Prognostic relevance of integrated genetic profiling in adult T-cell acute lymphoblastic leukemia

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Supplementary Table 1. Immunophenotype markers (% positive cells) in adult T-ALL

Sample#	HLADR	TdT	CD133	CD123	CD117	CD34	cCD3	CD5	mfi_CD5	CD1	CD7	CD2	CD3	CD62l	alpha_beta	gamma_delt	CD4	CD8	CD10	CD33	CD13	CD11b	CD56
1	NA	NA	NA	NA	NA	0	99	99	20	NA	99	99	99	0	NA	NA	0	99	93	0	0	NA	NA
2	32	99	NA	0	0	36	99	99	NA	0	92	25	0	80	NA	NA	0	0	0	99	0	62	0
3	33	21	NA	NA	0	96	90	87	NA	0	92	96	0	0	NA	NA	0	0	60	91	92	95	93
4	NA	NA	NA	NA	79	99	75	0	NA	0	88	97	0	58	NA	NA	0	0	0	0	94	NA	NA
5	0	38	0	0	0	0	94	96	60.5	91	97	98	0	84	nt	nt	95	98	0	0	0	0	0
6	0	89	0	0	0	0	99	99	28.5	99	99	99	99	99	0	0	99	99	99	0	0	0	0
7	0	99	0	0	0	99	96	99	51.5	0	99	99	99weak	99	0	0	0	0	0	0	99	0	0
8	0	99	0	0	0	20	99	99	29.3	0	99	99	99	99	0	0	99	99	99	99	0	0	0
9	0	96	0	0	0	0	99	99	48.8	99	99	99	0	99	0	0	99	99	0	0	0	0	0
10	0	99	0	0	0	0	99	99	32.1	99	99	99	0	99	0	0	99	99	99	0	0	0	0
11	0	99	0	0	0	0	99	99	17.6	99	99	0	55	0	99	0	0	0	99	99	99	0	99
12	0	99	0	0	0	0	99	99	6.7	0	99	0	0	99	0	0	99	99	99	0	0	0	0
13	99	14	30	99	0	99	99	99	11.0	0	99	0	0	25	0	0	0	0	0	99	0	99	0
14	0	99	99	95	0	99	99	99	30.4	0	99	30	0	99	0	0	0	99	0	0	99	99	0
15	10	99	0	95	98	99	99	99	4.0	0	99	0	0	99weak	0	0	0	0	0	99	0	99	99
16	0	99	0	0	0	99	99	99	16.5	0	99	70	99	0	0	99	0	75	70	0	99	0	0
17	NA	NA	99	99	0	99	99	50	1	0	99	50	0	0	NA	NA	0	0	0	50	99	NA	NA
18	NA	NA	0	0	0	0	99	99	40	99	99	99	0	99	NA	NA	99	99	99	0	99	NA	NA
19	99	99	99	95	99	99	99	0	1.1	0	99	99	0	99	0	0	0	0	0	0	99weak	99	0
20	0	99	0	0	0	30	99	99	29.5	99	99	99	0	0	0	0	95	60	0	0	30	0	0
21	0	99	0	0	0	nt	99	99	21.9	35	99	76	99	99	0	99	99	99	99	0	0	0	0
22	0	99	0	0	0	99	99	99	17.8	0	99	99	99	99	0	0	0	0	0	0	99	0	0
23	0	99	0	0	0	0	99	99	22.6	99	99	99weak	0	0	0	0	99	99	0	0	0	0	0
24	0	99	0	0	0	0	99	99	28.6	99	99	99	40	99	0	0	99	99	99	0	99	0	0
25	0	92	0	0	0	99	99	99	8.5	0	99	99	99	99	0	0	99	99	99	0	99	0	0
26	0	99	95	99	99weak	99	99	99	9.3	0	99	0	0	99	0	0	0	0	0	95	95	99	0
27	NA	NA	99	99	0	99	99	0	NA	0	99	0	0	0	NA	NA	0	0	84	99	99	NA	NA
28	0	7	0	0	99	0	97	0	5.9	0	99	0	99	0	0	0	0	0	0	0	99	0	0
29	25	99	0	99	0	55	97	0	1.0	0	99	0	0	0	0	0	0	0	0	99	0?	0	0
30	0	99	0	0	0	0	99	99	18.0	99	98	99	0	99	0	0	99	99	99	0	0	0	0
31	0	90	0	0	99	0	99	93	16.4	nt	99	0	0	0	0	0	0	0	99	0	99	0	98
32	15	97	99	99	0	99	99	99	4.1	0	99	99weak	0	99weak	0	0	0	0	99weak	99	99	99	0
33	0	96	0	0	0	99	97	95	5.1	0	94	94	0	99	0	0	99	99	91	0	0	0	0
34	0	28	98	94	99	99	99	93	18.6	0	99	90	0	0	0	0	0	99	0	0	0	0	93
35	99	91	nt	98	99	99	99	0	1.9	0	98	99	0	0	0	0	0	0	0	99weak	99	95	0
36	96	94	99	99	99	99	99	0	1.1	0	99	44	0	0	0	0	0	0	0	0	99	98	0
37	0	99	0	0	0	0	99	99	18.2	0	99	0	0	20	0	0	0	0	99	0	99	0	0
38	0	30	95	96	0	99	99	99	10.7	0	99	0	99	99weak	0	0	0	0	0	99	99weak	99	99
39	99	99	0	99	0	99	99	99	8.9	0	99	99	0	99	0	0	0	99	0	0	98	99	96
40	30	99	97	97	99	98	99	0	1.2	0	99	99	0	99	0	0	0	0	0	0	98	20	0
41	0	99	0	99	0	99	99	95	32.7	0	99	99	0	99	0	0	0	99	99	0	99	0	0
42	99	15	99	95	40	20	99	0	1.7	0	99	0	0	0	0	0	0	0	0	99	0	90	0
43	65	99	99	95	0	99	99	95	6.7	0	99	99weak	0	99weak	0	0	29	0	99weak	99	95	90	0
44	0	0	0	0	0	0	99	0	1.1	0	99	50	0	0	0	0	0	0	0	0	99	0	0
45	0	58	0	0	0	0	99	99	5.7	95	99	99	99	99	0	0	99	99	0	0	0	0	0
46	0	20	0	95	95	99	99	99	4.1	0	98	0	0	0	0	0	0	95	0	96	95	0	0
47	0	99	0	0	0	0	99	99	17.8	0	99	0	45	90	0	0	0	0	99	0	90	0	NA
48	0	99	0	0	99	0	99	99	15.2	95	99	99	0	99	0	0	95	95	99	0	0	0	0
49	NA	NA	0	98	0	99	99	99	1	0	99	99	0	99	NA	NA	0	0	99	0	99	NA	NA
50	99	20	95	95	0	99	99	99	11.1	0	99	0	0	99	0	0	0	0	99weak	99	99	0	0
51	0	99	90	99	56	99	99	99	13.1	0	99	99weak	0	0	0	0	0	0	0	99	99weak	99	0
52	0	99	0	90	99	0	99	0	1.7	0	99	0	99	0	0	0	0	99	0	0	99	0	0
53	0	0	0	0	0	0	99	99	15.6	0	99	99	99	0	0	0	0	99	0	0	0	0	0

Supplementary Table 2. Copy number alterations (size and number) identified in adult T-ALL

	Deletions			Amplifications			
Sample #	micro (<1MB)	macro (>1Mb)	total	micro (< 1MB)	macro(>1Mb)	total	Total (gains+losses)
1	2	1	3	2	1	3	6
2	0	1	1	1	0	1	2
3	2	0	2	0	0	0	2
4	0	2	2	0	0	0	2
5	2	2	4	2	0	2	6
6	6	1	7	2	0	2	9
7	4	0	4	0	0	0	4
8	4	2	6	2	0	2	8
9	4	1	5	0	0	0	5
10	3	2	5	1	0	1	6
11	0	1	1	1	1	2	3
12	8	0	8	1	0	1	9
13	1	4	5	1	1	2	7
14	5	0	5	2	0	2	7
15	1	3	4	0	0	0	4
16	2	4	6	1	1	2	8
17	5	2	7	2	0	2	9
18	12	1	13	1	0	1	14
19	2	0	2	1	0	1	3
20	3	8	11	0	2	2	13
21	1	4	5	1	0	1	6
22	3	0	3	0	0	0	3
23	1	0	1	0	0	0	1
24	0	5	5	1	2	3	8
25	1	1	2	0	0	0	2
26	1	0	1	1	0	1	2
27	0	5	5	0	0	0	5
28	2	0	2	0	2	2	4
29	0	9	9	0	1	1	10
30	3	0	3	0	0	0	3
31	0	1	1	0	0	0	1
32	2	0	2	1	0	1	3
33	6	0	6	0	0	0	6
34	1	0	1	0	0	0	1
35	0	0	0	0	0	0	0
36	3	1	4	0	2	2	6
37	2	6	8	0	8	8	16
38	3	8	11	0	0	0	11
39	1	0	1	0	0	0	1
40	0	1	1	0	1	1	2
41	1	3	4	0	1	1	5
42	0	3	3	0	2	2	5
43	5	4	9	0	0	0	9
44	0	10	10	0	3	3	13
45	4	11	15	1	0	1	16
46	0	0	0	0	0	0	0
47	0	7	7	0	0	0	7
48	5	3	8	0	0	0	8
49	4	0	4	0	0	0	4
50	0	8	8	0	1	1	9
51	1	1	2	0	0	0	2
52	1	0	1	1	2	3	4
53	1	0	1	0	2	2	3

