1746.

High-dose Methylprednisolone (HDMP)-Rituximab

Methylprednisone	1 g/m^2/d	d1–3
Rituximab	375 mg/m^2 IV	q4 wks x 3 cycles OR
Rituximab	750 mg/m^2 IV od	q4 wks x 3 cycles OR
Rituximab	750 mg/m^2 IV weekly x 3 in C1 and	
	750 mg/m^2 IV od x 3 in C2–3	

Reference: Castro JE et al. Leukemia. 2009 October;23(10):1779–1789.

Alemtuzumab IV

Premedications:		
Diphenhydramine	50 mg P.O.	
Acetaminophen	500–1000 mg P.O.	
Alemtuzumab	start at 3 mg/d IV, increase to 10 mg/d and 30 mg/d as soon	
as tolerated, then 30 mg/d IV over 2 hours tiw up to 12–16 weeks		
Bactrim DS	1 tab P.O. b.i.d.	tiw
Famciclovir	250 mg P.O. b.i.d	

Note: Approved by FDA on 9/19/07
Reference:
Hillmen P et al. J Clin Oncol 2007;25:5616.
Keating, MJ et al. Blood 2002;99:3554.
Rai, KR et al. J Clin Oncol 2002;20:3891.

Alemtuzumab S.C. +/- Fludarabine

Alemtuzumab	30 mg/d S.C.	tiw (after dose escalation in first week) x 24 wks
Add Fludarabine	40 mg/m^2/d P.O. for 3 days q4w for patients failing to response to Alemtuzumab	
Acyclovir and cotrimoxazole prophylaxis		

Reference: Sayala HA et al. 2006 ASH annual meeting. Abstract 34.

Alemtuzumab S.C. +/- Fludarabine

Alemtuzumab	30 mg/d S.C.	tiw (after dose escalation in first week) x 24 wks
Add Fludarabine	30 mg/m^2/d P.O. for 3 days	
q4w		
Acyclovir and cotrimoxazole prophylaxis		

Reference: Elter T et al. 2006 J Clin Oncol. 2005 Oct 1;23(28):7024-31.

Rituximab-Alemtuzumab

Rituximab	375 mg/m^2/d	qw	x week 1-4
Alemtuzumab	loading-dose schedule of 3 mg, 10 mg, and 30 mg		1-3
followed by 30 mg on d3, 5			x weeks 2-4
Valacyclovir, cotrimoxazole and antibiotic prophylaxis x 2 mths			

Reference: Faderl S et al. Blood. 2003 May 1;101(9):3413-5.

Ofatumumab

Ofatumumab	300 mg IV	qw	x week 1-8
followed by			
Ofatumumab 1-4	2000 mg IV	every month	x month

Reference: Wierda WG et al. J Clin Oncol. 2010 Apr 1;28(10):1749-55.

Chlorambucil + Prednisone

Chlorambucil	30 mg/m^2 P.O.	d1
Prednisone	80 mg P.O. qd	d1-5
Q2w		

Reference: Raphael B et al. J Clin Oncol 1991;9:770.

Fludarabine + Prednisone

Fludarabine	30 mg/m^2/d IV	d1-5
Prednisone	30 mg/m^2/d P.O.	d1-5
Q4w		

Reference: O'Brien S et al. Blood 1993;82:1695.

Fludarabine + Cyclophosphamide (FC)

IV Regimen 1

Fludarabine	25-30 mg/m^2/d IV	d1-3
Cyclophosphamide	250 mg/m^2/d IV	d1-3
Q4w x 6 cycles		

Reference:
Catovsky D et al. Lancet 2007;370:230.
Eichhorst BF et al. Blood 2006;107:885.

IV Regimen 2		
Fludarabine	20 mg/m^2/d IV	d1–5
Cyclophosphamide	600 mg/m^2 IV	d1
Q4w x 6 cycles		

Reference: Flinn IW et al. J Clin Oncol 2007;25:793.

PO regime		
Fludarabine	24 mg/m^2/d P.O.	d1–5
Cyclophosphamide	150 mg/m^2/d P.O.	d1–5
Q4w x 6 cycles		

Reference: Catovsky D et al. Lancet 2007;370:230.

Fludarabine + Rituximab

Fludarabine	25 mg/m^2/d IV	d1–5
Rituximab	375 mg/m^2 IV	d1 and 4 of cycle 1,
		then
		d1 only for cycles 2–6
Q4w x 6 cycles		
2 months later:		
Rituximab	375 mg/m^2 IV	qw x 4 doses

Reference:
Byrd JC et al. Blood 2003;101:6.
Byrd, JC et al. Blood 2005;105:49.

Fludarabine + Cyclophosphamide + Rituximab (FCR)

Fludarabine	25 mg/m^2/d IV	d1–3
Cyclophosphamide	250 mg/m^2/d IV	d1–3
Rituximab	375 mg/m^2 IV	d1 cycle 1
	and	
	500 mg/m^2 IV	d1 cycle 2–6
Q4w x 6 cycles		
Allopurinol	300 mg P.O. qd	d1–7 cycle 1
Bactrim DS	1 P.O. b.i.d. twice a week	
Valacyclovir	500 mg P.O. qd	

Reference:
Hallek M et al. Lancet 2010 Oct 2;376(9747):1164-74.
Robak T et al. J Clin Oncol. 2010 Apr 1;28(10):1756-65
Tam CS et al. Blood 2008:12:275
Keating M et al. J Clin Oncol 2005;22:4079.
Wierda W et al. J Clin Oncol. 2005 Jun 20;23(18):4070-8.

Cladribine + Mitoxantrone + Cyclophosphamide (CMC)

Cladribine	0.12 mg/kg/d IV over 2 hrs	d1–3
Mitoxantrone	10 mg/m^2 IV	d1
Cyclophosphamide	650 mg/m^2 IV	d1
Q4w x 6 cycles		

Reference: Robak T et al. Blood 2006;108:473.

CVP

Cyclophosphamide	300 mg/m^2/d P.O.	d1–5
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg/m^2/d P.O.	d1–5
Q3w up to 18 months		

Reference: Raphael B et al. J Clin Oncol 1991;9:770.

CHOP

Vincristine	1 mg/m^2 IV	d1
Cyclophosphamide	300 mg/m^2/d P.O.	d1–5
Prednisone	40 mg/m^2/d P.O.	d1–5

Reference: Leporrier M et al. Blood. 2001 Oct 15;98(8):2319-25.

Lenalidomide

Regimen 1

Lenalidomide	5 mg P.O. qd,	
	escalate by	
	5 mg every 1–2 weeks to 25 mg P.O. qd d1–21 q4w	
until molecular CR or unacceptable toxicity		
Allopurinol	300 mg P.O. qd for 14 days starting 2–3 days before lenalidomide	

Reference: Chanan-Khan A et al. J Clin Oncol 2006;24:5343

Regimen 2

Lenalidomide	10 mg P.O.	qd for 28 days,
	then increase by	
	5 mg every 28 days to 25 mg qd	
until progression or unacceptable toxicity		

Reference: Ferrajoli A et al. Blood 2008;111:5291.

Lenalidomide + Rituximab

Lenalidomide	25 mg P.O. qd	d1–21
Rituximab	375 mg/m^2 IV	d1, 8 and 15 of cycle 1, then d1 and 15 of cycles 2–6
Q4w		

Reference: Chanan-Khan A et al. J Clin Oncol 2006;24:5343.

Pentostatin + Cyclophosphamide + Rituximab (PCR)

Regimen 1

Pentostatin	2 mg/m^2 IV	d1 cycles 1–6
Cyclophosphamide	600 mg/m^2 IV	d1 cycles 1–6
Rituximab	100 mg/m^2 IV	d1 and 375 mg/m^2 d3 and 5 for cycle 1, then 375 mg/m^2 d1 for cycles 2–6
Q3w x 6 cycles		
Allopurinol	300 mg P.O. qd	d1–15 cycle 1
Filgrastim support		
Bactrim DS	1 P.O. b.i.d. tiw x 1 year	
Acyclovir	800 mg P.O. b.i.d. x 1 year	

Reference:
Shanafelt TD et al. 2006 ASH annual meeting. Abstract 36.
Kay NE et al. Blood 2007;109:405.

Regimen 2

Pentostatin	4 mg/m^2 IV	d1 cycles 1–6
Cyclophosphamide	600 mg/m^2 IV	d1 cycles 1–6
Rituximab	375 mg/m^2 IV	d1 cycles 2–6
Q3w x 6 cycles		
Filgrastim support		
Bactrim DS	1 P.O. b.i.d.	tiw
Acyclovir	800 mg P.O.	b.i.<<d

Reference: Lamanna N et al. J Clin Oncol 2006;24:1575.

Cyclophosphamide + Fludarabine + Alemtuzumab + Rituximab (CFAR)

Cyclophosphamide	250 mg/m^2/d IV	d3–5
Fludarabine	25 mg/m^2/d IV	d3–5
Alemtuzumab	30 mg IV	d1, 3 and 5
Rituximab	375–500 mg/m^2 IV	d2
Q4w x 6 cycles		
Allopurinol	300 mg P.O. qd	d1–7 cycle 1
Pegfilgrastim support		
Bactrim DS	1 P.O. b.i.d.	tiw till 2 months after chemoimmunotherapy
Valganciclovir	till 2 months after chemoimmunotherapy	

Reference: Wierda WG et al. 2006 ASH annual meeting. Abstract 31.

Oral Cladribine

Cladribine	10 mg/m^2 P.O. daily	days1–3
To be repeated every 3 weeks.		

Refrence: Karlsson K et al. Br J Haematol. Mar;116(3):538-48, (2002)

Oxaliplatin + Fludarabine + Cytarabine + Rituximab (OFAR)

Oxaliplatin	30 mg/m^2/d IV	d1–4
Rituximab	375 mg/m^2 IV	d3
Fludarabine	30 mg/m^2/d IV	d2–3
Cytarabine	0.5 g/m^2 IV	d1, 3 and 5 Q4w
Fludarabine and Cytarabine were given on D2–3 (level 1), D2–4 (level 2), or D2–5 (level 3) (phase I) every 4 wks.		
Pegfilgrastim	6 mg	d6

Reference: Tsimberidou AM et al. J Clin Oncol 28:15s, 2010 (suppl; abstr 6521)

PART – II
Hematological Malignancies

Chronic Myelogenous Leukemia

CHRONIC MYELOGENOUS LEUKEMIA

As per the NCI data, 5,050 new cases and 470 deaths are estimated in the US. Chronic myelogenous leukemia (CML) is one of a group of diseases called the myeloproliferative disorders. CML is a clonal disorder that is usually easily diagnosed because the leukemic cells of more than 95% of patients have a distinctive cytogenetic abnormality, the Philadelphia chromosome (Ph1). The Ph1 results from a reciprocal translocation between the long arms of chromosomes 9 and 22, which is demonstrable in all hematopoietic precursors. Chronic myelogenous leukemia (CML) accounts for only 5% of all childhood leukemia and 80% of the cases occur after 4 years of age. CML is characterized by a marked leukocytosis and is often associated with thrombocytosis, sometimes with abnormal platelet function. Bone marrow aspiration or biopsy reveals hypercellularity with relatively normal granulocytic maturation and no significant increase in leukemic blasts. Although reduced leukocyte alkaline phosphatase activity is seen in CML, this is not a specific finding.

CML has 3 clinical phases: chronic, accelerated, and blast crisis. Chronic phase, which lasts for approximately 3 years, usually presents with side effects secondary to hyperleukocytosis such as weakness, fever, night sweats, bone pain, respiratory distress, priapism, left upper quadrant pain (splenomegaly), and, rarely, hearing loss and visual disturbances. The accelerated phase is characterized by progressive splenomegaly, thrombocytopenia, and increased percentage of peripheral and bone marrow blasts, along with accumulation of karyotypic abnormalities in addition to the Ph chromosome. Blast crisis is notable for the bone marrow, showing greater than 30% blasts and a clinical picture that is indistinguishable from acute leukemia. Approximately two thirds of blast crisis is myeloid and the remainder lymphoid, usually of B lineage. Patients in blast crisis will die within a few months.

The introduction of imatinib mesylate as a therapeutic drug targeted at inhibiting the bcr-abl fusion kinase has revolutionized the treatment of patients with CML. Imatinib mesylate treatment can achieve clinical, cytogenetic, and molecular remissions (as defined by the absence of bcr-abl fusion transcripts) in a high proportion of patients when treated in chronic phase. Imatinib mesylate has essentially replaced the use of alpha-interferon, which has a lower response rate and has significantly more severe adverse side effects

CHEMOTHERAPY REGIMENS

Imatinib

Imatinib	400 – 800 mg P.O.	qd

Reference:
Cortes JE et al. J Clin Oncol. 2010 Jan 20;28(3):424-30.
de Lavallade H et al. J Clin Oncol 2008;26:3358.
Pye SM et al. Blood 2008;111:5505.
Hochhaus A et al. Blood 2008;111:1039.

Imatinib Mesylate-Cytarabine

(Philadelphia-positive chronic phase CML)

Imatinib Mesylate	400 mg/d P.O.	once daily
Cytarabine	20 mg/m^2/d S.C.	days 15 – 28
To be repeated every 28 days.		

Note: Hydroxyurea to be stopped at least 7 days before starting Imatinib Mesylate.
Refrence: Martine G et al. Blood;102:4298-4305, (2003)

Dasatinib

Dasatinib	70 mg P.O.	b.i.d
	or	
	100 mg P.O.	qd

Note: Approved by FDA on 6/28/2006.
Reference:
Tam CS et al. Blood 2008;112:516.
Kantarjian H et al. Blood 2007;109:5143.

Nilotinib

Nilotinib	400 – 600 mg P.O.	b.i.d
Avoid food 2 hours before and 1 hour after taking a dose		
Prolongs QT interval. Should not be used in patients with hypokalemia, hypomagnesemia or long QT syndrome. Obtain ECGs to monitor QTc at baseline, 7 days after initiation, and periodically thereafter, as well as following dose adjustments		

Note: Approved by FDA on 10/29/07
Reference:
Tam CS et al. Blood 2008;112:516.
Coutre PL et al. Blood 2008;111:1834.
Kantarjian H et al. N Eng J Med 2006;354:2542.

Interferon

Interferon	5 MIU/m^2 daily until cytogenic remission

Reference: Italian Co-operative study group. Blood 92:1541, (1998).

Hydroxyurea

(Pretransplant in chronic phase)

Hydroxyurea	3 - 5 g P.O. daily
	(until WBC counts fall between 5 x 109 - 15 x 109/L)
Maintenance dose from 500 - 2000 mg/day	

Reference: Goldman JM et al. Blood 82(6):2235-2238, (1993).

Busulphan

Busulphan	0.1 mg/kg/day P.O. intermittently
	(discontinued at WBC coun ~ < 20 x 109/L, resumption at 50 x 109/L)

Reference: Hehlmann R et al. Blood 82(2):398-407, (1993).

Decitabine

(Imatinib refractory CML)

Decitabine	10 - 15 mg/m^2 IV over 1 hour	days 1 - 5 and 8 - 13
To be repeated every 6 weeks.		

Refrence: Jean-Pierre JI et al. J ClinOncol 23:3948-3956, (2005)

PART – II
Hematological Malignancies

Hair Cell Leukemia

HAIRY CELL LEUKEMIA

Hairy cell leukemia is a cancer of the blood and bone marrow. Hairy cell leukemia is a chronic lymphoproliferative disorder that is easily controlled. This rare type of leukemia gets worse slowly or does not get worse at all. The disease is called hairy cell leukemia because the leukemia cells look "hairy" when viewed under a microscope. The decision to treat is based on symptomatic cytopenias, massive splenomegaly, or the presence of other complications. About 10% of all patients will never require therapy.

In hairy cell leukemia, too many blood stem cells develop into lymphocytes. These lymphocytes are abnormal and do not become healthy white blood cells. They may also be called leukemic cells. The leukemic cells can build up in the blood and bone marrow so there is less room for healthy white blood cells, red blood cells, and platelets. This may cause infection, anemia, and easy bleeding. Some of the leukemia cells may collect in the spleen and cause it to swell.

CHEMOTHERAPY REGIMENS

Cladribine

Regimen # 1

Cladribine	0.1 mg/kg/d civi	d1–7

Reference:
Chadha P et al. Blood 2005;106:241.
Saven et al. Blood 92(6):1918-1926, (1998).

Regimen # 2

Cladribine	0.014 mg/kg/d S.C. bolus	day 1–5

Reference: Rohr VA et al. Annals of Oncology 13:1641-1649, (2002)

Pentostatin

Pentostatin	4 mg/m^2 IV
Q2w x 6 cycles	

Reference: Cassileth PA et al. J Clin Oncol 1991;9:243.

Interferon α

Interferon α	2 MIU/m^2 S.C. 3 times weekly
	or
	3 MIU S.C. daily for 6 months,
	then 3 times weekly
Continue for approximately 1 year.	

Reference: Capnist G et al. leukemia and Lymphoma 14(5-6):457-464, (1994).

Fludarabine

Fludarabine	25 mg/m^2/d IV	day 1–5 every 4 weeks for 6–10 months

Reference: Morrison et al. J Clin OncoI19(16):3611-3621, (2001).

Rituximab

Rituximab	375 mg/m^2 IV	weekly for 4 weeks

Reference: Nieva J et al. Blood Aug 1;102(3):810-3, (2003)

LYMPHOMA

PART – II
Hematological Malignancies

Hodgkin's Lymphoma

HODGKIN'S LYMPHOMA

Hodgkin's lymphoma is characterized by a variable number of characteristic multinucleated giant cells (Reed-Sternberg cells) or large mononuclear cell variants (Hodgkin's cells) in an inflammatory milieu. This inflammatory milieu consists of small lymphocytes, histiocytes, epithelioid histiocytes, neutrophils, eosinophils, plasma cells, and fibroblasts in different proportions depending on the histologic subtype.

As per the NCI data, 9,060 new cases and 1,190 deaths are estimated in the US in year 2012. More than 75% of all newly diagnosed patients with adult Hodgkin's lymphoma (HL) can be cured with combination chemotherapy and/or radiation therapy.

Prognosis for a given patient depends on several factors. The most important factors are the presence or absence of systemic symptoms, the stage of disease, presence of large masses, and the quality and suitability of the treatment administered. Other important factors are age (therapy for very young children requires special attention), sex, erythrocyte sedimentation rate, extent of abdominal involvement, hematocrit, and absolute number of nodal sites of involvement.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Brenner H, Gondos A, Pulte D: Blood 111(6):2977-83, (2008).
Cosset JM et al. Eur J Cancer 28A(11):1847-50, (1992).

CHEMOTHERAPY REGIMENS

ABVD

Doxorubicin	25 mg/m^2 IV	d1 and 15
Bleomycin	10 U/m^2 IV	d1 and 15
Vinblastine	6 mg/m^2 IV	d1 and 15
Dacarbazine	375 mg/m^2 IV	d1 and 15
Q4w		

Reference:
Gianni AM et al. 2008 ASCO annual meeting. Abstract 8506.
Engert A et al. J Clin Oncol 2007;25:3495.
Bonadonna G et al. J Clin Oncol 2004;22:2835.
Carde, P et al. J Clin Oncol 1993;11:2258.
Canellos GP et al. N Eng J Med 1992;327:1478.

BEACOPP

Bleomycin	10 IU/m^2 IV	d8
Etoposide	100 mg/m^2/d IV	d1–3
Doxorubicin	25 mg/m^2 IV	d1
Cyclophosphamide	650 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d8
Procarbazine	100 mg/m^2 P.O. qd	d1–7
Prednisone	40 mg/m^2 P.O. qd	d1–7
Q3w		

Reference: Dann EJ et al. Blood 2007;109:905.

Increased-dose BEACOPP

Bleomycin	10 IU/m^2 IV	d8
Etoposide	200 mg/m^2/d IV	d1–3
Doxorubicin	35 mg/m^2 IV	d1
Cyclophosphamide	1250 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d8
Procarbazine	100 mg/m^2 P.O. qd	d1–7
Prednisone	40 mg/m^2 P.O. qd	d1–14
Filgrastim support		
Q3w		

Reference:
Diehl V et al. 2007 ASCO annual meeting. Abstract LBA 8015.
Diehl V et al. N Eng J Med 2003;348:2386.
DieW V et al. J Clin Oncol 16:3810-3821, (1998).

Stanford V

Nitrogen mustard	6 mg/m^2 IV	d1
Doxorubicin	25 mg/m^2 IV	d1 and 15
Vinblastine	6 mg/m^2 IV	d1 and 15
Vincristine	1.4 mg/m^2 IV	d8 and 22
Bleomycin	5 U/m^2 IV	d8 and 22
Etoposide	60 mg/m^2 IV	d15 and 16
Prednisone	40 mg P.O. qod x 10 weeks,	
	then taper by 10 mg every other day between weeks 10 and 12	
Q4w x 3 cycles (12 weeks)		

For patients older than 50, reduce
Vinblastine to 4 mg/m^2 and Vincristine to 1 mg/m^2 in cycle 3.

Bactrim DS	po	b.i.d
Acyclovir	200 mg P.O.	tid
Ketoconazole	200 mg P.O.	qd

2–4 weeks after chemotherapy
Consolidation radiotherapy to 36 Gy for lymph nodes > or equal to 5 cm and/or macroscopic nodules in spleen.

Reference: Horning SJ et al. J Clin Oncol 2000;18:972.

MOPP

Nitrogen mustard	6 mg/m^2 IV	d1 and 8
Vincristine	1.4 mg/m^2 IV	d1 and 8
Procarbazine	100 mg/m^2 P.O. qd	d1–14
Prednisone	40 mg/m^2 P.O. qd	d1–14
Q4w x 6 cycles		

Reference:
Canellos GP et al. N Eng J Med 1992;327:1478.
Somers R et al. J Clin Onco112:279, (1994).

C-MOPP alternating with ABVD

Cyclophosphamide	500 mg/m^2 IV	d1 and 8
Vincristine	1.4 mg/m^2 IV (max 2 mg)	d1 and 8
Procarbazine	100 mg/m^2 P.O. qd	d1–14
Prednisone	40 mg/m^2 P.O. qd	d1–3, 8–10
Doxorubicin	25 mg/m^2 IV	d1 and 15
Bleomycin	9 mg/m^2 IV (max 15 mg)	d1 and 15
Vinblastine	6 mg/m^2 IV (max 10 mg)	d1 and 15
Dacarbazine	250 mg/m^2 IV	d1 and 15
Q4w		

Reference: Takenaka T et al. Jpn J Clin Oncol. 2000 Mar;30(3):146-52.

GVD

For transplant-naive patients:		
Gemcitabine	1000 mg/m^2 IV	d1, 8
Vinorelbine	20 mg/m^2 IV	d1, 8
Pegylated liposomal doxorubicin	15 mg/m^2 IV	d1, 8
Q3w		

For post-transplant patients:		
Gemcitabine	800 mg/m^2 IV	d1, 8
Vinorelbine	15 mg/m^2 IV	d1, 8
Pegylated liposomal doxorubicin	10 mg/m^2 IV	d1, 8
Q3w		

Reference: Bartlett NL et al. Ann Oncol 2007;18:1071.

Rituximab

(for relapsed lymphocyte-predominant Hodgkin lymphoma)		
Rituximab	375 mg/m^2 IV	qw x 4

Reference: Schulz H et al. Blood 2008;111:109.

Gemcitabine

(Relpased or refractory disease)		
Gemcitabine	1000 mg/m^2 IV	day 1, 8
To be repeated every 3 weeks.		

Refrence: Venkatesh H Clinical Lymphoma, Myeloma & Leukemia. 2004 Sep;5(2):110-5

VEPEMB

Cyclophosphamide	500 mg/m^2 IV	day 1
Bleomycin	10 mg/m^2 IV	day 1, 15
Vinblastine	6 mg/m^2 IV	day 1, 15
Procarbazine	100 mg/m^2 P.O.	day 1–5
Etoposide	60 mg/m^2 P.O.	days 15–19
Mitoxantrone	6 mg/m^2 IV	day 15
Prednisone	30 mg/m^2 P.O.	days 1–5
To be repeated every 28 days		
RT to be administered		

Reference: Levis A et al. Annals Oncol 15;123-128, (2004)

ABVDm

Doxorubicin	25 mg/m^2 IV	day 1, 14
Bleomycin	10 mg/m^2 IV	day 1, 14
Vinblastine	6 mg/m^2 IV	day 1, 14
Dacarbazine	375 mg/m^2 IV	day 1, 14
Methylprednisone	120 mg/m^2 IV	day 1, 14
To be repeated every 4 weeks.		
RT to be administered.		

Reference: Maignan CL et al. Blood, 1 January 2004.Vol 103, No.1, 58-66

GDP

Gemcitabine	1000 mg/m^2 IV over 30 min	day 1 & 8
Dexamethasone	40 mg/m^2 P.O. in divided doses	day 1–4
Cisplatin	75 mg/m^2 IV over 60 min	day 1 & 8

Note: Cisplatin should be administered following Gemcitabine.
Cycle to repeated every 21 days.
Reference: Baetz T et al. Annals of OncoIogy 14:1762-1767, (2003).

VBM

Vinblastine	6 mg/m^2 IV	day 1 & 8
Bleomycin	10 mg/m^2 IV	day 1 & 8
Methotrexate	30 mg/m^2 IV	day 1 & 8
Cycle to repeated every 28 days.		
RT to be administered.		

Reference: Goobi PG et al. Cancer 98:2393-2401, (2003).

PEND

(Previously treated with both ABVD and MOPP)

Prednisone	40 mg/m^2 P.O.	day 1–5
Etoposide	50 mg/m^2 P.O.	day 1–14
Mitoxantrone	5 mg/m^2/d IV	day 1 & 3
Dacarbazine	200 mg/m^2/d IV over 24 hour's	day 1–5
Cycle to repeated every 28 days.		

Reference: Ibrahim D et al. Leuk Lymphoma. 2004 Oct;45(10):2079-84

MOPP/ABV HYBRID

Mechlorethamine	6 mg/m^2 IV	day 1
Vincristine	1.4 mg/m^2 IV (max dose 2 mg)	day 1
Procarbazine	100 mg/m^2 P.O.	day 1–7
Prednisone	40 mg/m^2 P.O.	day 1–14
Doxorubicin	35 mg/m^2 N	day 8
Bleomycin	10 Units/m^2 IV	day 8
Vinblastine	6 mg/m^2 IV	day 8

Note: Repeat the cycle every 28 days. Each dose ofbleomycin is preceded by 100 mg of hydrocortisone: If chemical phlebitis occurs from mechlorethamine, 600 mg/m^2 of cyclophosphamide may be substituted.
Reference: Glick JH et al. J Clin Onco116:19, (1998).

CHLVPP

Chlorambucil	6 mg/m^2/day P.O.	day 1–14
Vinblastine	6 mg/m^2 IV	day 1, 8
Procarbazine	100 mg/m^2 P.O.	day 1–14
Prednisone	40 mg/day (total) P.O.	day 1–14
Repeat every 28 days for six courses.		

Reference: Vose JM, et al. J Clin OncoI 9:1421-1425, (1991).