Supplementary Table 3. Copy number alterations (location and genes) identified in adult T-ALL

Sample ID#	Chromosome	Location (Mb)	Defect	Size (Mb)	Number of probes	Number of genes	Gene anotation
1	4q25	109.22-109.31	het del	0.09	many	1	LEF1 (5' region)
	6p22.1	29.20-29.27	het del	0.07	many	1	OR2J2
	6q14.3	86.64-87.26	gain of 1 copy	0.62	many	0	
	6q23.2	135.55-135.77	gain of 1 copy	0.22	many	3	MYB mir548a-2 AHI1
	14q11.2-q13.2	22.03-36.10	gain of 1 copy (subclone)	14.07	many	>20	NKX2-1
	14q23.2-qter	63.74-106.35	het del	42.61	many	>20	
2	12q13.13	51.44-54.45	het del	3.01	8	1	KRT76
	Xq22.3	104.32-104.92	gain of 1 copy	0.6	many	2	IL1RAPL2 TEX13A
3	4q26	117.56-117.62	het del	0.06	10	0	
	15q21.1	44.89-44.90	het del	0.01	5	0	
4	11p14.1-p12	30.75-38.06	het del	7.31	many	>20	WT1 LMO2 RAG1 RAG2 TRAF6
	16qarm het deleted	37-88.7	het del	51.7	many	>20	
5	1p22.2	91.92-92.03	het del	0.11	many	1	TGFBR3 (intragenic)
	6p22.3	24.19-24.29	gain of 1 copy (subclone)	0.1	many	2	NRSN1 DCDC2
	8q23.1	107.83-107.89	gain of 1 copy (subclone)	0.06	many	2	OXR1 ABRA
	9p21.3	19.83-22.72	homo del	2.89	many	>20	CDKN2A CDKN2B
	9q34.3	138.52-138.56	het del	0.04	many	1	NOTCH1
6	4q34.1	175.40-175.97	het del (subclone)	0.57	many	4	FBXO8 KIAA1712 HPGD GLRA3
	5q13.2	74.02-74.03	het del	0.01	8	1	HEXB
	9p21.3	21.21-21.36	het del	0.15	many	6	IFN genes KLHL9
		21.36-22.15	homo del	0.79	many	9	IFN genes LOC554202 MTAP C9ORF53 CDKN2A CDKN2B
		22.15-22.77	het del	0.62	many	1	DMRTA1
	9p13.2	37.79-38.31	het del	0.52	many	3	WDR32 MCART1 SHB
	10q21.2	63.14-63.26	het del	0.12	many	1	C10orf107
	13q33.1	100.19-100.55	gain of 1 copy	0.36	many	1	NALCN
	16q23.1	74.81-74.86	het del	0.05	many	0	
	Xp21.1	33.26-33.81	gain of 1 copy	0.55	many	1	DMD
7	1p33	47.47-47.55	het del	0.08	many	2	STIL TAL1
	9p21	21.87-21.99	hom del	0.12	many	3	C9orf53 CDKN2A CDKN2B (partial deletion)
	18q12.1	27.78-27.87	het del	0.09	many	1	RNF125
8	1q41	217.78-219.22	het del	1.44	many	12	SLC30A10 EPRS BPNT1 IARS2 SNORA36B RAB3GAP2

							AURKPS1 MARK1 C1orf115 MOSC2 MOSC1 HLX
	9p21	21.06-21.96	het del	0.9	many	19	IFNW1 IFNA gene cluster KLHL9 MTAP LOC554202
		21.96-22.21	hom del	0.25	many	3	C9orf53 CDKN2A CDKN2B
		22.21-23.18	het del	0.97	many	1	DMRTA1
	9q34.11	132.59-133.08	gain of 1 copy (subclone)	0.49	many	6	NUP214-ABL1 ABL1 (at breakpoint) QRFP FIBCD1 LAMC3 AIF1L NUP214 (at breakpoint)
	13q14.2	47.88-47.97	hom del	0.09	many	3	RB1 (del 3' region) P2RY5 RCBTB2 (del 3' region)
	18p11.23	8.203-8.215	het del	0.01	7	1	PTPRM (intragenic)
	Yq11.221	14.68-14.69	gain of 1 copy	0.01	9	2	VCY VCY1B
9	7q11.22	69.82-69.86	het del	0.04	many	1	AUTS2
	9p21.3	21.95-21.97	hom del	0.02	many	2	CDKN2A C9orf53
	11p13	33.91-34.05	het del	0.14	many	1	CAPRIN1 adjacent to LMO2
	16q21	58.11-64.83	het del	6.72	many	3	CDH8 CDH11 LOC283867
10	3p12.3	78.91-79.04	het del	0.13	many	1	ROBO1 (intragenic)
	5q11.2	58.19-58.44	het del	0.25	many	2	PDE4D (3' region) RAB3C (3' region)
	6q23.2	135.52-135.74	gain of 1 copy	0.22	many	3	MYB mir548a-2 AHI1
	9p21.3	20.67-21.73	het del	1.06	many	20	
		21.73-21.97	homo del	0.24	many	3	MTAP C9orf53 CDKN2A
		21.97-22.7	het del	0.73	many	2	CDKN2B DMRTA1
	12p13.2-p13.1	11.47-13.02	het del	1.55	many	>20	CDKN1B DUSP16 ETV6
11	6q23.1	135.35-135.71	gain of 1 copy	0.36	many	4	HBS1L MYB mir548a-2 AHI1
	9q (complete q arm)	59.00-140.00	gain of 1 copy (subclone)	81	many	>20	
	17p (complete p arm)	0-21.00	het del	21	many	>20	
12	6q16.1	95.10-95.11	het del	0.01	7	0	
	7p22.2	4.793-4.896	het del	0.103	many	3	KIAA0415 (at breakpoint) RADIL PAPOLB
	8q24.2	130.09-130.26	gain of 1 copy	0.17	many	0	
	9p21	21.97-22.00	hom del	0.03	many	2	CDKN2A

							CDKN2B
	13q14.2	47.88-47.97	hom del	0.09	many	3	RB1 (3' region) P2RY5 RCBTB2 (3' region)
		47.97-48.07	het del	0.1	many	1	RCBTB2 (5' region)
	16q21	65.15-65.17	het del	0.02	13	2	CMTM1 CKLF
13	1p33	49.69-49.77	het del	0.08	many	1	AGBL4
	2p21	43.86-43.93	gain of 1 copy	0.07	many	4	DYNC2LI1 ABCG5 ABCG8 LRPPRC
	9q21.32-q31.2	82.27-107.59	het del	25.32	many	>20	
	9q34.11-q34.13	130.50-133.01	het del	2.51	many	>20	SET and NUP214 (at breakpoint); SET-NUP214 fusion
	11p14.3-p11	25.19-44.38	het del	19.19	many	>20	WT1 LMO2 RAG1 RAG2 TRAF6
	17pter-p11	0-18.86	het del (subclone)	18.86	many	>20	
	gain of X chromosome (subclone)						
14	6q23.2	135.52-135.85	gain of 1 copy	0.33	many	3	MYB mir548a-2 AHI1
	8q24.2	130.15-130.65	gain of 1 copy	0.5	many	0	
	9p21	21.95-22.00	hom del	0.05	many	3	C9orf53 CDKN2A CDKN2B
	16q23.1	75.097-75.101	hom del	0.004	3	1	CNTNAP4
	Xp21.3	26.43-26.50	het del	0.07	many	1	VENTXP1
15	6p21.33	31.42-31.74	het del	0.32	many	20	HLA-B MICA HCP5 HCG26 MICB MCCD1 BAT1 ATP6V1G2 NFKB1L1 LTA TNF LTB LST1 NCR3 AIF1 BAT2 BAT3 APOM BAT4 C6orf47
	9q22-q31.3	95.39-110.98	het del	15.59	many	>25	PHF2 (at breakpoint) KLF4 TAL2 FANCC PTPDC1 many other genes
	13q13-q21	32.76-52.83	het del	20.07	many	>20	FOXO1 SMAD9 PHF11 RB1 many other genes
	17q11	25.59-27.29	het del	1.7	many	21	BLMH TMIGD1

							CPD GOS1R TBC1D29 LRRC37B2 SUZ12P CRLF3 ATAD5 C17orf42 ADAP2 RNF135 DPRXP4 NF1 OMG EVI2B EVI2A RAB11FIP4 C17orf79 UTP6 SUZ12 (at breakpoint)
16	5q35.1	170.95-172.8	het del	1.85	many	15	adjacent to TLX3 and NPM1 FBXW11 STK10 UBTD2 SH3PXD2B NEURL1B DUSP1 ERGIC1 LOC100268168 RLP26L1 ATP6VOE1 SNORA748 C5orf41 BNIP1 NKX2-5 STC2
	6q23.2	135.49-135.80	gain of 1 copy	0.31	many	3	MYB mir548a-2 AHI1
	14q24.1	67.70-70.15	het del	2.45	many	20	RAD51L1 (at breakpoint) ZFP36L1
	14q24.3-q32.12	77.10-93.16	het del	16.06	many	>25	CALM1 PTPN21
	14q32.12	93.40-94.64	het del	1.24	many	>20	DICER 1 (3' region)
	16q21	66.17-66.33	het del	0.16	many	8	CTCF RLTPR ACD PARD6A C16orf48 C16orf86 GFOD2 RANBP10 (at breakpoint)
	17q23.3	61.84-61.91	het del	0.07	many	1	PRKCA (intragenic)
	trisomy 21 (subclone)						
17	6q14	84.199-84.205	het del	0.006	4	0	
	6q22.31	121.55-121.57	het del	0.002	6	1	C6orf140 (intragenic)
	7p22.3	2.23-2.32	gain of 1 copy	0.09	many	4	MAD1L1 (at breakpoint) FTSJ2 NUDT1 SNX8
	7p21.3	13.06-13.24	gain of 1 copy	0.18	many	0	
	8q22.1	97.418-97.421	het del	0.003	3	0	
	13q31.3	92.263-92.267	het del	0.004	3	1	GPC5 (intragenic)
	19q13.43	57.45-57.46	het del	0.01	many	0	