LOPP/EVAP

LOPP

Chlorambucil	10 mg (total) P.O.	day 1–10
Vincristine	1.4 mg/m^2 IV (max 2 mg)	day 1, 8
Procarbazine	100 mg/m^2 P.O. (max 200 mg)	day 1–10
Prednisone	25 mg/m^2 P.O. (max 60 mg)	day 1–14
Repeat the cycle every 28 days. Prednisone is given in cycles 1 and 4 only.		

EVAP

Etoposide	150 mg/m^2/day P.O. (max 200 mg)	day 1–3
Vinblastine	6 mg/m^2 IV (mas 10 mg)	day 1, 8
Doxorubicin	25 mg/m^2 IV	day 1, 8
Prednisone	25 mg/m^2/day P.O. (max 60 mg)	day 1–14

Note: Give 4 courses of LOPP alternating with 4 courses of EVAP (LOPP, EVAP, LOPP, EVAP...) Until complete remission (CR) and then a total of 4 additional alternating courses to a maximum response, e.g., if CR occurred after the sixth course, give a total of 10 courses; if CR occurred after the 8th course, give a total of 12 courses.
Reference: Hancock BW et al. J Clin OncoI 10:1252-1258, (1992).

EVA

Etoposide	100 mg/m^2/day IV	day 1-3
Vinblastine	6 mg/m^2 IV	day 1
Doxorubicin	50 mg/m^2 IV	day 1
Cycle to be repeated every 28 days		

Refrence: Canellos GP et al. Annals of Oncology 14:268-272, (2003)

Ifosfamide-Carboplatin-Etoposide (ICE)

Etoposide	100 mg/m^2/day IV	day 1-3
Carboplatin	AUC 5 IV (max dose=8 mg)	day 2
Ifosfamide	5 g/m^2 IV	day 2
Mesna	5 g/m^2 civi	day 2
G-CSF	5 µg/kg IV	day 5-12
Cycle to be repeated every 28 days		

Refrence:
Moskovitz CH et al. Blood. 2001 Feb 1;97(3):616-23.
Abali H et al. Cancer Invest. 2008 May;26(4):401-6.

DHAP

Dexamethasone	40 mg IV	day 1-4
Cisplatin	100 mg/m^2 civi	day 1
Cytarabine	2 g/m^2 IV	day 2
G-CSF	5 µg/kg IV	day 4-13
Cycle to be repeated every 28 days		

Refrence: Josting A et al. Ann Oncol. 2002 Oct;13(10):1628-35.

MINE-ESHAP

MINE

Ifosfamide	1.5 g/m^2 IV	day 1-3
Etoposide	80 mg/m^2 IV	day 1-3
Mitoxantrone	10 mg/m^2 IV	day 1
Mesna	2250 mg/m^2 IV	day 1-3

ALTERNATING WITH ESHAP

Etoposide	40 mg/m^2 IV	day 1-4
methylprednisolone	250 mg/d	day 1-4
Cytarabine	2 g/m^2 IV	day 5
Cisplatin	25 mg/m^2 21 hr civi	day 1-4
Q 4W x 2 cycles each		

Reference:
Fernandez de Larrea C et al. Ann Oncol. 2010 Jun;21(6):1211-6.
Aparicio J et al. Ann Oncol 1999;10(5):593

MINE

Mesna	1.33 g/m^2 IV od	day 1-3
	500 mg P.O. od 4 hrs after each IV dose	day 1-3
Ifosfamide	1.33 g/m^2 IV od	day 1-3
Given concurrently with Mesna		
Etoposide	65 mg/m^2 IV od	day 1-3
Mitoxantrone	8 mg/m^2 IV	day 1
Q3-4w		

Reference: Rodriguez MA et al. Ann Oncol. 1995 Jul;6(6):609-11.

IGEV

Ifosfamide	2000 mg/m^2 IV	day 1-4
Gemcitabine	800 mg/m^2 IV	day 1-4
Vinorelbine	20 mg/m^2 IV	day 1
Prednisolone	100 mg	day 1-4

Refrence: Santoro A et al. Haematologica. 2007 Jan;92(1):35-41.

GCDR

Gemcitabine	1000 mg/m^2 IV	day 1-8
Carboplatin	AUC 5 IV	day 1
Dexamethasone	40 mg P.O. od	day 1-4
Rituximab	375 mg/m^2 IV	day 8
Q3w x 2-4 cycles		

Refrence: Gopal AK et al. Leuk Lymphoma. 2010 Aug;51(8):1523-9.

MINI-BEAM

BCNU	60 mg/m^2 IV	day 1
Etoposide	75 mg/m^2 IV	day 2-5
Cytarabine	100 mg/m^2 b.i.d.	day 2-5
Melphalan	30 mg/m^2	day 6

Reference:
Colwill R et al. J Clin Oncol. 1995 Feb;13(2):396-402.
Martin A et al. Hematol 2001;113(1):161.

PART – II
Hematological Malignancies

Non-Hodgkin's Lymphoma

NON-HODGKIN'S LYMPHOMA

As per the NCI, 70,130 new cases and 18,940 deaths from non-Hodgkin's lymphoma (NHL) are estimated in the United States in year 2012.

ADULT NHL

The Non Hodgkin's Lymphomas are heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment. Like Hodgkin's lymphoma, NHL usually originates in lymphoid tissues and can spread to other organs. NHL, however, is much less predictable than Hodgkin's lymphoma and has a far greater predilection to disseminate to extranodal sites. The prognosis depends on the histologic type, stage, and treatment.

NHL can be divided into 2 prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent NHL types have a relatively good prognosis, with median survival as long as 10 years but usually not curable in advanced clinical stages. Early stage (stage I and stage II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. Of patients with aggressive NHL, 30% to 60% can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in patients with a divergent histology of both indolent and aggressive disease. Aggressive lymphomas are increasingly seen in HIV-positive patients; treatment of these patients requires special consideration.

CHILDHOOD NHL

Lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma) is the third most common childhood malignancy, and NHL accounts for approximately 7% of cancers in children younger than 20 years. In the United States, about 800 new cases of NHL are diagnosed each year. Incidence is approximately 10 per 1,000,000. Although there is no sharp age peak, NHL occurs most commonly in the second decade of life, and occurs less frequently in children younger than 3 years.

With current treatments, 5 year survival rate is $>$80%, though outcome is variable depending on a number of factors, including clinical

stage and histology. Patients with localized disease have an excellent prognosis (a 5-year survival rate of approximately 90%), regardless of histology. Patients with NHL arising in bone have an excellent prognosis regardless of histology. Patients with leukemic involvement or CNS involvement at diagnosis require intensive therapy.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012.
Armitage JO: N Engl J Med 328(14):1023-30, (1993).
Cabanillas F et al. Blood 79(4):1024-8, (1992).
National Cancer Institute, SEER Program, 1999. NIH Pub. No. 99-4649., pp. 35-50.
Sandlund JT, Downing JR, Crist WM: N Engl J Med 334(19):1238-48, (1996).
Burkhardt B et al. Br J Haematol 131(1):39-49, (2005).
Link MP et al. N Engl J Med 337(18):1259-66, (1997).
Reiter A et al. Blood 95(2):416-21, (2000).
Woessmann W et al. Blood 105(3):948-58, (2005).
Gerrard M et al. Br J Haematol 141(6):840-7, (2008).
Seidemann K et al. Blood 97(12):3699-706, (2001).

CLINICAL STAGES (CS)

Stage I — Involvement of a single lymph node region (I), or localized involvement of a single extralymphatic organ or site (I)

Stage II — Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of a single extralymphatic organ or site and its regional lymph node(s) with or without involvement of other node regions on the same side of the diaphragm (IIF)

Note: The number of lymph node regions involved may be indicated by a subscript (e.g.II3)

Stage III — Involvement of lymph node regions on both sides of the, diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), or by involvement of the phatic organ or site (IIIE), or by involvement of the spleen (IIIs), or both (IIIE+S)

Stage IV — Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement

Note: The site of Stage N disease is identified further by specifying sites according to the notations listed above.

A AND B CLASSIFICATION (SYMPTOMS)

Each stage should be divided into A and B according to the absence or presence of defined general symptorns. These are:

I. Unexplained weight loss of more than 10% of the usual body weight in the 6 months prior to first attendance

2. Unexplained fever with temperature above 38ºC

3. Night sweats

Note: Pruritus alone does not qualify for B classification nor does a short, febrile illness associated with a known infection.

SUMMARY

Stage	Disease	Substage
Stage I	Single node region Localized single extralymphatic organ/site	 IE
Stage II	Two or more node regions, same side of diaphragm Localized single extralymphatic organ/site with its regional nodes, other node regions same side of diaphragm	IIE
Stage III	Node regions both sides of diaphragm ± Localized single extralymphatic organ/site Spleen Both	
Stage IV	Diffuse or multifocal involvement of extralymphatic organ(s) ± regional nodes: isolated extralymphatic organ and non-regional nodes	
All Stages	divided Without weight loss/fever/ sweats With weight loss/fever/sweats	A B

CHEMOTHERAPY REGIMENS

- Indolent lymphoma
- Mantle cell lymphoma
- Aggressive lymphoma
- Highly aggressive lymphoma

INDOLENT LYMPHOMA

Chlorambucil

Chlorambucil	10 mg P.O.	qd

Reference: Ardeshna, KM et al. Lancet 2003;362:516.

Cyclophosphamide

Cyclophosphamide	100 mg/m^2 P.O.	qd

Reference: Peterson, BA et al. J Clin Oncol 2003;21:5.

Fludarabine

Fludarabine	25 mg/m^2 IV qd	d1–5 q4w

Reference: Klasa, RJ et al. J Clin Oncol 2002;20:4649.

Rituximab

Regimen 1

Rituximab	375 mg/m^2 IV	qw x 4
	followed by	
	375 mg/m^2 IV	q2m x 4

Reference: Ghielmini, M et al. Blood 2004;103:4416.

Regimen 2

Rituximab	375 mg/m^2 IV	qw x 4
	followed by	
	375 mg/m^2 IV	qw x 4
every 6 months		

Reference: Hainsworth, JD et al. J Clin Oncol 2005;23:1088.

Bendamustine

Bendamustine d1 and 2	120 mg/m^2 IV over 30–60 min
Q3w x 12 cycles	

Reference: Friedberg JW et al. J Clin Oncol 2008;26:204.

Oxaliplatin (for MALT lymphoma)

Oxaliplatin	130 mg/m^2 IV over 2 hours
Q3w x 6 cycles	

Reference: Raderer M et al. J Clin Oncol 2005;23:8442.

CVP

Regimen 1		
Cyclophosphamide	750 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	40 mg/m^2 P.O. qd	d1–5
Q3w x 8 cycles		

Reference: Marcus, R et al. Blood 2005;105:1417.

Regimen 2		
Cyclophosphamide	1000 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1–5
Q3w x 6–8 cycles		

Reference: Hochster HS et al. 2005 ASH annual meeting. Abstract 349.

R-CVP

Rituximab	375 mg/m^2 IV	d1
Cyclophosphamide	750 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	40 mg/m^2 P.O. qd	d1–5
Q3w x 8 cycles		

Reference:
Marcus RE et al. 2006 ASH annual meeting. Abstract 481.
Marcus RE et al. Blood 2005;105:1417.

CVP + maintenance R

Cyclophosphamide	1000 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1–5
Q3w x 6–8 cycles		
Followed by		
Rituximab	375 mg/m^2 IV qw x 4, q6m x 4 (2 years)	

Reference: Hochster HS et al. 2005 ASH annual meeting. Abstract 349.

CHOP

Cyclophophamide	750 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1-5
Q3w x 6-8 cycles		

Reference: Czuczman, MS et al. J Clin Oncol 2004;23:4711.

R-CHOP

Rituximab	375 mg/m^2 IV	d1
Cyclophophamide	750 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1-5
Q3w x 6-8 cycles		

Reference:
Buske C et al. 2006 ASH annual meeting. Abstract 482.
Czuczman, MS et al. J Clin Oncol 2004;23:4711.

R-R-CVP or R-CHOP

Rituximab	375 mg/m^2 IV	qw x 4
Followed by		
R-CVP or R-CHOP	q3w x 3 cycles	

Reference: Hainsworth, JD et al. J Clin Oncol 2005;23:1500.

R-CHOP + maintenance R

R-CHOP x 6 cycles		
followed by		
Rituximab	375 mg/m^2 IV	q3m x 2 yrs

Reference: van Oers MHJ et al. Blood 2006;108:3295.

FM

Fludarabine	25 mg/m^2 IV qd	d1-3
Mitoxantrone	10 mg/m^2 IV	d1
Q3w		

Reference: Zinzani, PL et al. J Clin Oncol 2004;22:2654.

R-FCM

Rituximab	375 mg/m^2 IV	d0
Fludarabine	25 mg/m^2 IV over 30 min qd	d1–3
Cyclophosphamide	200 mg/m^2 IV over 4 hrs qd	d1–3
Mitoxantrone	8 mg/m^2 IV over 30 min	d1
Q4w x 4 cycles		

Reference: Forstpointner, R et al. Blood 2004;104:3064.

R-FCM + maintenance R

R-FCM as above			
Followed by			
Rituximab	3	75 mg/m^2 IV	qw x 4 doses at 3 and 9 months

Reference: Forstpointner R et al. Blood 2006;108:4003.

R-MCP

Rituximab	375 mg/m^2 IV	d1
Mitoxantrone	8 mg/m^2 IV	d3–4
Chlorambucil	3 mg/m^2 P.O. tid	d3–7
Prednisone	25 mg/m^2 P.O. qd	d3–7
Q4w x 8 cycles		

Reference: Herold M et al. J Clin Oncol 2007;25:1986.

R-GemOx

Rituximab	375 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 (in 500 ml normal saline) IV at 10 mg/m^2/min	d2
Oxaliplatin	100 mg/m^2 IV over 2 hrs	d2
Q2w x 8 cycles		

Reference: Gnaoui TE et al. Ann Oncol 18:1363–1368, (2007).