	Yp11.2	102.51-103.65	hom del	1.14	4	1	TTTY22
18	4q25	109.21-109.30	het del	0.09	many	1	LEF1 (intragenic)
	4q31.33	154.50-154.72	het del	0.22	many	2	MND1 KIAA0922
	6q23.2	135.43-135.80	gain of 1 copy	0.37	many	3	MYB mir548a-2 AHI1
	7q32.1-q35	127.97-147.87	het del	19.9	many	>20	
	9p22.2	17.60-17.92	het del	0.32	many	1	SH3GL2
	9p21.3	20.42-20.61	het del	0.19	many	1	MLLT3
	9p21.3	21.58-21.85	het del	0.27	many	1	MTAP
		21.85-22.21	homo del	0.36	many	2	CDKN2A CDKN2B
		22.21-22.84	het del	0.63	many	1	DMRTA1
	11q13.1	63.79-63.87	het del	0.08	many	8	BAD GPR137 KCNK4 C11orf20 ESRRA HSPC152 PRDX5 HSPC152
	13q14.2	47.88-47.97	hom del	0.09	many	3	RB1 (3' region) P2RY5 RCBTB2 (3' region)
	17q21.2	39.19-39.95	het del	0.8	many	>20	
19	7q21.2	92.23-92.51	het del	0.28	many	1	CDK6 (5' region)
	14q32.2	98.40-98.59	het del	0.19	many	0	adjacent to BCL11B
	17q24.2	64.78-64.81	gain of 1 copy	0.03	11	1	ABCA5
20	1p36.31-p36.33	2.37-3.44	het del	1.07	many	12	
		3.44-6.10	homo del	2.66	many	17	TP73 CHD5 (at breakpoint)
		6.10-6.64	het del	0.49	many	20	CHD5 (at breakpoint)
	1q31.3	197.33-198.17	het del	0.84	many	0	
	2p24.1	23.90-25.76	het del	1.86	many	21	ATAD2B (in breakpoint) UBXN2A MFSD2B C2orf44 FKBP1B SF3B14 TP53I3 PFN4 LOC375190 C2orf84 ITSN2 NCOA1 C2orf79 CENPO ADCY3 DNAJC27 EFR3B POMC DNMT3A mir-1301 DTNB
	6q24.3-qter	146.42-169.07	het del	22.65	many	>25	
	7pter-p14.1	0-38.26	gain of 1 copy (subclone)	38.26	many	>20	
	7q34-qter	142.03-157.56	het del	15.53	many	>20	
	9p21	19.53-21.09	het del	1.56	many	5	SLC24A2 MLLT3 KIAA1797 PTPLAD2 IFNB1

		21.09-21.94	homo del	0.9	many	>20	CDKN2A
		21.94-22.92	het del	0.98	many	2	CDKN2B DMRTA1
	10q24.32-q25.1	104.60-106.14	het del	1.54	many	25	AS3MT CNNM2 NT5C2 LOC729020 INA PCGF6 TAF5 mir-1307 USMG5 PDCD11 CALHM2 CALHM1 CALHM3 NEURL SH3PXD2A OBFC1 SLK mir-936 COL17A1 C10orf78 C10orf79 GSTO1 GSTO2 ITPRIP CCDC147 (at breapoint)
	13q31.2-qter	88.71-113.12	gain of 1 copy	24.41	many	>20	
	16q21-22.1	66.21-66.71	het del	0.5	many	>20	CTCF, NFATC3
	21q22.12-q22.2	34.90-40.66	het del	5.76	many	>20	RUNX1 ERG
21	6q23.2	135.49-135.74	gain of 1 copy	0.25	many	3	MYB mir548a-2 AHI1
	7q21.3-q31.2	92.24-114.63	het del	22.39	many	>20	CDK6 (at breakpoint)
	9p21	21.56-22.98	hom del	1.42	many	5	MTAP C9orf53 CDKN2A CDKN2B DMRTA1
	11q14.1-q24.1	83.52-123.28	het del	39.76	many	>20	PICALM
	19p13.2	10.75-11.51	het del	0.76	many	>25	CARM1 EPOR SMARCA4
22	1p33	47.46-47.55	het del	0.09	many	2	TAL1 STIL
	9p21.3	21.82-21.98	hom del	0.16	many	3	MTAP C9orf53 CDKN2A
23	3q26.1	168.51-168.52	het del	0.01	4	1	ZBBX (intragenic)
24	4pter-p15.33	0-10.95	het del	10.95	many	>20	
	9p (complete chromosome arm)	0-55	het del	55	many	>20	
	9p21.3	19.98-22.32	homo del	2.34	many	>20	CDKN2A CDKN2B
	13q31.1-qter	84.05-114	gain of 1 copy (subclone)	29.95	many	>20	
	17pter-p11.2	0-19.08	het del	19.08	many	>20	
	17p11.2-qter	19.08-78.6	gain of 1 copy	59.52	many	>20	
	Yq11.22	14.64-14.89	gain of 1 copy	0.25	many	2	VCY VCY1B
25	9p21	21.12-21.80	het del	0.68	many	17	
		21.80-21.98	homo del	0.18	many	3	MTAP C9orf53

							CDKN2A
		21.98-22.23	het del	0.25	many	1	CDKN2B
26	1p31.1	69.86-69.87	het del	0.01	5	0	
	17q25.3	78.55-78.65	gain of 1 copy (subclone)	0.1	many	2	B3GNTL1 METRNL
27	5q21.1-5q31.2	97.98-138.97	het del	40.99	many	>20	
	5q35.1-qter	170.72-180.64	het del	9.92	many	>20	NPM1 (at breakpoint) FBXW11 deleted
	6pter-p21.1	0-30.49	het del	30.49	many	>20	
	6p21.2	36.91-40.35	het del	3.44	many	>20	
	6p21.1	41.08-43.51	het del	2.43	many	>25	
	6p12.3-q14.1	49.10-81.53	het del	32.43	many	>20	
28	2p21	44.38-44.49	het del	0.11	many	3	SLC3A1 PREPL C2orf34
	trisomy chr 6 (subclone)						
	11q14.1-11q14.2	85.20-86.10	het del	0.9	many	6	ME3 CCDC81 C11orf73 EED PICALM CCDC83
	17q21.32-qter	45.81-78.63	gain of 1 copy	32.82	many	>25	
29	1p36.23-1p36.31	6.14-10.38	het del	4.24	many	>20	CAMTA1 CHD5 (at breakpoint)
	2q37.1-37.3	232.90-240.71	het del	7.81	many	>20	HDAC4 CXCR7 INPP5D
	4q26-qter	118.37-191.15	gain of 1 copy	72.78	many	>20	
	8q23.1-8q24.11	108.62-118.45	het del	9.83	many	19	RSPO2 EIF3E TTC35 TMEM74 TRHR NUDCD1 ENY2 PKHD1L1 EBAG9 GOLSYN KCNV1 CSMD3 mir-2053 TRPS1 EIF3H UTP23 RAD21 C8orf85 SLC30A8
	9q34.12-9q34.2	130.51-133.05	het del	2.54	many	>20	SET and NUP214 at breakpoints
	12p13.1-12p13.31	8.48-14.65	het del	6.17	many	>20	CDKN1B ETV6 DUSP16
	12q23.3	108.38-109.79	het del	1.41	many	24	UBE3B (at breakpoint) MMAB MVK MGC14436 C12orf34 TRPV4 GLTP TCHP GIT2 ANKRD13A

							IFT81 ATP2A2 ANAPC7 ARPC3 GPN3 C12orf24 VSP29 RAD9B PPTC7 TCTN1 HVCN1 PPP1CC CCDC63 (at breakpoint)
	13q14.2-13q14.3	47.8-52.05	het del	4.25	many	>20	RB1 (3' region) DLEU7 miR-15/16a
	18q22.1-qter	62.37-76.11	het del	13.74	many	>25	
	19q13.33-q13.41	50.88-53.53	het del	2.65	many	>25	
30	9p21	21.95-22.35	hom del	0.4	many	3	C9orf53 CDKN2A CDKN2B
	14q32.2	98.72-98.83	het del	0.11	many	1	BCL11B (5' part)
31	17q11	26.05-27.45	het del	1.4	many	17	NF1
32	1p35	25.27-25.30	het del	0.03	8	0	adjacent to to RUNX3
	1q43	23.76-23.80	het del	0.04	many	1	CHRM3
	17p13.2	6.90-6.98	gain of 1 copy (subclone)	0.77	many	2	CLEC10A ASGR2
33	5q22.2	112.29-112.30	het del	0.01	4	0	
	7q33	136.30-136.31	het del	0.01	5	1	CHRM2
	9p21	21.93-22.03	hom del	0.1	many	3	C9orf53 CDKN2A CDKN2B
	9q21.13	77.19-77.20	het del	0.01	3	0	
	16p12.1	27.24-27.26	het del	0.02	6	1	IL4R
34	8p22	13.09-13.18	het del	0.09	many	1	DLC1
35	no defects found						
36	trisomy chr 4 (subclone)						
	6q24.3	147.89-147.91	het del	0.02	4	1	SAMD5 (intragenic)
	7q31.31	119.15-119.26	het del	0.11	many	0	
	15q22.2	57.69-57.71	het del	0.02	9	1	GCNT3
	16p13.3-q21 (subclone)	4.77-60.12	Gain 1 copy	55.35	many		
	21q21.1-q21.2	21.71-23.92	het del	2.21	many	1	NCAM2 (at breakpoint)
37	3p13	72.17-72.54	het del	0.37	many	1	RYBP
	trisomy chr 6 (subclone)						
	6p21-22	30.99-32.72	het del	1.73	many	>20	NOTCH4 TNF many other genes
	7p12.2-pter	0-50.24	het del	50.24	many	>20	
	7p12.2-qter	50.24-158.82	gain of 1 copy	108.58	many	>20	
	8p21.2-pter	0-23.55	het del	23.55	many	>20	
	8p21.2-p21.2	23.55-27.34	gain of 1 copy	3.79	many	15	EBF2 (at breakpoint) NKX3-1 NKX2-6 STC1 ADAM28 ADAMDEC1 ADAM7 NEFM NEFL DOCK5 GNRH1 KCTD9 CDCA2