CHOP-Bleo

Cyclophosphamide	150 mg/m^2 IV	day 1
Doxorubicin	50 mg/m^2 IV	day 1
Vincristine	1.4 mg/m^2 (max daily dose 2 mg)	day 1
Prednisone	100 mg P.O.	day 1–5
Bleomycin	4 units/m^2 IV	day 1–5
To be repeated every 3 weeks.		

Reference: Seymour JF et ai. Ann Oncol 7(2):1.57, (1996).

Rituximab-Cladribine

Rituximab	375 mg/m^2	day 1
Cladribine	0.12 mg/kg/day	day 2 - 6
To be repeated every 4 weeks		

Reference: Robok T et aI. Cancer;2006 Oct 1;107(7):1542-50.

Rituximab-Cladribine-Cyclophosphamide

Rituximab	375 mg/m^2	day 1
Cladribine	0.12 mg/kg/day	day 2 - 4
Cyclophosphamide	250 mg/m^2/day	day 2 - 4
To be repeated every 4 weeks		

Reference: Robok T et aI. Cancer. 2006 Oct 1;107(7):1542-50.

FC-R

Fludarabine	25 mg/m^2 IV	day 1 - 3
Cyclophosphamide	250 mg/m^2/IV	day 1 - 3
Rituximab	375 mg/m^2 IV	day 1
Cycle repeated every 28 days		

Reference: Tam CS et al. Cancer;2006 Jun 1;106(11):2412-20.

MANTLE CELL LYMPHOMA

R-CHOP

Rituximab	375 mg/m^2 IV	d0
Cyclophophamide	750 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1 - 5
Q3w x 6 cycles		

Reference: Lenz G et al. J Clin Oncol 2005;23:1984.

R-FCM

Rituximab	375 mg/m^2 IV	d0
Fludarabine	25 mg/m^2 IV over 30 min qd	d1 - 3
Cyclophosphamide	200 mg/m^2 IV over 4 hrs qd	d1 - 3
Mitoxantrone	8 mg/m^2 IV over 30 min	d1
Q4w x 4 cycles		

Reference: Forstpointner, R et al. Blood 2004;104:3064.

R-FCM + maintenance R

R-FCM as above		
Followed by		
Rituximab	375 mg/m^2 IV	qw x 4 doses at 3 and 9 months

Reference: Forstpointner R et al. Blood 2006;108:4003.

Bortezomib

Bortezomib	1.3–1.5 mg/m^2 IV	d1, 4, 8 and 11
Q3w		

Note: Approved by FDA on 12/8/06
Reference: Strauss SJ et al. J Clin Oncol 2006;24:2105.
Goy, A et al. J Clin Oncol 2005;23:667.
O'Connor, OA et al. J Clin Oncol 2005;23:676.

R-GemOx

Rituximab	375 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 (in 500 ml normal saline) IV	d1
Oxaliplatin	100 mg/m^2 IV over 2 hrs	d1
Q2–3w x 8 cycles		

Reference:
Rodriguez J et al. Leuk Lymphoma 2007;48:2172.
Gnaoui TE et al. Ann Oncol 18:1363–1368, (2007).

Rituximab + Thalidomide

Rituximab	375 mg/m^2 IV	qw x 4
Thalidomide	200 mg P.O.	qd x 2 weeks
	then	
	400 mg P.O.	qd
until disease progression		

Reference: Kaufmann H et al. Blood 2004;104:2269.

Rituximab + Lenalidomide

Rituximab	375 mg/m^2 IV	qw x 4
Lenalidomide	20 mg P.O. qd	d1–21 q4w until disease progression

Reference: Wang M et al. 2007 ASCO annual meeting. Abstract 8030.

Temsirolimus

Regimen 1	
Temsirolimus	250 mg IV over 30 min qw
For a total of 12 months or 2 months after CR	
Premedication Diphenhydramine	25–50 mg IV

Reference: Witzig TE et al. J Clin Oncol 2005;23:5347.

Regimen 2	
Temsirolimus	25 mg IV qw
For a total of 12 months or 2 months after CR	
Premedication Diphenhydramine	25–50 mg IV

Reference: Ansell SM et al. 2006 ASCO annual meeting. Abstract 7532.

Regimen 3		
Temsirolimus	175 mg IV	qw x 3
	followed by	
	75 mg IV	qw
Premedication Diphenhydramine	25–50 mg IV	

Reference: Hess G et al. 2008 ASCO annual meeting. Abstract 8513.

Cisplatin-Fludarabine-Cytarabine

Cisplatin	100 mg/m^2 IV cont infusion	day 1–4
Fludarabine	30 mg/m^2 IV (over 15 mins)	day 3, 4
Cytarabine	500 mg/m^2 IV (over 1 hr)	day 3, 4
(4 hrs after Fludarabine)		
Cycle repeated every 28 days		

Reference: Sevmour JF et al. Cancer 2002;94:585–593.

AGGRESSIVE LYMPHOMA

CHOP

Cyclophophamide	750 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1–5
Q3w x 6–8 cycles		

Reference: Feugier P et al. J Clin Oncol 2005;23:4117.

R-CHOP

Rituximab	375 mg/m^2 IV	d1
Cyclophophamide	750 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1–5
Q3w x 6–8 cycles		

Note: Approved by FDA on 2/10/2006
Reference:
Habermann TM et al. J Clin Oncol 2006;24:3121.
Feugier P et al. J Clin Oncol 2005;23:4117.

R-CHOP-14

Rituximab	375 mg/m^2 IV	d1
Cyclophophamide	750 mg/m^2 IV	d1
Doxorubicin	50 mg/m^2 IV	d1
Vincristine	1.4 mg/m^2 (max 2 mg) IV	d1
Prednisone	100 mg P.O. qd	d1–5
Q2w x 6 cycles		

Reference: Pfreundschuh M et al. 2006 ASH annual meeting; Abstract 205.

CEPP (non-anthracycline-containing regimen)

Cyclophosphamide	600 mg/m^2 IV	d1 and 8
Etoposide	70 mg/m^2/d IV	d1–3
Procarbazine	60 mg/m^2/d P.O.	d1–10
Prednisone	60 mg/m^2/d P.O.	d1–10
Q4w x 6 cycles		

Reference: Chao NJ et al. Blood 1990;76:1293.

ICE

Regimen 1

Ifosfamide	1000 mg/m^2/d IV over 1 h	d1–2 (hours 0 and 1)
Etoposide	150 mg/m^2/d IV over 11 hrs after ifosfamide	d1–2 (hours 1–11)
Carboplatin	200 mg/m^2/d IV over 1 h after etoposide	d1–2 (hours 11–12)
Etoposide	150 mg/m^2/d IV over 11 hrs after carboplatin	d1–2 (hours 12–24)
Mesna	333 mg/m^2 IV 30 minutes before ifosfamide	
	repeat 4 and 8 hrs after ifosfamide	
Q4w x 2 cycles		

Reference: Fields KK et al. J Clin Oncol 1994;12:544.

Regimen 2

Ifosfamide	5000 mg/m^2 mixed with Mesna 5000 mg/m^2 IV over 24 hrs	d2
Carboplatin	AUC 5 (max 800 mg) IV	d2
Etoposide	100 mg/m^2/d IV	d1–3
Filgrastim	5 ug/kg S.C. qd	d5–12
Q2w x 3 cycles		

Reference: Moskowitz, CH et al. J Clin Oncol 1999;17:3776.

RICE

Rituximab	375 mg/m^2 IV	d1 q2w x 3 cycles
ICE regimen 2 as above		

Reference: Kewalramani, T et al. Blood 2004;103:3684.

ESHAP

Etoposide	40 mg/m^2/d IV over 1 hr	d1-4
Methylprednisolone	500 mg/d IV over 15 min	d1-5
Cisplatin	25 mg/m^2/d civi	d1-4
Cytarabine	2000 mg/m^2 IV over 2 hr	d5
Q3-4w x 6-8 cycles		

Reference: Velasquez, WS et al. J Clin Oncol 1994;12:1169.

EPOCH

Etoposide	50 mg/m^2/d civi	d1-4
Prednisone	60 mg/m^2/d P.O.	d1-5
Vincristine	0.4 mg/m^2/d civi	d1-4
Doxorubicin	10 mg/m^2/d civi	d1-4
Cyclophosphamide	750 mg/m^2 IV over 15 min	d5
Bactrim DS	1 tablet P.O. b.i.d. tiw	
Filgrastim	5 mcg/kg S.C. qd beginining on d6 till ANC >10,000/uL	
Q3w x 6-8 cycles		

Reference:
Wilson WH et al. J Clin Oncol 1993;11:1573.
Gutierrez, M et al. J Clin Oncol 2000;18:3633.

Dose-adjusted EPOCH

Etoposide	50 mg/m^2/d civi	d1-4
Prednisone	60 mg/m^2/d P.O.	d1-5
Vincristine	0.4 mg/m^2/d civi	d1-4
Doxorubicin	10 mg/m^2/d civi	d1-4
Cyclophosphamide	750 mg/m^2 IV over 15 min	d5
Bactrim DS	1 tablet P.O. b.i.d. tiw	
Filgrastim	5 mcg/kg S.C. qd beginining on d6 till ANC >5,000/uL	
Q3w x 6-8 cycles		

Dose-adjustment paradigm based on twice weekly CBC (dose adjustment above starting doses apply to Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytoxan). dose adjustment below starting dose apply to Cyclophosphamide (Cytoxan) only):

If nadir ANC >500/uL
20% increase in Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytoxan) above last cycle

If nadir ANC < 500/uL on 1 or 2 measurements
same doses as last cycle

If nadir ANC < 500/uL on at least 3 measurements, or nadir platelet < 25,000/uL on 1 measuremen,
20% decrease in Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytoxan) below last cycle

Reference: Wilson WH et al. Blood 2002;99:2685.

MINE

Mesna	1330 mg/m^2/d IV over 1 hr with ifosfamide	d1 - 3
	then	
	500 mg P.O. 4 hrs after ifosfamide	d1 - 3
Ifosfamide	1330 mg/m^2/d IV over 1 hr	d1 - 3
Mitoxantrone	8 mg/m^2 IV	d1
Etoposide	65 mg/m^2/d IV over 1 hr	d1 - 3
Q3w		

Reference:
Rodriguez MA et al. Ann Oncol 1995;6:609.
Rodriguez, MA et al. J Clin Oncol 1995;13:1734.

DHAP

Dexamethasone	40 mg P.O. qd	d1 - 4
Cisplatin	100 mg/m^2 IV over 24 hrs	d1
Cytarabine	2000 mg/m^2 IV q12 hrs for 2 doses	d2
Q3 - 4w		

Reference:
Velasquez, WS et al. Blood 1988;71:117.
Guglielmi C et al. J Clin Oncol 16(10):3264-3269, (1998).

R-GemOx

Rituximab	375 mg/m^2 IV	d1
Gemcitabine	1000 mg/m^2 IV	d2
Oxaliplatin	100 mg/m^2 IV over 2 hrs	d2
Q2 - 3w x 8 cycles		

Reference:
Lopez A et al. Eur J Haematol 2008;80:127.
Gnaoui TE et al. Ann Oncol 2007; Advanced access published May 11, (2007).

R-ADOx

(In heavily pretreated patients with diffuse large B-cell lymphoma)		
Rituximab	375 mg/m^2 IV	day 1
Cytarabine	1000 mg/m^2/BD IV	day 2
Dexamethasone	40 mg IV	day 1 - 4
Oxaliplatin	130 mg/m^2 IV over 2 hours	day 2
Cycle repeated every 21 days		

Reference: Woehrer S et aI. Oncology;2005;69(6):499-502. Epub 2006 Jan 16.

MIFAP

(Relapsing and refractory lymphoma)		
Fludarabine	15 mg/m^2 q 12 hrs	day 1 - 4
Cytarabine	50 mg/m^2 CI over 22 hrs	day 1 - 4
Cisplatin	25 or 30 mg/m^2 CI over 24 hrs	day 1 - 4
Mitoxantrone	4 mg/m^2	day 2 - 5

Refrence: Hanel M et al. J Cancer Res Clin Oncol. 2001;127(6):387-95

Alternating Triple Therapy (ATT)

ASHAP		
Doxorubicin	10 mg/m^2 IV civi	day 1 - 4
Cisplatin	25 mg/m^2 IV civi	day 1 - 4
Cytarabine	1.5 mg/m^2 IV over 2 hours	day 5
Methylprednisolone	500 mg IV 15 min infusion	day 1 - 5

m-BACOS		
Methotrexate	1,000 mg/m^2 IV over 3 hours	day 10
Leucovorin	15 P.O. 6 hour x 8	day 11, 12
Doxorubicin	50 mg/m^2 IV civi	day 1
Vincristine	1.4 mg/m^2 (max daily dose 2 mg IV)	day 1
Bleomycin	10 units/m^2 IV 15 min infusion	day 1
Cyclophosphamide	750 mg/m^2 IV over 15 min	day 1
Methylprednisolone	500 mg/m^2 IV over 15 min	day 1 - 3

MINE		
Ifosfarnide	1,500 mg/m^2 IV over 1 hour	day 1 - 3
(With mesna)		
Mitoxantrone	10 mg/m^2 IV 15 min infusion	day 1
Etoposide	80 mg/m^2 IV over 30 min	day 1 - 3

Note: Given in alternating fashion for a total of x 9 courses. ATT appears to be more effective than standard therapy for patients <60 years old with unfavourable tumour scores.
Reference: Cabanillas F et al. Ann Oncol 9(5):511-518, (1998).

MINE/ESHAP

(Salvage treatment program for relapsing lymphoma)

MINE		
Ifosfamide	1,333 mg/m^2 IV over 1 hour	day 1–3
(with mesna)		
Mitoxantrone	8 mg/m^2 IV over 15 min	day 1
Etoposide	65 mg/m^2 IV over 1 hour	day 1–3
To be treated every 3 weeks.		
For a maximum of 6 courses followed by:		

ESHAP		
Etoposide	60 mg/mv IV over 1 hour	day 1–4
Methylprednisolone	500 mg/m^2 IV over 15 min	day 1–4
Cytarabine	2,000 mg/m^2 IV over 2 hour	day 5
Cisplatin	25 mg/m^2 IV civi	day 1–4
To be repeated every 3 weeks.		

Note: For 3 courses to consolidate a complete response or for a maximum of 6 courses after a partial response or no response to MINE.
Reference: Rodriguez MA et al. J Clin Oncol 13(7):1734-1741, (1995).

High-Dose Therapy

(With haematopoietic stem cell support)

Preparative regimens used before autologous transplantation in intermediate-grade lymphoma

CBV		
Cyclophosphamide	1,800 mg/m^2	day 6, 5, 4, 3
Carmustine (BCNU)	400 mg/m^2	day 2
Etoposide	2,400 mg/m^2	day 7

BFAM		
Carmustine (BCNU)	300 mg/m^2	day 6
Etoposide	200 mg/m^2	day 5, 4, 3, 2
Ara-C	200 mg/m^2	day 5, 4, 3, 2
Melphalan	140 mg/m^2	day 1

Reference: Haioun C et al. J Clin Oncol 15(3):1131-1137, (1997).

HIGHLY AGGRESSIVE LYMPHOMA

BURKITT'S LYMPHOMA

CODOX-M/IVAC (for high risk patients: do not meet low risk below)

Cycle 1 and 3 (CODOX-M)		
Cyclophosphamide	800 mg/m^2 IV	d1
Cyclophosphamide	200 mg/m^2/d IV	d2–5
Doxorubicin	40 mg/m^2 IV	d1
Vincristine	1.5 mg/m^2 IV	d1, 8 for cycle 1 and d1, 8, 15 for cycle 3
Methotrexate	1200 mg/m^2 IV over 1 h	d10
	then 240 mg/m^2 per hour civi for the next 23 hrs	
Leucovorin	50 mg IV q6h begins 36 hrs from the start of MTX till MTX	
	level $<$ 0.05 uM	
Filgrastim	begins 24 hrs from the start of Leucovorin till ANC $>$1000/mL	
CNS prophylaxis:		
Intrathecal Cytarabine	70 mg	d1 and 3
Methotrexate	12 mg	d15
CNS treatment:		
Cycle 1:		
Intrathecal Cytarabine	70 mg	d1, 3 and 5
Methotrexate	12 mg	d15 and 17
Cycle 3:		
Intrathecal Cytarabine	70 mg	d1 and 3
Methotrexate	12 mg	d15

Cycle 2 and 4 (IVAC)		
Ifosfamide	1500 mg/m^2/d IV	d1–5
Etoposide	60 mg/m^2/d IV	d1–5
Cytarabine	2000 mg/m^2 IV q12h	d1 and 2 (total 4 doses)
Filgrastim	begins 24 hrs after completion of chemotherapy till ANC $>$1000/mL	
CNS prophylaxis:		
Intrathecal Methotrexate	12 mg	d5
CNS treatment:		
Cycle 2:		
Intrathecal Methotrexate	12 mg	d5
Cytarabine	70 mg	d7 and 9
Cycle 4:		
Intrathecal Methotrexate	12 mg	d5
Radiotherapy for CNS disease and testicular involvement		

Modified CODOX-M

(for low risk patients: single extraabdominal mass or completely resected abdominal mass and normal serum LDH)

Cyclophosphamide	800 mg/m^2 IV	d1
Cyclophosphamide	200 mg/m^2/d IV	d2–5
Doxorubicin	40 mg/m^2 IV	d1
Vincristine	1.5 mg/m^2 IV	d1, 8
Methotrexate	1200 mg/m^2 IV over 1 h	d10
	then 240 mg/m^2 per hour civi for the next 23 hrs	
Leucovorin	50 mg IV q6h begins 36 hrs from the start of MTX till MTX level $<$0.05 uM	
Filgrastim	begins 24 hrs from the start of Leucovorin till ANC $>$1000/mL	
CNS prophylaxis:		
Intrathecal Cytarabine	70 mg	d1
Methotrexate	12 mg	d3
Total of 3 cycles		

Reference: Magrath, I et al. J Clin Oncol 1996;14:925.

CALGB 9251

Cycle 1		
Cyclophosphamide	200 mg/m^2/d IV	d1–5
Prednisone	60 mg/m^2/d P.O.	d1–7

Cycle 2, 4, 6		
Ifosfamide	800 mg/m^2/d IV over 1 hr	d1–5
Mesna	200 mg/m^2 IV at 0, 4 and 8 hrs after ifosfamide	d1–5
Methotrexate	150 mg/m^2 IV over 30 minutes	d1
	followed by	
	1350 mg/m^2 civi over 23.5 hrs	
Leucovorin	50 mg/m^2 IV 36 hrs after start of MTX	
	followed by	
	15 mg/m^2 IV q6h till MTX level $<$0.05 uM	
Vincristine	2 mg IV	d1
Cytarabine	150 mg/m^2/d civi	d 4 and 5
Etoposide	80 mg/m^2/d IV over 1 hr	d 4 and 5
Dexamethasone	10 mg/m^2/d P.O.	d1–5

Cycle 3, 5, 7		
Cyclophosphamide	200 mg/m^2/d IV	d1–5
Methotrexate	150 mg/m^2 IV over 30 minutes	d1
	followed by	
	1350 mg/m^2 civi over 23.5 hrs	
Leucovorin	50 mg/m^2 IV 36 hrs after start of MTX	
	followed by	
	15 mg/m^2 IV q6h till MTX level $<$ 0.05 uM	
Vincristine	2 mg IV	d1
Doxorubicin	25 mg/m^2/d IV bolus	d4 and 5
Dexamethasone	10 mg/m^2/d P.O.	d1–5

Intrathecal (cycle 2–7)		
Methotrexate	15 mg	d1
Cytarabine	40 mg	d1
Hydrocortisone	50 mg	d1
Brain radiation 24 Gy post chemotherapy if bone marrow involvement		
Start cycle 2 right after cycle 1, cycle 2–7 are given q3w		

Reference:
Rizzieri, DA et al. Cancer 2004;100:1438.
Lee EJ et al. J Clin Oncol 2001;19:4014.

Pre-B or T lymphoblastic lymphoma
Hyper-CVAD/MTX-Ara-C

Cycle 1, 3, 5, 7 (3–4 wks/cycle)		
Cyclophosphamide	300 mg/m^2 IV over 2 hrs q12 hrs x 6 doses	d1–3
Mesna	600 mg/m^2/d civi d1–3 to start 1 h before cyclophosphamide till 12 hrs after completion of cyclophosphamide	
Vincristine	2 mg IV	d4, 11
Doxorubicin	50 mg/m^2 IV over 24 hrs (over 48 hrs if LVEF $<$ 50%)	d4
Dexamethasone	40 mg P.O. or IV qd	d1–4 and d11–14

Cycle 2, 4, 6, 8 (3–4 wks/cycle)		
Methotrexate	200 mg/m^2 IV over 2 hrs	
	followed by	
	800 mg/m^2 civi over 22 hrs	d1
Cytarabine	3 g/m^2 (1 g/m^2 for patients over 60 years old) IV over 2 hrs	
	q12 hrs x 4 doses	d2–3
Leucovorin	50 mg IV q6 hrs starting 12 hrs after completion of MTX till MTX level $<$ 0.05 uM	
Intrathecal chemotherapy		

Prophylaxis	
Methotrexate	12 mg d2 of each cycle for a total of 3–4 treatments
Cytarabine	100 mg d8 of each cycle for a total of 3–4
treatments	
Therapeutic	
Intrathecal chemotherapy twice a week (Methotrexate 12 mg and Cytarabine 100 mg respectively) till no more cancer cells in CSF, then decrease intrathecal chemotherapy to once a week x 4, followed by Methotrexate 12 mg d2, Cytarabine 100 mg d8 for the remaining chemotherapy cycles.	
Cranial radiotherapy 24–30 Gy if cranial nerve palsies	

Reference: Thomas, DA et al. Blood 2004;104:1624.

CALGB 9111

Cycle 1 (4 wks)		
Cyclophosphamide	1200 mg/m^2 IV	d1
Doxorubicin	45 mg/m^2/d IV	d1, 2, 3
Vincristine	2 mg IV	d1, 8, 15, 22
Prednisone	60 mg/m^2 P.O. or IV	qd d1–21
L-Asparaginase	6000 IU/m^2 S.C. or I.M.	d5, 8, 11, 15, 18, 22
Reduce doses if patients older than 60:		
Cyclophosphamide	800 mg/m^2 IV	d1
Doxorubicin	30 mg/m^2/d IV	d1, 2, 3
Prednisone	60 mg/m^2 P.O. qd	d1–7
Filgrastim	5 mcg/kg S.C. qd	d4 till ANC >1000/uL

Cycle 2 (4 wks, repeat once)		
Cyclophosphamide	1000 mg/m^2 IV	d1
6-Mercaptopurine	60 mg/m^2/d P.O.	d1–14
Cytarabine	75 mg/m^2/d S.C.	d1–4 and 8–11
Vincristine	2 mg IV	d15, 22
L-Asparaginase	6000 IU/m^2 S.C. or I.M.	d15, 18, 22, 25
Intrathecal Methotrexate	15 mg	d1
Filgrastim	5 mcg/kg S.C. qd	d2 till ANC >5000/uL

Cycle 3 (12 wks)		
6-Mercaptopurine	60 mg/m^2/d P.O.	d1–70
Methotrexate	20 mg/m^2 P.O.	d36, 43, 50, 57, 64
Intrathecal Methotrexate	15 mg	d1, 8, 15, 22, 29
Brain radiation	24 Gy	d1–12

Cycel 4 (8 wks)		
Doxorubicin	30 mg/m^2/d IV	d1, 8, 15
Vincristine	2 mg IV	d1, 8, 15
Dexamethasone	10 mg/m^2/d P.O.	d1–14

Cyclophosphamide	1000 mg/m^2 IV	d29
6-Thioguanine	60 mg/m^2/d P.O.	d29 – 42
Cytarabine	75 mg/m^2/d S.C.	d29 – 32 and 36 – 39

Cycle 5 (16 months)		
Vincristine	2 mg IV	d1 qm
Prednisone	60 mg/m^2/d	d1 – 5 qm
Methotrexate	20 mg/m^2/d P.O.	d1, 8, 15, 22
6-Mercaptopurine	60 mg/m^2/d P.O.	d1 – 28

Reference: Larson RA et al. Blood 1998;92:1556.

PART – II
Hematological Malignancies

Primary CNS Lymphoma

PRIMARY CNS LYMPHOMA

Lymphocytes travel in and out of the central nervous system (CNS). It is thought that some of these lymphocytes become malignant and cause lymphoma to form in the CNS. Primary CNS lymphoma can start in the brain, spinal cord, or meninges. Because the eye is so close to the brain, primary CNS lymphoma can also start in the eye (ocular lymphoma). Patients who have AIDS or other immune disorders or who have had a kidney transplant have a increased risk of primary CNS lymphoma.

CHEMOTHERAPY REGIMENS

High dose Methotrexate

Methotrexate	8 g/m^2 IV over 4 hrs	q2w till CR or up to 8 cycles, followed by
	8 g/m^2 IV	qm x 11 months

Reference: Batchelor, T et al. J Clin Oncol 2003;21:1044.

MPV + RT + Ara-C

Methotrexate	3.5 g/m^2 IV over 2 hours	d1
Leucovorin	10 mg q6h x 12 doses starting 24 hours after MTX infusion	
Vincristine	1.4 mg/m^2 (max 2.8 mg) IV	d1
Procarbazine	100 mg/m^2 P.O. qd	d1–7 cycles 1, 3, 5 only
Q2w x 5 cycles		
Intra-ommaya Methotrexate	2 mg on alternate weeks after systemic MTX	
Leucovorin	10 mg q6h x 8 doses starting 24 hours after intra-ommaya MTX	
3–5 weeks after MPV,		
whole-brain radiotherapy (WBRT)	1.8 Gy/d x 25 days to a total of 45 Gy for patients younger than 60 years	
3 weeks after WBRT,		
consolidation Cytarabine	3 g/m^2/d IV over 3 hours for 2 days.	
A second cycle of Cytarabine (Ara-C) is given 1 month later		

Reference:
Garvrilovic IT et al. J Clin Oncol 2006;24:4570.
Abrey LE et al. J Clin Oncol 2000;18:3144.