							mir548h-4
							PTK2B (at breakpoint)
	8p21.2-p12	27.34-28.89	gain of 2 copies	1.55	many	17	PTK2B (at breakpoint)
							CHRNA2
							EPHX2
							CLU
							SCARA3
							CCDC25
							ESCO2
							PBK
							SCARA5
							ELP3
							PNOC
							ZNF395
							FBXO16
							FZD3
							EXTL3
							INTS9
							HMBOX1 (at breakpoint)
	8p12	28.89-30.51	gain of 1 copy	1.62	many	10	
	8p12	32.22-34.47	loss of 1 copy	2.25	many	6	NRG1 (at breakpoint)
							FUT10
							MAK16
							C8orf41
							RNF122
							DUSP26
	8p12-q21.3	34.47-89.02	gain of 1 copy	54.55	many	>20	
	8q21.3	89.02-90.19	loss of 1 copy	1.17	many	1	MMP16
	8q21-3-qter	90.19-146.3	gain of 1 copy	56.11	many	>20	
	9p21	20.60-21.89	het del (subclone)	1.29	many	>20	
		21.89-22.04	hom del (subclone)	0.15	many	3	C9orf53
							CDKN2A
							CDKN2B
38	7p15.2-p14.3	27.3-31.8	het del	4.5	many	>20	HOXA gene cluster
	7q11.22	65.9-70.1	het del	4.2	many	7	RABGEF1
							C7orf42
							SBDS
							TYW1
							PMS2L4
							STAG3L4
							AUTS2
	7q21.11-q21.13	84.7-89.6	het del	4.9	many	17	
	7q22.2-q31.33	104.6-126.5	het del	21.9	many	>20	
	7q34	139.40-139.88	het del	0.48	many	6	DENND2A (at breakpoint)
							MKRN1
							RAB19
							SLC37A3
							JHDM1D
							PARP12 (at breakpoint)
	7q35-q36	142.67-150.97	het del	8.3	many	>20	
	14q23.1-24.2	60.52-70.86	het del	10.34	many	>20	ZPF36L1
	14q32.2	98.05-98.65	het del	0.6	many	1	C14orf177
							defect is next to BCL11B gene
	16q24.1-qter	83.83-88.69	het del	0.14	many	>25	FANCA
	18q12.1-q12.2	24.4-33.37	het del	8.97	many	>20	part of NOL4 gene not deleted
							breakpoint in BRUNOL4
39	7p22.2	3.803-3.824	het del	0.021	10	1	SDK1 (intragenic)
40	11q13.4-qter	73.76-134.45	gain of 1 copy	60.69	many	>20	
	15q22.32-qter	64.71-100.30	het del	35.59	many	>20	
41	8q21.13	82.62-84.45	gain of 1 copy	1.83	many	5	SNX16
							CHMP4C
							ZFAND1
							SLC10A5

							IMPA1
	13q14.12	44.53-45.82	het del	1.29	many	14	GTF2F2 KCTD4 TPT1 LOC100190939 SNORA31 SLC25A30 COG3 FLJ32682 SPERT SIAH3 ZC3H13 CPB2 LCP1 C13orf18 (in breakpoint)
	13q14.3	49.38-51.81	het del	2.43	many	>20	DLEU7 miR-15/16a
	17q11	25.59-27.29	het del	1.7	many	>20	NF1
	20q11.21	30.48-30.68	het del	0.2	many	2	ASXL1 (3' region) c20orf112
42	7p (complete arm)	0-60	het del (small subclone)	60	many	>20	
	7q (complete arm)	60-159	gain of 1 copy (small subclone	99	many	>20	
	12p13.31-12.3	9.17-15.97	het del	6.8	many	>20	CDKN1B DUSP16 ETV6
	17pter-p11.2	0-19	het del	19	many	>20	
	17p11.2-qter	19-78.65	gain of 1 copy	59.65	many	>20	
43	4q21.22	84.088-84.098	het del	0.01	5	1	LIN54
	4q27	122.81-122.82	het del	0.01	5	1	ANXA5
	5p14.3-pter	0-22.50	het del (subclone)	22.5	many	>25	CDH12 (in breakpoint)
	5q22.1-qter	110.21-180	het del (subclone)	69.79	many	>25	
	7p	complete p arm	het del (subclone)	60	many	>20	
	7q36.3	156.328-156.336	het del	0.008	4	1	LMBR1 (intragenic)
	12p12.1-pter	0-24.25	het del (subclone)	24.25	many	>20	SOX5 (at breakpoint) CDKN1B
	16q23.3	83.40-83.44	het del	0.04	many	1	CRISPLD2 (5' region)
	19p13.12	15.528-15.540	het del	0.012	5	0	
44	4q22.1	93.52-94.64	het del	1.12	many	1	GRID2
	4q25	111.81-113.29	het del	1.48	many	1	c4orf32 (at breakpoint)
	4q28.1-q28.3	126.64-132.21	het del	5.57	many	13	FAT4 (at breakpoint) mir-2054 INTU SLC25A31 HSPA4L PLK4 MFSD8 C4orf29 LARP2 PGRMC2 PHF17 SCLT1 C4orf33
	4q28.3	134.62-138.38	het del	3.76	many	1	PABPC4L
	4q30	140.83-146.36	het del	5.53	many	21	MGST2 (at breakpoint) MAML3 SCOC CLGN ELMOD2 UCP1 TBC1D9 RNF150 ZNF330 IL15

							INPP4B USP38 GAB1 SMARCA5 LOC441046 GYPE GYPB GYPA HHIP ANAPC10 ABCE1 (at breakpoint)
	4q31.22-q32.1	147.66-157.54	het del	9.88	many	>20	FBXW7
	trisomy chr 6 (subclone)						
	9p22.2-centromere	18.63-45 (centromere)	het del	26.37	many	>20	CDKN2A CDKN2B
	12p13.2-p12.3	9.83-14.62	het del	4.79	many	>20	CDKN1B ETV6 DUSP16
	13q13.3-q21.32	37.59-65.69	het del	28.1	many	>20	RB1
	14q32.2-qter	97.89-106.36	gain of 1 copy (subclone)	8.47	many	>20	
	15pter-q21.1	0-46.57	het del	46.57	many	>20	FBN1 (at breakpoint)
	trisomy chr 16 (subclone) from pter up to	0-84.82	gain of 1 copy	84.82	many	>20	
45	1p36.32	2.68-3.68	het del	1.0	many	13	TP73
	1p36.23-1p36.22	5.86-8.34	het del	2.48	many	>20	CHD5
	1p35.3	29.25-30.35	het del	1.1	many	5	EPB41 (at breakpoint) TMEM200B SFRS4 MECR PTPRU
	1p34.3	36.22-37.48	het del	1.26	many	14	EIF2C3 (at breakpoint) TEKT2 ADPRHL2 COL8A2 TRAPPC3 MAP7D1 THRAP3 C1orf113 STK40 OSCP1 MRPS15 CSF3R GRIK3
	2q34	212.98-213.17	het del	0.19	many	1	ERBB4 (5' region)
	2q37.3	238.98-241.50	het del	2.52	many	20	
	3p24.3	17.86-18.04	gain of 1 copy	0.18	many	0	
	9p21.3	20.70-21.90	het del	1.2	many	>20	
		21.90-22.15	hom del	0.25	many	3	C9orf53 CDKN2A CDKN2B
		22.15-23.46	het del	1.31	many	1	DMRTA1
	10q22.2	74.25-76.84	het del	2.59	many	>25	
	10q23.1	83.11-85.08	het del	1.97	many	1	NRG3
	10q26.2-q26.3	128.55-133.19	het del	4.64	many	11	DOCK1 (at the breapoint) c10orf141 NPS FOXI2 CLRN3 PTPRE MKI-67 MGMT EBF3 GLRX3 TCERG1L