R-MPV + RT + Ara-C

Rituximab	500 mg/m^2 IV over 5 hours	d1 of each cycle
Methotrexate	3.5 g/m^2 IV over 2 hours	d2 of each cycle
Leucovorin	20–25 mg q6h starting 24 hours after MTX infusion for 72 hours or until serum MTX level <1 x 10–8 mg/dL. Increase leucovorin to 40 mg q4h if MTX level >1 x 10–5 mg/dL at 48 hours or >1 x 10–8 mg/dL at 72 hours	
Vincristine	1.4 mg/m^2 (max 2.8 mg) IV	d2 of each cycle
Procarbazine cycles only	100 mg/m^2 P.O. qd	d1–7 of odd-numbered
Filgrastim	5 mcg/kg/d S.C. for 3 to 5 days starting 24 hours after the last dose of procarbazine during odd-numbered cycles, and starting 96 hours after MTX infusion or when MTX levels <1 x 10–8 mg/dL during even-numbered cycles	
If positive CSF cytology:		
intra-ommaya Methotrexate	12 mg between days 5 and 12 of each cycle	
Q2w x 5 cycles		
After 5 cycles of R-MPV:		
If CR,		
whole-brain radiotherapy (WBRT)	1.8 Gy/d for 13 days to a total of 23.4 Gy beginning	
3–5 weeks after the completion of R-MPV		
If PR,		
2 more additional cycles of R-MPV.		
If CR after 7 cycles of R-MPV,		
WBRT	1.8 Gy/d x 13 days to a total of 23.4 Gy beginning 3–5 weeks after the completion of R-MPV.	
If persistent disease after 7 cycles of R-MPV,		
WBRT	1.8 Gy/d x 25 days to a total of 45 Gy beginning 3–5 weeks after the completion of R-MPV	
If stable disease or progressive disease after 5 cycles of R-MPV,		
WBRT	1.8 Gy/d x 25 days to a total of 45 Gy beginning 3–5 weeks after the completion of R-MPV	
3 weeks after completion of WBRT,		
consolidation Cytarabine	3 g/m^2/d (max 6 g) IV over 3 hours for 2 days	
Filgrastim	5 mcg/kg/d S.C. for 10 days starting 48 hours after completion of Ara-C	
A second cycle of Cytarabine is given 1 month later		

Reference: Shah GD et al. J Clin Oncol 2007;25:4730.

Bonn protocol

Cycle A (3 wks)		
Methotrexate	5 g/m^2 (3 g/m^2 for patients over 65 years old) civi over 24 hrs d1	
Vincristine	2 mg IV	d1
Ifosfamide	800 mg/m^2/d IV over 1 h	d2–5
Dexamethasone	10 mg/m^2/d P.O.	d2–5
Prednisone	2.5 mg intraventricularly qd	d2–4
Methotrexate	3 mg intraventricularly qd	d2–4
Cytarabine	30 mg intraventricularly	d5

Cycle B (3 wks)		
Methotrexate	5 g/m^2 (3 g/m^2 for patients over 65 years old) civi over 24 hrs d1	
Vincristine	2 mg IV	d1
Cyclophosphamide	200 mg/m^2/d IV over 1 h	d2–5
Dexamethasone	10 mg/m^2/d P.O.	d2–5
Prednisone	2.5 mg intraventricularly qd	d2–4
Methotrexate	3 mg intraventricularly qd	d2–4
Cytarabine	30 mg intraventricularly	d5

Cycle C (3 wks)		
Cytarabine	3 g/m^2/d IV over 3 hrs	d1–2
Vindesine	5 mg IV	d1
Dexamethasone	20 mg/m^2/d P.O.	d3–7
Prednisone	2.5 mg intraventricularly qd	d3–6
Methotrexate	3 mg intraventricularly qd	d3–6
Cytarabine	30 mg intraventricularly	d7
Sequence of cycles: A (d1–5), B (d22–26), C (d43–49).		
Repeat cycles A, B and C once for a total of 6 cycles.		

Reference: Pels, H et al. J Clin Oncol 2003;21:4489.

MTX + Ara-C + ASCT + RT

Methotrexate	8 g/m^2 IV over 4 hours	d1, 10, 20
Leucovorine rescue	15 mg/m^2 q6h until MTX clearance	
Cytarabine	3 g/m^2 IV over 3 hours	d30 and 31
Thiotepa	40 mg/m^2 IV	d31
Carmustine	400 mg/m^2 IV	d50
Thiotepa	5 mg/kg IV	d51, 52
Autologous stem-cell transplantation (ASCT)		d56
Hyperfractionated whole brain radiation 2 cycles of 1 Gy/d to 45 Gy for patients with CR or 50 Gy for patients with PR starting d90		

Reference: Illerhaus G et al. J Clin Oncol 2006;24:3865.

Temozolomide

Temozolomide	150 mg/m²/d P.O.	d1–5 q4w

Reference: Reni M et al. Br J Cancer 2007;96:864.

CYVE + ASCT		
Cytarabine	2 g/m²/d IV over 3 hours	d2–5 (if 60 years of age and older, reduce to 2 g/m²/d d2–4)
Cytarabine	50 mg/m²/d IV over 12 hours	d1–5
Etoposide	200 mg/m²/d IV over 2 hours	d2–5 (if 60 years of age and older, reduce to 150 mg/m²/d d2–5)
Q4w x 2 cycles		
Thiotepa	250 mg/m²/d IV	d9–7
Busulfan	total dose 10 mg/kg P.O. or 8 mg/kg IV	d6–4 (if 60 years of age and older, reduce dose by 40%)
Cyclophosphamide	60 mg/kg/d	d3–2
Autologous stem cell transplantation (ASCT) on		d0

Reference:
Soussain C et al. J Clin Oncol 2008;26:2512.
Soussain C et al. J Clin Oncol 2001;19:742.

Methotrexate-Cytarabine

Methotrexate	3.5 g/m²/d	d1
Cytarabine	2 g/m²/d b.i.d.	d2–3
Q3w		

Reference: Ferreri AJ et al. Lancet 2009 Oct 31;374(9700):1512-20.

High-dose Methotrexate

Methotrexate	4 g/m²/d	d1 x 6 cycles q2w
Followed by		
Methotrexate	4 g/m²/d	
Ifosfamide	1.5 g/m²/d	
d3–5 x 6 cycles q2w		

Reference: Thiel E et al. Lancet Oncol. 2010 Nov;11(11):1036-47.

Methotrexate

Methotrexate	8 g/m²/q2w

Reference: Batchelor T et al. J Clin Oncol. 2003 Mar 15;21(6):1044-9.

High-dose Methotrexate-Rituximab

Induction	
Methotrexate	8 g/m^2/dose
Rituximab	375 mg/m^2/dose
Biweekly x 4–6 cycles, followed by	
Maintenance	
Methotrexate	8 g/m^2/dose q 4w for 4 cycles

Reference: Chamberlain MC et al. Neuro Oncol. 2010 Jul;12(7):736-44.

PART - II

Hematological Malignancies

Multiple Myeloma

MULTIPLE MYELOMA

Multiple myeloma is a systemic malignancy of plasma cells that is highly treatable but rarely curable. It is potentially curable when it presents as a solitary plasmacytoma of bone or as an extramedullary plasmacytoma. As per the NCI data 21,700 new cases and 10,710 deaths from multiple myeloma in the United States are estimated in 2012.

The disease is staged by estimating the myeloma tumor cell mass on the basis of the amount of monoclonal (or myeloma) protein (M protein) in the serum and/or urine, along with various clinical parameters, such as the hemoglobin and serum calcium concentrations, the number of lytic bone lesions, and the presence or absence of renal failure. The stage of the disease at presentation is a strong determinant of survival, but it has little influence on the choice of therapy since almost all patients, except for rare patients with solitary bone tumors or extramedullary plasmacytomas, have generalized disease. Treatment selection is influenced by the age and general health of the patient, prior therapy, and the presence of complications of the disease.

The initial approach to the patient is to evaluate the following parameters:

1. Detection of an M protein in the serum or urine
2. Detection of $>10\%$ plasma cells on a bone marrow examination
3. Detection of lytic bone lesions or generalized osteoporosis in skeletal x-rays
4. Presence of soft tissue plasmacytomas
5. Serum albumin and beta-2-microglobulin levels
6. Detection of free kappa and lambda serum immunoglobulin light chain

The median survival in the prechemotherapy era was about 7 months. After the introduction of chemotherapy, prognosis improved significantly with a median survival of 24 to 30 months and a 10-year survival of 3%. Even further improvements in prognosis have occurred because of the introduction of newer therapies such as pulse corticosteroids, thalidomide, bortezomib, and autologous and allogeneic stem cell transplantation with median survivals of 45 months to 60 months.

Reference:
American Cancer Society.: Cancer Facts and Figures 2012
Rajkumar SV, Kyle RA: Mayo Clin Proc 80(10):1371-82, (2005).
Dispenzieri A et al. Leukemia 23(2):215-24, (2009).
Kumar SK et al. Blood 111(5):2516-20, (2008).
Ludwig H et al. Blood 111(8):4039-47, (2008).
Brenner H, Gondos A, Pulte D: Blood 111(5):2521-6, (2008).

STAGING SYSTEM FOR MULTIPLE MYELOMA

Stage	Durie-Salmon Criteria	ISS Criteria
I	All of the following:	
	• Hemoglobin value >10 g/dL	• Serum beta-2 microglobulin <3.5 mg/L
	• Serum calcium value normal or ≤12 mg/dL	
	• Bone x-ray, normal bone structure or solitary bone plasmacytoma only	• Serum albumin ≥3.5 g/dL
	• Low M-component production rate - IgG value <5 g/dL; - IgA value <3 g/dL - Bence Jones protein <4 g/24 h	
II	Neither stage I nor stage III	Neither stage I nor stage III
II	One or more of the following:	
	• Hemoglobin value <8.5 g/dL	
	• Serum calcium value >12 mg/dL	
	• Advanced lytic bone lesions	
	• High M-component production rate - IgG value >7 g/dL; - IgA value >5 g/dL - Bence Jones protein >12 g/24 h	• Serum beta-2 microglobulin ≥5.5 mg/L

Subclassification criteria

A Normal renal function (serum creatinine level <2.0 mg/dL)

B Abnormal renal function (serum creatinine level ≥2.0 mg/dL)

Reference: NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. V.2. 2010

CHEMOTHERAPY REGIMENS

MP

Regimen 1		
Melphalan	0.15 mg/kg P.O.	qd x 7 days
Prednisone	20 mg P.O.	tid x 7 days
Q6w		

Regimen 2		
Melphalan	0.25 mg/kg P.O.	qd x 4 days
Prednisone	2 mg/kg P.O.	qd x 4 days
Q6w		

Reference: Facon T et al. Blood 2006;107:1292.

Regimen 3		
Melphalan	9 mg/m^2 P.O.	qd d1–4
Prednisone	60 mg/m^2 P.O.	qd d1–4
Q6w x 9 cycles		

Reference: San Miguel JF et al. NEJM 2008;359:906.

Dexamethasone

Dexamethasone	40 mg P.O. qd	d1–4, 9–12, 17–20
		or
		d1–4 only
Q4–6w		

Reference: Facon T et al. Blood 2006;107:1292.

VAD

Vincristine	0.4 mg IV over 30 min	qd d1–4
Doxorubicin	9 mg/m^2 IV over 30 min	qd d1–4
Dexamethasone	40 mg P.O.	qd d1–4, 9–12, 17–20
Q4w		

Reference: Segeren, CM et al. Br J Haematol 1999;105:127.

DVD

Pegylated liposomal doxorubicin	40 mg/m^2 IV	d1
Vincristine	2 mg IV	d1
Dexamethasone	40 mg P.O.	qd d1–4
Q4w		

Reference:
Hussein, MA et al. Cancer 2002;95:2160.
Rifkin RM et al. Cancer;106:848-58, (2006)

Thal/Dex

Thalidomide	100–200 mg P.O.	qd
Dexamethasone	40 mg P.O.	qd d1–4, 9–12, 17–20 for odd cycles and d1–4 only for even cycles q4w

Reference:
Rajkumar SV et al. J Clin Oncol 2008;26:2177.
Rajkumar SV et al. J Clin Oncol 2006;24:431.
Weber, D et al. J Clin Oncol 2003;21:16.
Rajkumar, SV et al. J Clin Oncol 2002;20:4319.

Thal/Dexa (Salvage therapy)

Thalidomide	100 mg P.O.	qd
Dexamethasone	40 mg P.O.	qd d1–4 of every month

Reference:
Palumbo A et al. Haematologica. 2001 Apr;86(4):399-403.
Palumbo A et al. Hematol J. 2004;5(4):318-24.

Rev/Dex low dose

Lenalidomide	25 mg P.O.	qd d1–21
Dexamethasone	40 mg P.O.	d1, 8, 15, 22
Q4w		

Reference:
Rajkumar SV et al. 2007 ASCO annual meeting. LBA8025.
Zonder JA et al. Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 77
Rajkumar SV et al. Blood (ASH Annual Meeting Abstracts) 2006 108: Abstract 799
RajkumarSV et al. Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 74
Rajkumar SV et al. Lancet Oncol. 2010 Jan;11(1):29-37.

Rev/Dex high dose

Lenalidomide	25 mg P.O. qd	d1–21
Dexamethasone	40 mg P.O. qd	d1–4, 9–12, 17–20 for the first 4 cycles, then d1–4 only
Aspirin	81 or 325 mg P.O.	qd
Q4w until disease progression		

Note: Approved by FDA on 6/29/2006
Reference:
Dimopoulos M et al. N Eng J Med 2007;357:2123.
Weber DM et al. N Eng J Med 2007;357:2133.
Rajkumar SV et al. Blood 2005;106:4050.

Rev +/–Dex

Lenalidomide	30 mg P.O. qd	d1–21 q4w
Dexamethasone	40 mg P.O. qd	d1–4 q2w

Reference:
Richardson PG et al. Blood 2006;108:3458.

Lenalidomide (Maintenance therapy)

Lenalidomide	10–15 mg P.O. qd

Reference:
McCarthy PL et al. Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 3416
McCarthy PL et al. Hematol 2011;96(S1):S23
Attal M et al. Hematol 2011;96(S1):S23

Bortezomib/Lenalidomide/Dexamethasone (VDR)

Bortezomib	1–1.3 mg/m^2 IV bolus	d1, 4, 8 and 11
Lenalidomide	15–25 mg P.O.	qd d1–14
Dexamethasone	20–40 mg P.O.	d1, 2, 4, 5, 8, 9, 11, 12
Q4w		

Reference:
Richardson PG et al. Blood 2010;116(5):679.
Richardson PG et al. Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 187
Richardson PG et al. Blood (ASH Annual Meeting Abstracts) 2008 112: Abstract 92

Bortezomib/Dexamethasone/Lenalidomide (VDR)

Bortezomib	1.3 mg/m^2 IV	d1, 4, 8 and 11
Lenalidomide	25 mg P.O.	qd d1–14
Dexamethasone	40 mg P.O.	d1, 8, 14

Reference:
Roussel M et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 624
Roussel M et al. Recent Results Cancer Res. 2011;183:189-206.

Bortezomib/Dexamethasone/Cyclophosphamide/Lenalidomide (VDCR)

Bortezomib	1.3 mg/m^2 IV	d1, 4, 8 and 11
Dexamethasone	40 mg P.O.	d1, 8, 15
Cyclophosphamide	500 mg/m^2 IV	d1, 8
Lenalidomide	15 mg P.O.	qd d1–14

Reference:
Kumar S et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 621
Kumar S et al. Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 127

Bortezomib/Cyclophosphamide/Dexamethasone (VCD/CyBorD)

Bortezomib	1.3 mg/m^2 IV	d1, 4, 8 and 11
Cyclophosphamide	300 mg/m^2 P.O.	d1, 8, 15, 22
Dexamethasone	40 mg P.O.	d1–4, 9–12, 17–20
Q4w x 4 cycles		

Reference: Reeder CB et al. Leukemia. 2009 Jul;23(7):1337-41.

Bortezomib/Cyclophosphamide/Dexamethasone (VCD)

Bortezomib	1.3 mg/m^2 IV	d1, 4, 8 and 11
Cyclophosphamide	900 mg/m^2	d1
Dexamethasone	40 mg P.O.	d1, 2, 4, 5, 8, 9, 11, 12
Q3w x 3 cycles		

Reference: Einsele H et al. Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 131

Bortezomib (Salvage therapy)

Bortezomib	1.3 mg/m^2 S.C. or IV	d1, 4, 8 and 11
q3w x 8 cycles		

Reference: Moreau P et al. Lancet Oncol. 2011 May;12(5):431-40.

BiRD

Clarithromycin	500 mg P.O.	b.i.d beginning on d2 of cycle 1
Lenalidomide	25 mg P.O.	qd d3 - 21 of cycle 1 and d1 - 21 of subsequent cycles
Dexamethasone	40 mg P.O.	d1, 2, 3, 8, 15, and 22 during cycle 1 and then qw
Q4w		
ASA	81 mg P.O.	qd
Omeprazole	20 mg P.O.	qd
Trimethoprim/ sulfamethoxazole DS	1 tab P.O.	b.i.d 3 times a week

Reference: Niesvizky R et al. Blood 2008;111:1101.

Melphalan + Prednisone + Thalidomide regimen 1

Melphalan	0.25 mg/kg/d P.O.	d1 - 4 q6w x 12 cycles
Prednisone	2 mg/kg/d P.O.	d1 - 4 q6w x 12 cycles
Thalidomide	100 - 400 mg P.O.	qd

Reference:
Facon T et al. Lancet 2007;370:1209.
Hulin C et al. J Clin Oncol. 2009 Aug 1;27(22):3664-70.
Hulin C et al. Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 75

Melphalan + Prednisone + Thalidomide regimen 2

Melphalan	4 mg/m^2/d P.O.	d1–7 qm x 6 cycles
Prednisone	40 mg/m^2/d P.O.	d1–7 qm x 6 cycles
Thalidomide	100 mg P.O.	qd till disease progression
Prophylactic Enoxaparin	40 mg S.C.	qd during first 4 cycles of therapy

Reference:
Palumbo A et al. Blood 2008; First Edition Paper, prepublished online May 27.
Palumbo A et al. Lancet 2006;367:825.

Melphalan + Prednisone + Thalidomide regimen

Melphalan	0.25 mg/kg/d P.O.	d1–4 q6w x 12 cycles
Prednisone	2 mg/kg/d P.O.	d1–4 q6w x 12 cycles
Thalidomide	200 mg P.O.	qd

Reference: Wijermans P et al. J Clin Oncol. 2010 Jul 1;28(19):3160-6.

Melphalan + Prednisone + Lenalidomide

Melphalan	0.18 mg/kg P.O.	qd d1–4
Prednisone	2 mg/kg P.O.	qd d1–4
Lenalidomide	10 mg P.O.	qd d1–21
Q4w x 9 cycles		
Maintenance		
Lenalidomide	10 mg P.O.	qd d1–21 q4w until progression
Ciprofloxacin	500 mg P.O.	b.i.d for antibiotic prophylaxis
Aspirin	100 mg P.O.	qd for thrombosis prophylaxis

Reference:
Palumbo A et al. J Clin Oncol 2007;25:4459.
Palumbo A et al. Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 613
Palumbo A et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 622

Maintenance Prednisone

Prednisone	50 mg P.O.	qod

Reference: Berenson, JR et al. Blood 2002;99:3163.

Bortezomib

Bortezomib	1.3 mg/m^2 IV	d1, 4, 8 and 11
Q3w		

Reference:
Richardson PG et al. Blood 2007;110:3557.
Richardson, PG et al. N Engl J Med 2005;352:2487.
Richardson, PG et al. N Engl J Med 2003;348:2609.

Bortezomib + Pegylated liposomal doxorubicin

Bortezomib	1.3 mg/m^2 IV bolus	d1, 4, 8 and 11
Pegylated liposomal doxorubicin	30 mg/m^2 IV over 1 h	d4
Q3w until progression		

Note: Approved by FDA on 5/17/07
Reference: Orlowski RZ et al. J Clin Oncol 2007;25:3892.

PAD (HOVON-65/GMMG-HD4 STUDY)

Bortezomib	1.3 mg/m^2 IV bolus	d1, 4, 8, 11
Dexamethasone	40 mg P.O.	d1-4, 8-11, 15-18 of cycle 1, d1-4 of cycles 2-4
Doxorubicin	9 mg/m^2 IV	qd d1-4
Q3w x 4 cycles		

Reference:
Soneveld P et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 40
Oakervee HE et al. Br J Haematol 2005;129:755.

VMP

Bortezomib	1.3 mg/m^2 IV bolus	d1, 4, 8, 11, 22, 25, 29, 32 q6w x 4 cycles, then d1, 8, 22, 29 q6w x 5 cycles
Melphalan	9 mg/m^2 P.O.	qd d1-4 q6w x 9 cycles
Prednisone	60 mg/m^2 P.O.	qd d1-4 q6w x 9 cycles

Note: Approved by FDA on 6/20/08.
Reference:
San Miguel JF et al. NEJM 2008;359:906.
Mateos MV et al. J Clin Oncol. 2010 May 1;28(13):2259-66. (VISTA trial)
Harousseau JL et al. Blood. 2010 Nov 11;116(19):3743-50.

Bortezomib-Melphalan

Induction		
Bortezomib	1.3 mg/m^2 IV bolus	d1, 4, 8, 11
Intensification		
Melphalan	200 mg/m^2 P.O.	

Reference: Avet-Loiseau H et al. J Clin Oncol. 2010 Oct 20;28(30):4630-4.

VMPT

Bortezomib	1-1.3 mg/m^2 IV bolus	d1, 4, 15, 22
Melphalan	6 mg/m^2 P.O.	qd d1-5
Prednisone	60 mg/m^2 P.O.	qd d1-5
Thalidomide	50 mg P.O.	qd
Q35days x 6 cycles		

Reference: Palnmbo A et al. Blood 2007;109:2767.

Maintenance thalidomide after ASCT

Regimen 1		
Thalidomide	100 mg P.O.	qd starting 3 months after ASCT for 6 months

Reference: Abdelkefi A et al. Blood 2008;111:1805.

Regimen 2		
Thalidomide	400–50 mg P.O.	qd
Pamidronate	90 mg IV	q4w

Reference: Attal M et al. Blood 2006;108:3289.

Melphalan/Bortezomib/Thalidomide/Dexamethasone

(Conditioning before autologous hematopoietic cell infusions)		
Melphalan	50 mg/m^2	day 6 & 3
Bortezomib	1.3 mg/m^2	day 6 & 3
Thalidomide	200 mg/day	days 6 till 3
Dexamethasone	20 mg P.O.	days 6 till 3

Note: Hematopoietic Stem cell support on day 0.
Reference: Palumbo A et al. Clin Lymphoma Myeloma & Leukemia May;6(6):475-7, (2006)

VTD (Bortezomib/Thalidomide/Dexamethasone)

Bortezomib	1.3 mg/m^2	day 1, 4, 8, 11
Dexamethasone	40 mg P.O.	on each day of and after Velcade
administration		
Thalidomide	200 mg/day	days 1–63

Reference:
Cavo M et al. Blood (ASH Annual Meeting Abstracts) 2008 112: Abstract 158
Cavo M et al. Lancet 2010 Dec 18;376(9758):2075-85.
Rosinol L etl al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 307

VTD (Bortezomib/Thalidomide/Dexamethasone)

Bortezomib	1.3 mg/m^2	day 1, 4, 8, 11
Dexamethasone	20 mg P.O.	d1, 2, 4, 5, 8, 9, 11, 12 (C 1-4), d1, 2, 4, 5 (C5-8)
Thalidomide	100 mg/day	days 1-21
Q3w x 8 cycles; Followed by		
Maintenance Bortezomib	1.6 mg/m^2/week	day 1, 8, 15, 22 x q5w x 5 cycles
(25 weeks)		

Reference:
Neisvizky R et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 619
Neisvizky R et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 3026

Bortezomib/Dexamethasone

(As induction treatment prior to autologous stem cell transplantation)

Bortezomib	1.3 mg/m^2	day 1, 4, 8 & 11
Dexamethasone	40 mg P.O.	days 1-4 & 9-12

Note:
Dexamethasone to be administered orally on days 1-4 and 9-12 for the first 2 cycles and on days 1-4 only for the followings cycles.
To be repeated every 21 days.
Reference:
Harousseau JL et al. Haematologica 91:1498-1505, (2006)
Harousseau JL et al. J Clin Oncol. 2010 Oct 20;28(30):4621-9.

Bortezomib/Dexamethasone

(Salvage therapy)

Bortezomib	1.3 mg/m^2	day 1, 4, 8 & 11
Dexamethasone	20 mg P.O.	days 1-4 & 9-12
Q3w x 8 cycles		

Note:Dexamethasone 20 mg/d was added the day of and day after each bortezomib dose for progressive disease after > or = 2 cycles or for stable disease after > or = 4 cycles
To be repeated every 21 days.
Reference:
Mikhael JR et al. Br J Haematol. 2009 Jan;144(2):169-75.
Jagannath S et al. Haematologica. 2006 Jul;91(7):929-34.

Bortezomib/Lenalidomide/Dexamethasone

(Salvage therapy)		
Bortezomib	1.3 mg/m^2	day 1, 4, 8 & 11
lenalidomide	15 mg P.O. od	days 1–14
Dexamethasone	40/20 mg P.O.	Cycle 1–4
Dexamethasone	20/10 mg P.O.	Cycle 5–8, d1, 2, 4, 5, 8, 9, 11, 12
Q3w x 8 cycles		
Maintenance therapy		
Bortezomib	1.3 mg/m^2	day 1, 8
Lenalidomide	15 mg P.O. od	days 1–14
Dexamethasone	40/20 mg P.O.	day 1, 2, 8, 9
Q3w x 8 cycles		

Reference:
Richardson PG et al. Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 3049

Bortezomib/Cyclophosphamide/Dexamethasone (VCD)

Bortezomib	1.3 mg/m^2 IV	d1, 4, 8 and 11
q3w x 8 cycles, followed by		
Bortezomib	1.3 mg/m^2 IV	d1, 8, 15 and 22
q5w x 3 cycles		
Dexamethasone	20 mg P.O.	d1, 2, 4, 5, 8, 9, 11, 12/d15, 16, 22, 23
Cyclophosphamide	50 mg P.O. od	d1

Reference: Krpoff M et al. Br J Haematol. 2007 Aug;138(3):330-7.

Bendamustine

Bendamustine	100 mg/m^2	d1, 2 per cycle

Reference: Knop S et al. Haematologica. 2005 Sep;90(9):1287-8.

Thalidomide/Incadronate/Dexamethasone

(Refractory and relapsed multiple myeloma)		
Thalidomide	300 mg/day P.O.	
Incardonate	10 mg/day IV	weekly
Dexamethasone	12 mg/day	day 1–4
To be repeated every 3 weeks.		

Reference: Ochiai N et al. Int J Hematol Oct;82(3):243-7, (2005)

Thalidomide/Dexamethasone/Pegylated Liposomal Doxorubicin (ThaDD)

(Elderly patients with newly diagnosed multiple myeloma)

Thalidomide	100 mg/day P.O.	at bed time
Dexamethasone	40 mg/day P.O.	days 1-4 & 9-12
Pegylated Liposomal Doxorubicin	40 mg/m^2 IV	day 1
To be repeated every 28 days.		

Reference: Offidani M et al. Blood Oct 1;108(7):2159-64, (2006)

Cyclophosphamide/Thalidomide/Dexamethasone (CTD)

(Newly diagnosed, relapsed or VAD-refractory multiple myeloma)

Cyclophosphamide	500 mg P.O.	day 1, 8 & 15
Thalidomide	100-200 mg/day P.O.	at bed time
Dexamethasone	40 mg/day P.O.	days 1-4 & 15-18
To be repeated every 28 days.		

Reference: Haematologica 91:862-863, (2006)

Doxorubicin/Vincristine/Dexamethasone (VAd)

Dexamethasone	40 mg/day P.O.	days 1-4
Doxorubicin	9 mg/m^2/day (cont IV infusion)	day 1-4
Vincristine	0.4 mg IV/day	
To be repeated every 28 days.		