	11p14.3	24.79-26.56	het del	1.77	many	3	LUZP3 (at the breakpoint) MUC15 ANO3 (at the breakpoint)
	11p13	31.65-34.51	het del	2.86	many	>20	WT1 LMO2
	Xq13.1-q22.3	70.75-107.98	het del	37.23	many	>25	
46	No defects found						
47	3p14.1-centromere	63.83-90.37	het del	26.54	many	>20	
	4q31-qter	152.55-191.15	het del	38.6	many	>20	FBXW7
	5q34-qter	170.72-180.64	het del	9.92	many	>20	NPM1 FBXW11 DUSP1
	9p21.3-centromere	21.11-22.45	hom del	1.34	many	>20	CDKN2A CDKN2B
		22.45-45	het del	22.55	many	>20	
	13q13.3-q31.1	43.59-80.60	het del	37.01	many	>20	RB1
48	3p13	72.58-72.71	het del	0.13	many	0	adjacent to RYBP
	9p21	21.64-22.88	hom del	1.24	many	5	MTAP C9orf53 CDKN2A CDKN2B DMRTA1
		22.88-24.04	het del	1.16	many	1	ELAVL2
	10q23.31	92.65-92.70	het del	0.05	many	2	RPP30 (at breakpoint) ANKRD1
	13q14.11	44.70-44.72	het del	0.02	8	1	GTF2F2
	13q14.2	47.88-47.97	hom del	0.09	many	3	RB1 (3' region) P2RY5 RCBTB2 (3' Part)
		47.97-48.07	het del	0.1	many	1	RCBTB2 (5' Part)
	19p13.3	3.70-5.38	het del	1.68	many	>25	
49	6q24.1	138.553-138.558	het del	0.005	4	1	KIAA1244
	7q21.3	94.551-94.558	het del	0.007	5	1	PPP1R9A
	8q24.12	119.487-119.494	het del	0.07	5	1	SAMD12
	10p11.22	32.5661-32.5662	het del	0.001	3	0	
50	5pter-q11.2	0-55.70	gain of 1 copy	55.70	many	>20	
	5q11.2-qter	55.70-180.48	het del	124.78	many	>20	
	9pter-p13.2	0-37.42	het del	37.42	many	>20	CDKN2A CDKN2B
	10q21.1	56.48-58.49	het del	2.01	many	1	ZWINT
	13q14.11-q14.12	40.62-52.67	het del	12.05	many	>20	RB1
	13q32.2-q33.1	98.51-103.05	het del	4.54	many	>20	
	17pter-p13.1	0-10.93	het del	10.93	many	>20	TP53
	17p12-p11.2	14.44-20.66	het del	6.22	many	>25	
	19q13.32	58.58-59.73	het del	1.15	many	>25	
51	7q34	142.54-142.60	het del	0.06	many	2	PIP TAS2R39
	7q34-q36.3	143.92-156.84	het del	12.92	many	>20	TPK1 (at breakpoint) MLL3 PTPRU
52	2q34	212.72-212.82	het del	0.1	many	1	ERBB4 (intragenic)
	3p22.3	35.66-35.72	gain 1 copy	0.06	many	1	ARPP-21
	trisomy chr 8						
	trisomy chr 21						
53	1p33	47.47-47.55	het del	0.08	many	2	STIL TAL1
	5pter-p12	0-42.53	gain of 1 copy	42.53	many	>20	
	13q31.1-qter	84.27-114	gain of 1 copy	29.73	many	>20	

Supplementary Table 4. Genetic lessions identified by DNA sequencing. 1=mutated; 0=wild type

Sample	*NOTCH1*	*FBXW7*	*IDH1*	*IDH2*	*FLT3*	*NRAS*	*DNMT3A*	*GATA3*	*RUNX1*	*PTEN*	*IL7R*	*DNM2*	*PHF6*	*BCL11B*	*WT1*	*SUZ12*	*EZH2*	*ETV6*
1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0
2	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1
3	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1
4	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	1	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	0
9	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
11	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
12	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
13	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	0	1
16	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
17	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0
19	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0
20	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	0
21	0	1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
22	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
28	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0
29	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1
30	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
31	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
32	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
33	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
38	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
39	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
40	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
41	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0
42	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1
43	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
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47	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
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50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
51	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1
52	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

Supplementary Table 5. Cox regression model using Lasso.

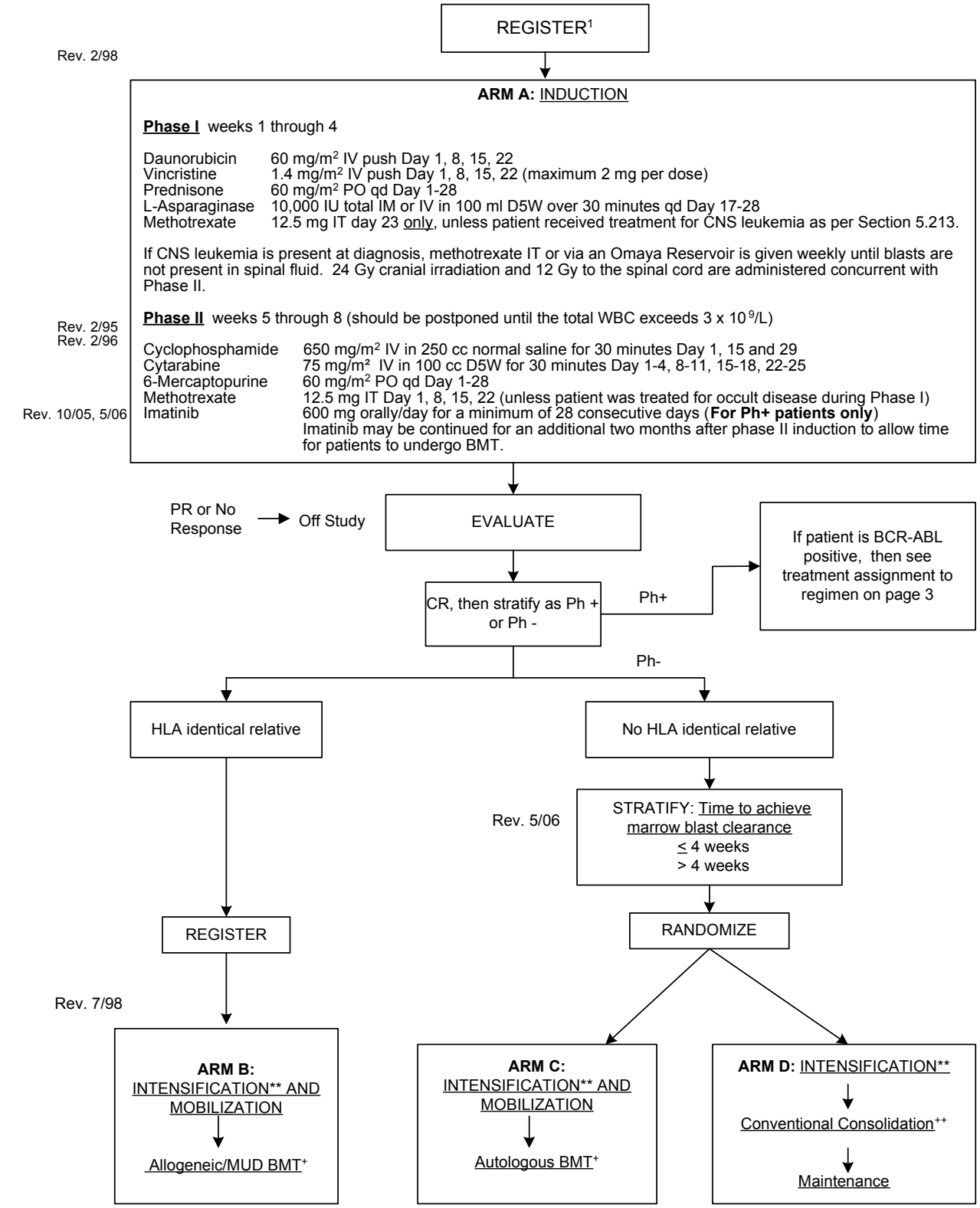
	coef	exp(coef)	se(coef)	z	Pr(>|z|)
CD62L	-1.15856	0.31394	0.44970	-2.576	0.009986*
CD8	-0.04396	0.95699	0.53958	-0.081	0.935064
CD13	1.32619	3.76667	0.51708	2.565	0.010325*
DNMT3A	2.14861	8.57297	0.67061	3.204	0.001355*
TP53_17q	2.39930	11.01550	0.62363	3.847	0.000119*
CDKN2A/2B_hom	-0.87772	0.41573	0.67528	-1.300	0.193676
NOTCH1/FBXW7	-0.88880	0.41115	0.44743	-1.986	0.046984*

	exp(coef)	exp(-coef)	lower .95	upper .95
CD62L	0.3139	3.18535	0.13004	0.7579
CD8	0.9570	1.04494	0.33237	2.7555
CD13	3.7667	0.26549	1.36715	10.3776
DNMT3A	8.5730	0.11665	2.30308	31.9119
TP53_17q	11.0155	0.09078	3.24468	37.3970
CDKN2A/2B_hom	0.4157	2.40540	0.11067	1.5618
NOTCH1/FBXW7	0.4111	2.43221	0.17106	0.9882

Rev. 7/04

SCHEMA

Rev. 12/04 ***AS OF ADDENDUM #12, ALPHA-INTERFERON USE HAS BEEN DISCONTINUED FOR ALLOGENEIC/MUD BMT, AUTOLOGOUS BMT, AND MAINTENANCE THERAPY.***



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Rev.12/04

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Begin 4 weeks from day one of Cycle **II** or when WBC > 3.0 x 10^9/L

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	6-Thioguanine	60 mg/m^2 PO Day 29-42