Reference: Rifkin RM et al. Cancer;106:848-58, (2006)

Melphalan/Arsenic Trioxide (ATO)/Ascorbic Acid (AA)-MAC

(Relapsed or refractory multiple myeloma)

Melphalan	0.1 mg/kg P.O.	day 1-4 of week 1
Arsenic Trioxide	0.25 mg/kg IV	days 1-4 of week 1
Ascorbic Acid	1 g IV	days 1-4 of week 1

Note: ATO & AO twice weekly during week 2-5 and no treatment during week 6 of cycle 1. During cycles 2-6 the schedule would remain same except ATO & AA to be given twice weekly in week 1.
Reference: Berenson JR et al. Br J Haematol Oct;135(2):174-83, (2006)

VBMCP (M-2 protocol)

Vincristine	1.2 mg/ml IV (max 2 mg)	day 1
BCNU	20 mg/ml IV	day 1
Melphalan	8 mg/ml P.O.	day 1-4
Cyclophosphamide	400 mg/ml P.O.	day 1
Prednisone	40 mg/ml P.O.	day 1-7
	and 20 mg/ml P.O.	day 8-14
To be repeated every 5 weeks.		

Reference: Oken et al. Cancer 79:1561-1567, (1997).

Interferon α

Interferon a 5 MIU 3 times a weeks Interferon a maintenance therapy following induction chemotherapy prolongs the duration of response (and possibly of survival).

Reference: Cunningham et al. Br J Haernatol 102:495-502, (1998).

Thalidomide

(In asymptomatic smoldering (SMM) or indolent multiple myeloma (IMM))

Thalidomide	200 mg/day for 2 weeks then increase as tolerated by 200 mg/day every two week to a maximum dose of 800 mg/day

Reference: Raj Kumar et al. Leukemia 15(8):1274-1276, (2001).

Cyclophosphamide–Prednisone

(Resistant myeloma)

Cyclophosphamide	a total of 3.6 g/m^2 in 2 doses	day 1, 3
Prednisone	2 mg/kg	days 1–4

Note: With G-CSF support
Reference: Palumbo et al. Haematologica 79:513-518, (1994).

High-Dose Therapy & Haematopoietic Rescue

High-dose therapy followed by autologous transplantation with bone marrow or peripheral blood stem cells as rescue is unlikely to be curative but, with growth factor support, can be carried out with relative safety and merits consideration as consolidation therapy in first remission or after relapse in patients with responsive disease.

Note: The most commonly used preparation regimens include high-dose melphalan, 200 mg/m², without total-body radiation.
Reference: Goldschmidt et al. Ann OncoI8:243-246, (1997).

PART – III
Appendix

ACS Guidelines for Early Detection of Cancer

AMERICAN CANCER SOCIETY GUIDELINES FOR THE EARLY DETECTION OF CANCER

These screening guidelines are recommended for those people at average risk for cancer (unless otherwise specified) and without any specific symptoms. People who are at increased risk for certain cancers may need to follow a different screening schedule, such as starting at an earlier age or being screened more often.

CANCER-RELATED CHECKUP

For people aged 20 or older having periodic health exams, a cancer-related checkup should include health counseling, and depending on a person's age and gender, might include exams for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, and ovaries, as well as for some non-malignant (non-cancerous) diseases. Special tests for certain cancer sites are recommended as outlined below.

BREAST CANCER

- Yearly mammograms are recommended starting at age 40 and continuing for as long as a woman is in good health.
- Clinical breast exam (CBE) should be part of a periodic health exam, about every 3 years for women in their 20s and 30s and every year for women 40 and over.
- Women should know how their breasts normally feel and report any breast change promptly to their health care providers. Breast self-exam (BSE) is an option for women starting in their 20s.
- Women at high risk (greater than 20% lifetime risk) should get an MRI and a mammogram every 6 months to 1 year. Women at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram. Yearly MRI screening is not recommended for women whose lifetime risk of breast cancer is less than 15%.

COLON AND RECTAL CANCER

Beginning at age 50, both men and women at average risk for developing colorectal cancer should use one of the screening tests below. The tests that are designed to find both early cancer and polyps are preferred.

Tests that find polyps and cancer

- flexible sigmoidoscopy every 5 years*
- colonoscopy every 10 years
- double contrast barium enema every 5 years*
- CT colonography (virtual colonoscopy) every 5 years*

Tests that mainly find cancer

- fecal occult blood test (FOBT) every year*,**
- fecal immunochemical test (FIT) every year*,**
- stool DNA test (sDNA), interval uncertain*

**Colonoscopy should be done if test results are positive.*
***For FOBT or FIT used as a screening test, the take-home multiple sample method should be used. A FOBT or FIT done during a digital rectal exam in the doctor's office is not adequate for screening.*

People should be screened more often if they have any of the following colorectal cancer risk factors:

- a personal history of colorectal cancer or adenomatous polyps
- a personal history of chronic inflammatory bowel disease (Crohns disease or ulcerative colitis)
- a strong family history of colorectal cancer or polyps (cancer or polyps in a first-degree relative [parent, sibling, or child] younger than 60 or in 2 or more first-degree relatives of any age)
- a known family history of hereditary colorectal cancer syndromes such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC)

CERVICAL CANCER

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years. Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with either the conventional or liquid-based Pap test, plus the HPV DNA test. Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection, or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be screened annually.
- Women 70 years of age or older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening. Women with a history of cervical cancer, DES exposure before birth, HIV infection or a weakened immune system should continue to have screening as long as they are in good health.
- Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer screening, unless the surgery was done as a treatment for cervical cancer or pre-cancer. Women who have had a hysterectomy without removal of the cervix should continue to follow the guidelines above.

ENDOMETRIAL (UTERINE) CANCER

At the time of menopause, all women should be informed about the risks and symptoms of endometrial cancer, and strongly encouraged to report any unexpected bleeding or spotting. For women with or at high risk for hereditary non-polyposis colon cancer (HNPCC), annual screening should be offered for endometrial cancer with endometrial biopsy beginning at age 35.

PROSTATE CANCER

Discuss the potential benefits and limitations of prostate cancer early detection testing with men before any testing begins. This discussion should include an offer for testing with the prostate-specific antigen (PSA) blood test and digital rectal exam (DRE) yearly, beginning at age 50, to men who are at average risk of prostate cancer and have at least a 10-year life expectancy. Following this discussion, those men who favor testing should be tested.

This discussion should take place starting at age 45 for men at high risk of developing prostate cancer and for men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65) and at age 40 for men at even higher risk (those with several first-degree relatives who had prostate cancer at an early age).

Reference:
American Cancer Society. Cancer Facts & Figures 2009.
Levin B et al. Published online March 5, 2008. CA Cancer J Clin. 2008;58.
Saslow D et al. CA Cancer J Clin. 2007;57:75-89.

PART – III
Appendix

Creatinine Clearance & Carboplatin Dosing

CREATININE CLEARANCE & CARBOPLATIN DOSING

CALCULATION OF CREATININE CLEARANCE (CRCL)

Estimated from age, weight, serum creatinine:	Method of Cockcroft and Gault	Males Weight (kg) x (140-age): 72 x serum creatinine (mg/dL)
		Females Weight (kg) x (140-age) x 0.85: 72 x serum creatinine (mg/dL)
	Method of feline	Creatinine Clearance/1.73 = (100/Serum Creatinine) –12
Calculated from timed urine collection***		Creatinine Clearance = (Urine Creatinine: Serum Creatinine) x Urine volume: Time

Units used in calculations are as follows: creatinine clearance (mL/min.; age (yr); serum crcatinine (mg/dL); time (min); urine creatinine (mg/dL); weight (kg); urine volume (mL).

****Time = duration of urine collection; 24 hours = 1,440 minutes; 12 hours = 720 minutes; 8 hours = 480 minutes; less than 20% variability with 8-, 12-, and 24 hours collection times. (From Baumann T EJ, Sraddon IE, Horst HM, et al. Minimum urine collection periods for accurate determination of creatinine clearance in critically ill patients. Clin Pharma G:393-398, 1987)*

From Cockcroft DW Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron I G:3141, (1976).

From Jeliffe RW; Estimation of creatinine clearance when urine cannot be collected. Lancer 1:975-97G, (1971).

CARBOPLATIN DOSING CALCULATIONS

Platelet Nadir Method*	Area Under the Curve Method**
Previously untreated patients Dose (mg/m^2) = 0.091 x (CrCl/BSA) x (Pre PC-Desired Nadir PC/Pre PC x 100) + 86.	Previously untreated patients Dose (mg) = Target AUC x (CrCl + 25): Target AUC 6 – 8 mg/mL/min
Previously treated patients Dose (mg/m^2) = 0.091 x (CrCl/BSA) x [(Pre PC-Desired Nadir PC/Pre PC x 100) – 17] + 86.	Previously treated patients Dose (mg) = Target AUC x (CrCl + 25): Target AUC 4 – 6 mg/mL/min

**CrCI = creatinine clearance; Pre PC = pretreatment platelet count; PC = Platelet count; (From Egorin MI, Van &ho DA, Olman EA, et al. Prospective validation of a pharmacologically based dosing scheme for the cis diamminedichloroplatinum(ll)analogue diamminecyclobutanedicarboxylatoplatinum. Cancer Res 45;6502-6506, (1985).*

***AUC = Area under the [plasma concentration] curve; CrCI = creatinine clearance. (From Calvert AH, Newell DR, Gumbrell LA. et al. Carboplatin dosage; Prospective evaluation of a simple formula based on renal function. J. Clin Oncol 7:1748-1756, 1989.)*

PART - III
Appendix

Performance Scale

PERFORMANCE SCALE

ECOG**		Karnofsky*	
0	Fully active, able to carry on all predisease performance without restriction	100%	Normal, no complaints, no evidence of disease
1	Restricted in physically strenuous activity but ambulatory and able to carty out work of a light or sedentary nature, e.g., light housework, office work	90%	Able to carry on normal activity; minor signs or symptoms of disease
		80%	Normal activity with effort; some signs or symptoms of disease
		70%	Cares for self; unable to carry on normal activity or to do active work
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours	60%	Requires occasional assistance, but is mostly able to care for himself
		50%	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care confined to bed or chair, requires assistance more than 50% of waking hours	40%	Disabled, requires special care
		30%	Severely disabled, hospitalization indicated; death not imminent
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20%	Very sick, hospitalization necessary, active supportive treatment necessary
		10%	Moribund, fatal processes, progressing rapidly
5	Dead	0%	Dead

**Modified from Karnofsky DA, Abelman WH, Craver LF, et al. Cancer 1:634-656, (1948).*
***Modified from Oken MM, Creech RH, Tormey DC, et al. Am J Clin Onco 5:649-655, (1982).*

PART - III
Appendix

Revised Recist (Version 1.1)

RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS:

REVISED RECIST (VERSION 1.1)

EVALUATION OF TARGET LESIONS

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sumdiameterswhile on study.

EVALUATION OF NON-TARGET LESIONS

Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

EVALUATION OF BEST OVERALL RESPONSE

Time point response: patients with target (+/- non-target) disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PDa
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.
a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] *If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.*

Reference:

E.A. Eisenhauer, P. Therasse, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1): European Journal of Cancer 45, (2009) 228-247

PART - III
Appendix

Special Precautions

SPECIAL PRECAUTIONS

1. The following maximal total doses of cytotoxic drugs should not be exceeded:

a) Doxorubicin	550 mg/m^2 (450 mg/m2) in patients previously treated with cytotoxic drugs or mediastinal irradiation
b) Epirubicin	1,000 mg/m^2
c) Mitoxantrone	160 mg/m^2
d) Vincristine	15–25 mg
e) Bleomycin	300 mg
f) Mitomycin	60 mg/m^2 (haemolytic-uremic syndrome)

2. Based on the haematological findings, dose adjustments of haemototoxic drugs are necessary. The following dose modifications are indicated or advisable:

Leukocytes (per mm^3)	**and/or**	**Platelets (per mm^3)**	**Dose (%)**
Over 3,000		over 150,000	100
2,500–3,000		100,000–150,000	75
2,000–2,500		75,000–100,000	50
Below 2,000		below 75,000	Stop drugs

Reduction of the dose at scheduled time of retreatment should be according to the above table. Alternatively, the treatment may be delayed for 1 week to allow for recovery of leucocytes and/or platelets, in order to deliver the full projected dose.

In the absence of toxic effects, the dose may be raised by 25% of the specified full amount (at the earliest after 4–6 weeks).

3. The following laboratory values also call for dose adjustments:

a. Creatinine	>1.5 mg%
b. bilirubin	>2 mg%
c. transaminases	>2–3 times the normal values
d. alkaline phosphatase	>2–3 times the normal values

4. For the individual patient creatinine-clearance guided dosing schedules for carboplatin have been developed to tailor a fully therapeutic but not unduly toxic dose.

5. Any treatment with ifosfamide should invariably be accompanied by the administration of mesna. The concurrent use of mesna is I also indicated in treatment with cyclophosphamide when doses in excess of 10 mg/kg ($\geq$ 400 mg/m^2) are given or where there are risk factors The principal risk factors are: prior radiotherapy in the region of the small pelvis, the development of cystitis during previous treatment with cyclophosphamide/ifosfamide and a history of urinary-tract disorders.
6. High dose of methotrexate should only be given if there are facilities to monitor the blood methotrexate levels and under Leucovorin rescue.

Delivering You A World-Class Performance

Fresenius Kabi is a leading global producer of i.v. injectables that offers customers one of the most comprehensive generic cancer therapy portfolios. Our expertise in research and development, manufacturing and supply chain ensures we deliver innovative and high quality medicines. Our customer commitment has made us a principal hospital supplier in Europe.

We are dedicated to bringing you the best – a world-class performance.

Trusted Generics: Total Care

FRESENIUS KABI
caring for life

FRESENIUS
KABI

caring for life

Fresenius Kabi Deutschland GmbH

Else-Kröner-Straße 1
61352 Bad Homburg v. d. H.
Germany
Phone: +49 (0) 6172-686-0
www.fresenius-kabi.com