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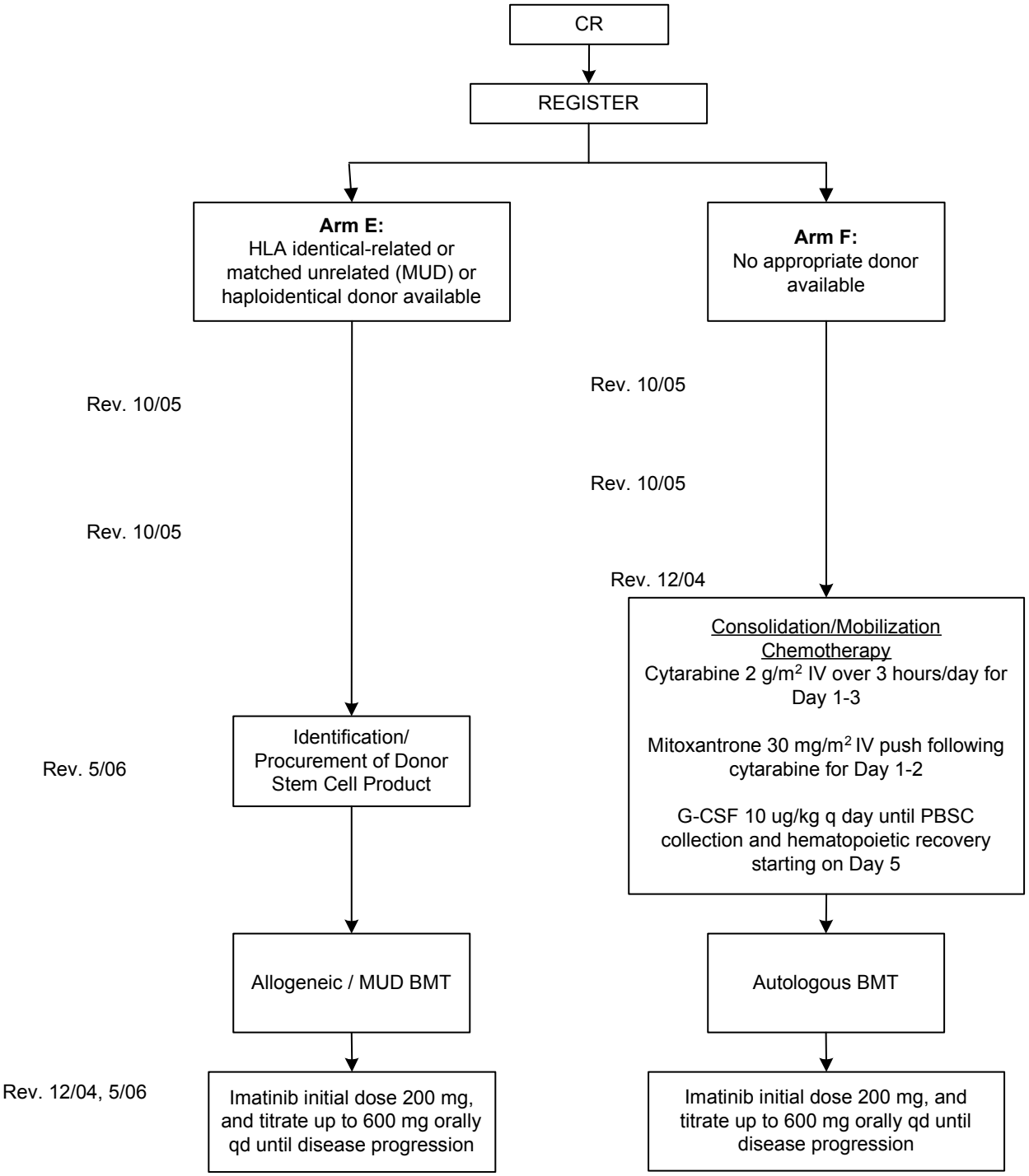

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REVISED
Revised 12/04, Addendum #14
Revised 5/06, Addendum #16
Revised 2/07, Addendum #17

EASTERN COOPERATIVE ONCOLOGY GROUP

Phase III Randomized Trial of Autologous and Allogeneic Bone Marrow Transplantation versus Intensive Conventional Chemotherapy in Acute Lymphoblastic Leukemia in First Remission

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Rev. 7/04	ECOG RADIATION ONCOLOGY CO-CHAIR:	Richard Whittington, M.D.
Rev. 2/95, 7/04	ECOG LEUKEMIA COMMITTEE CHAIR:	Martin Tallman, M.D.
Rev. 2/98	ECOG CYTOGENETICS CO-CHAIR:	Gordon Dewald, Ph.D.

Rev. 5/06

Version date: August 22, 2007

STUDY PARTICIPANTS
ECOG Entire Group
Medical Research Council
See attachment pages i-iii for participating transplant centers

STUDY ACTIVATED
April 1993

Addendum #1, 5/93 - Dr. Michael Chen added to Title Page, Replace pages: Index; BMT update; 9 - 18; 34; 58; Appendix I; Appendix III; Appendix VI and add Appendix VIII.

Addendum #2, 2/95-ENTIRE DOCUMENT REVISED; Replaced Peter Wiernik, M.D. with Jacob Rowe, M.D. (Title Page). Revised Cycles II and IV; put "for Ph+ randomized patients" after IFN-Alfa dose (Schema). Revised address for registration procedures (Section 4.0). Revised days for cyclophosphamide administration (Schema and Section 5.2221). Revised weeks for intensive therapy to beginning of week 12 and ending on week 16 (Schema and Section 5.31). Added "conventional" (Section 5.321). Added "IV" and "2 1/2 years" to methotrexate administration; added "with prednisone" to vincristine administration (Section 5.3221).Updated ADR address and phone number (Section 5.4111). Corrected numbering (Section 5. 236 and 5.347). Added PIN Contact Person (Index Page). Added BM aspirate and biopsy, PFT, and creatinine clearance to chart; changed footnote #3 to 28 days (Section 7.0). Added AML/MDS side effects and updated drug information (Section 8.0 and Consent Form). Updated Pathology Coordinating Office address (Section 10.11). Changed 10 fractions to 12 (Section 5.311 and Appendix VIII). Updated TBI table to include PA and AP sites (Appendix VI). Updated BMT and TBI Centers. Revised consent form language from 1st person to 2nd person (Appendix I); Revised Phase I use of Methotrexate (Schema). Moved 5.2221 of original activated copy to 5.2212 under Phase I (Section 5.22). Updated Fractionated TBI information (Section 5.3331). Clarified under CR that HLA identical siblings or Ph+ patients must be $\leq$ 50 (Schema). Changed BM aspirate after Phase I from 21 days to 28 days (Section 5.2212).

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Addendum #3, 2/96 - GM-CSF supplier and administration changed (Schema, Sec 5.336, 5.345, 8.8, Appendix I). Interferon Alpha availability information revised to refer to Interferon Alpha 2b only (Section 8.910). Sec 3.111 updated to specify signed, informed consent; Protocol updated to reflect MUD BMT acceptable (Schema, Sec 3.2, 4.0, 4.121, 5.1, 5.31, 5.311, 5.332); ECOG name and address updated (Sec 4.1, 4.3, 10.11, 11.0); Birthdate specified as MM/DD/YY (Sec 4.11332); Asparaginase availability information updated (Sec 5.2231 and 8.19); Information re:use of Interferon for Ph+ patients updated (Schema, Sec 5.3223 and 5.3461); Sec 5.32231 added; Sec 5.3222 and 5.3223 renumbered due to the addition of section 5.32231; ADR reporting requirements revised (Sec 5.4); 2nd Primary Cancer table/form added (Sec 5.45 and 11.0); Study parameters table updated to show creatinine clearance, cardiac ejection fraction and PFT prior to intensification (Sec 7.0); "if contacted per section II, in Appendix VIII" added to footnote 7 (Sec 7.0); ECOG Follow-Up forms added (Sec 11.0); Clarified length of Maintenance Therapy is 2 ½ years (Schema, Sec 5.3222). Cytarabine units corrected (Schema); Spelling and formatting corrected as necessary.

Addendum #4, 5/96 - Asparaginase (Erwinia preparation) availability and ADR reporting information corrected (Secs 5.2231, 8.19, & Appendix IX); GM-CSF deleted from the list of investigational agents in sec 5.44; Sec. 8.81 revised to specify Immunex as the manufacturer of the GM-CSF to be used in this trial; The reference to 250 mcg vials of GM-CSF deleted in section 8.9; A note added to section 8.9 that states that although the GM-CSF used in this trial is the commercial Immunex product, it must be accounted for by the pharmacy according to the NCI's usual guidelines for investigational drugs.

Addendum #5, 2/98 - Statistician changed (cover); Sec. 11.0 added to replace E1485 (Cover, Index, Schema, Secs. 3.12, 4.1, 4.3, 7.0, 10.14, 10.15, 11.0, 12.2, App. I); Updated PCO address (Sec. 10.0); Renumbered Sections (Secs. 12.0, 13.0, 14.0).

Addendum #6, 7/98 - Cycle 2 Consolidation Clarification (Schema); Clarification re: basing drug doses on weight (Schema); Changed percent cellularity for BMT (Schema); Updated Study Chair address (Index); Updated PIN Contact (Index); Randomization correction (Sec. 4.2); Typo fixed (Schema, Secs. 5.2221, 7.0); Dr. Chen's phone # added (Sec. 5.3331); Info deleted re: Stratification (Sec. 9.2); Added Sec. 5.324 permitting stem cell collection from bone marrow, peripheral blood, or both and describing when peripheral blood cells should be collected; Updated shipping instructions (Sec. 11.113); Revised harvest instructions (Schema); Changed "marrow" to "stem cells" (Sec. 5.1); Corrected instructions re: weight and drug dosing (Schema); Updated time points in footnote 4 (Sec. 7.0); Updated BMT ADR guidelines (Sec. 5.44).

Addendum #7, 5/99 - Added ECOG Pathology Submission Guidelines (Index, App. X); Added exemption for South Africa and Rambam Medical Center (Secs. 3.12, 11.0); Updated Pathology Review instructions (Sec. 10.0); Changed shipping address and phone (Sec 11.113); Added information about peripheral blood cell collection and transplantation and pathology sample storage to consent form (App. I).

Addendum #8, 10/00 - Changed statistician (Cover); Added notes (Sec. 5.223); Added dose administration for PEG and Erwinia Asparaginase (Secs. 5.2232, 5.2233); Renumbered sections (Sec. 5.2234, 5.2235); Updated QARC address (Sec. 5.3331); Updated footnote 2 (Sec. 7); Added page 9a.

Addendum #9, 4/01 - Updated stat section (Sec. 9.1).

Addendum #10, 2/03 - Updated registration paragraph (Sec. 4.11); Updated ECOG contact info (Sec. 4.1, 12.1); Updated Sec. 4.114 and 4.1224 re: Eligibility verification; Updated registration procedures in Sec. 4.1211; Changed "10,000 units/m^2" to "10,000 total" (Schema, Secs. 5.221, 5.31); Replaced entire Section8.16; Added "/Patient" to headers (Secs. 8.111, 8.3111, 8.412, 8.511, 8.610, 8.711, 8.811, 8.912, 8.1011, 8.1111, 8.1212, 8.139, 8.1412, 8.1512); Updated PCO contact info (Sec. 10.13, App. X, p. 2,3); Added Sec. 12.3; Added App. X, p. 5.

Addendum #11, 3/03 - Updated the new Adverse Event Reporting requirements (Sec. 5.4); Updated Records to be kept to reflect AE changes (Sec. 12.0); Added Appendix XI (Index).

Addendum #12, 7/04 - ENTIRE DOCUMENT REVISED

Addendum #13, 7/04

Addendum #14, 12/04

Addendum #15, 10/05

Addendum #16, 5/06

Addendum #17, 2/07

Addendum #18, 10/07

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Rev. 12/04

Rev. 7/04

SCHEMA

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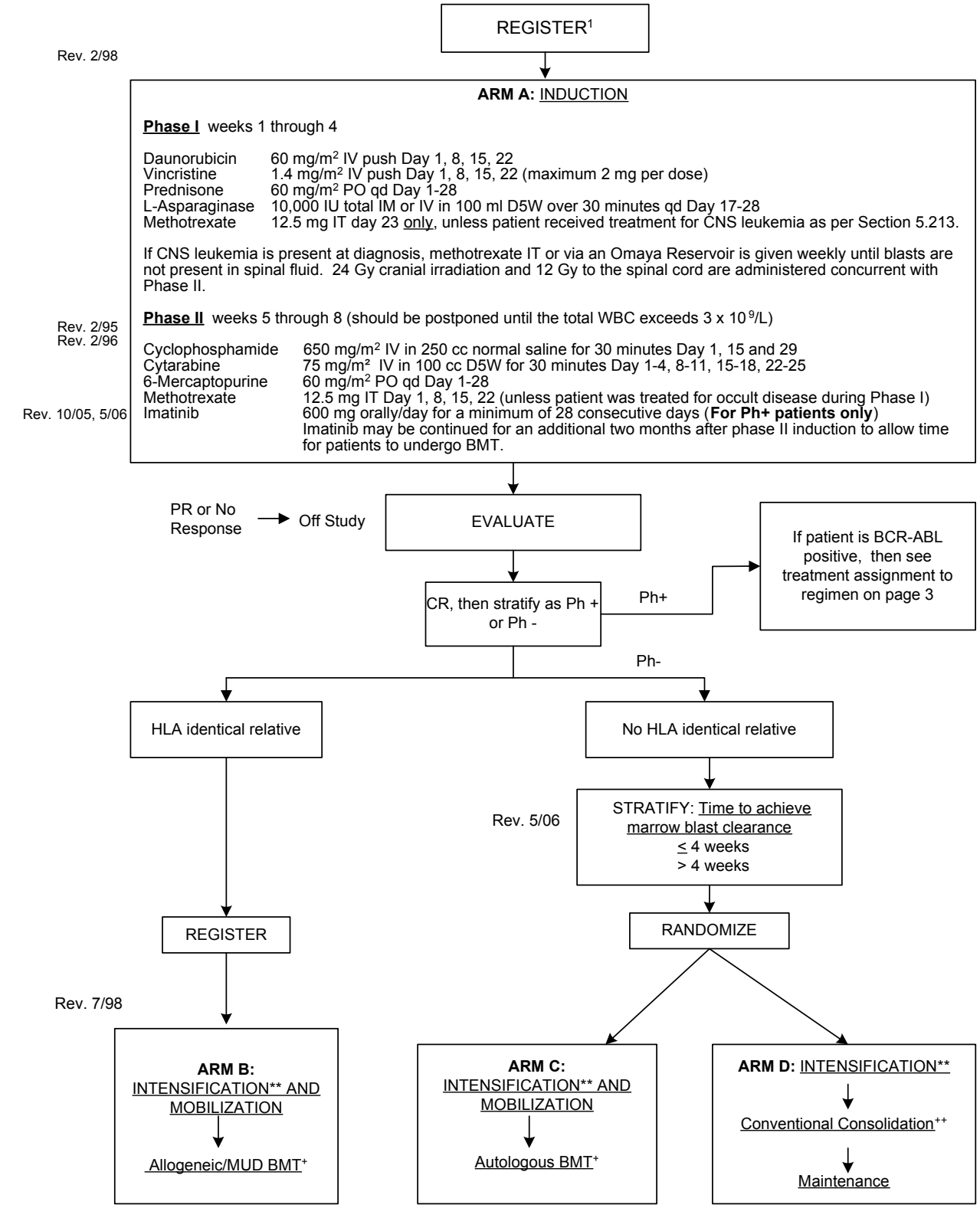

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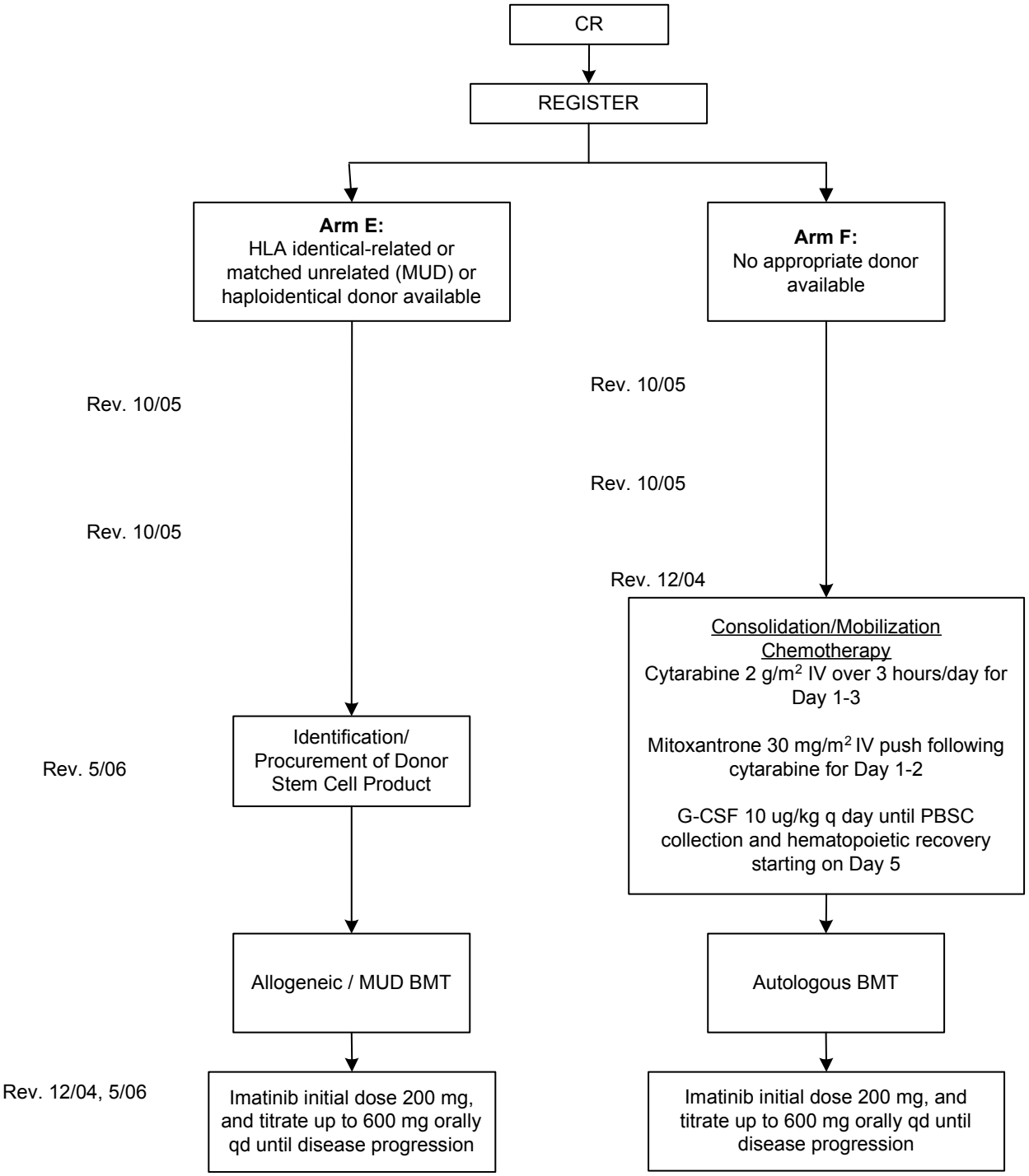

1.0 INTRODUCTION

Rev. 7/04 **NOTE:** Both allogeneic and autologous stem cell transplant (SCT) will refer to peripheral blood or bone marrow transplant.

Rev. 7/04 ### 1.1 Background

Adult patients with acute lymphoblastic leukemia (ALL) currently have a 75% chance or more to enter first complete remission (CR) with modern chemotherapy (1-3). Most patients, however, eventually relapse (4-8). The best approach to prevent relapse using consolidation therapy is controversial. Results of chemotherapy given as intensive consolidation followed by maintenance therapy have been highly variable with prolonged remissions being achieved in the range of 10% to 42% (1-3, 9, 10). Patients exhibiting a high risk for relapse -- defined as age more than 35 years, leukocyte count at diagnosis greater than 30 x 10^9/L, null cell phenotype, presence of Philadelphia chromosome (Ph+) and achievement of remission after more than 4 weeks of intensive chemotherapy -- have an overall probability of continuous CR at 5 years of only 18-28%. This result compares poorly with the few patients lacking these variables, who have a 60% 5 year disease-free survival (DFS)(2-3).

Use of allogeneic SCT in first CR ALL results in a 40% to 63% DFS for 2 to 10 years (11-13). The actuarial relapse rate for this group ranged from 10% to 40% with more than 90% of the recurrence occurring within the first 2 years.

Allogeneic SCT however is only available for the one third of patients, those who have a histocompatible sibling. The benefit of allogeneic SCT also declines with increasing age due to the heightened risk of death from infection and the increasing frequency and severity of graft-versus-host disease (GVHD) (14-16). In one recent study, older age (> 18 years) was the predominant clinical factor associated with acute GVHD (17). Of adults with ALL, > 50% are > 40 years old and this age group is less frequently referred for allogeneic SCT because of substantial hazards.

Autologous SCT is an alternative approach to allogeneic transplantation. Autologous SCT does not require a histocompatible donor, lacks the risk of GVHD, and can be used more safely in patients > 40 years old. Although autologous SCT permits the same intensive therapy as allogeneic transplantation, it lacks the potential benefit of graft-versus-leukemia, which in man is associated with GVHD (15, 16). Additionally, it has the potential disadvantage of reinfusion of stem cells contaminated with leukemia cells.

Nevertheless, autologous SCT is effective in ALL. When used in patients at high risk for relapsed ALL in association with *in vitro* bone stem cells purging, the fraction of "cured" patients following autologous SCT compares favorably with results in the same group treated with allogeneic SCT (18-20). The value of stem cells purging, however, has never been firmly established.

Autologous SCT in the European experience of more than 200 patients has shown a 41% DFS rate at 56 months for standard risk patients transplanted in CR, with no statistically significant difference between purging and non-purging (21). The 4 year probability of relapse was only 26± 12% (95% confidence interval) in this group (22). More recently Carey *et al.* reported their autologous SCT results for lymphoma and ALL without purging (23).

Actuarial DFS in the 13 patients with ALL in first CR receiving autologous SCT was 48% with a follow-up of 3 years. Gilmore *et al.* also reported a 32% DFS at 7 years among 27 high risk ALL patients in whom *in vitro* purging appeared not to improve patient outcome (24). Thus, autologous SCT in ALL without purging can be highly effective.

As noted above, treatment of Ph+ ALL with combination chemotherapy can produce an initial high rate of complete remissions, but with consolidation and maintenance chemotherapy alone, these patients have a dismal outcome with survival rates under 10% at four years (25-31).

Because of these poor results with chemotherapy, allogeneic blood and stem cell transplant (allo SCT) has been proposed as a treatment for Ph+ ALL. Results from multiple case series

have recently been summarized (32). For patients undergoing allogeneic stem cell transplant in first remission, two-year disease-free survival rates from 30-70% have been demonstrated using sources of stem cells from related or unrelated donors. Disease-free survival rates in patients beyond first remission have been lower or relapse rates have been higher. For patients in first remission, relapse rates vary from 11 to 34%. Interim results from the current trial described here (E2993 - MRC UK ALLXII) has assessed the outcome of 201 Ph+ patients. This group of patients was compared to a group of patients who were Philadelphia chromosome negative. The Ph+ patients had a lower CR rate by day 56 of the study (78% vs. 89%, $p<0.001$). The 49 Ph+ patients who received a related donor transplant had a five-year event-free survival of 43% compared to 27% for matched unrelated donors and 10% for the Ph+ ALL patients who did not undergo transplant (33).

A recent report of 23 consecutive Ph+ patients transplanted between 1984 and 1997 at City of Hope Medical Center who were conditioned with fractionated TBI and high-dose Etoposide had three-year probability of disease-free survival (DFS) and relapse of 65% and 12%, respectively. For patients transplanted after 1992, the DFS was 81% and the relapse rate was 11% (34). These results demonstrate that allogeneic stem cell transplantation has the potential to cure a subset of patients with Ph+ ALL.

Autologous stem cell transplantation has also been attempted in patients with Ph+ ALL. As anticipated , the relapse rate is high but a recent report in children indicated that 6 of 25 patients were maintained in continued complete remission (13). In a series of nine patients undergoing autologous stem cell transplantation for Ph+ ALL, there were eight patients in first or second remission and one in first relapse. At three years, disease-free survival was 26% with a relapse rate of 66% (35).

Imatinib mesylate (Gleevec®) is a 2-phenylaminopyrimidine that is a signal transduction inhibitor of the abl tyrosine kinase at submicromolar concentrations. It is equally effective against the aberrant tyrosine kinase, BCR-ABL (36). Imatinib competes with ATP at binding sites in the kinase domain of BCR-ABL. Thus, Imatinib prevents the phosphorylation of selected tyrosine residues on BCR-ABL. A phase I trial of Imatinib in patients with chronic phase CML who had failed alpha interferon therapy demonstrated complete hematologic responses in all patients who took more than 300 mg per day. No dose limiting toxicity was encountered and most patients remained asymptomatic. The main toxicities noted were nausea, muscle cramps, periorbital edema, diarrhea, and rash (37). A recent report of 20 patients with Ph+ ALL in relapse or lymphoid blast crisis of CML demonstrated a 70% response rate, but all except one patient eventually relapsed(38). Thus, Imatinib has definite activity in Ph+ ALL and may enhance the quality of remission in patients with newly diagnosed disease.

Rev. 12/04

Recent studies have demonstrated the importance of measurement of minimal residual disease (MRD) in ALL as a powerful prognastic factor for identifying patients at risk for relpase at varying staging of their treatment (39). Measurement of MRD at the completion of induction therapy or at a later time point is highly predictive of subsequent relapse. The use of the polymerase chain reaction (PCR) represents an extremely sensitive technique for measurement of MRD (40). The use of PCR for measurement of the BCR-ABL translocation in Ph+ ALL represents a sensitive technique to monitor MRD in these patients (reviewed in 41). Therefore, in this study, we will utilize PCR for measurment of BCR-ABL at various time points through the study in the subset of patients with Ph+ ALL to determine the ability of chemotherapy, Imatinib, and SCT to decrease the level of MRD through the course of treatment.

To date, there has been no on-going randomized trial aimed at establishing the value of SCT versus chemotherapy in first CR ALL. The recently retrospective comparison of chemotherapy and allogeneic SCT in 2 cohorts of German patients, showing no benefit of one treatment over the other has significant flaws and failed to identify all sources of bias in comparing the groups (42).

Rev. 7/04

1.2 Design

This Phase III study seeks to compare 3 forms of consolidation therapy in first CR ALL: assignment to allogeneic SCT versus randomization to autologous SCT or conventional consolidation/maintenance. Patients will receive a uniform induction therapy with a modified Hoelzer-Linker regimen (1, 10). This modification, in accordance with the risk-adapted German multicentric trial includes 4 courses of consolidation (for patients not treated with either allogeneic or autologous SCT) comprising Cytarabine and substituting Etoposide for VM-26 (43). This approach is considered to be the best available to date with CR rates of 80% and median remission duration of more than 24 months for all patients (17 months for the high-risk patients). A common course of high dose Methotrexate intensification has been added, to decrease both the risk of CNS relapse and the putative marrow contamination with residual blasts at time of marrow harvesting (44, 45).

It is the purpose of this study to examine the above mentioned 3 types of post-remission intensive consolidation therapy.

Rev. 5/06

The subset of patients with Ph+ ALL will be identified during the initial month of common induction therapy and will receive therapy with Imatinib during the second month of induction therapy in conjunction with chemotherapy (Phase II) to assess the ability of Imatinib to enhance the achievement of remission in these patients. It will also determine whether Imatinib can maintain remission following allogeneic or autologous stem cell transplantation. Patients who remain in remission following four weeks of Imatinib will undergo an allograft using a sibling donor (if available), a matched unrelated donor (MUD) or a haploidentical related donor. After recovery from transplant, all patients will receive maintenance therapy with Imatinib regardless of their MRD status. Patients lacking a related or unrelated donor will receive intensive consolidation therapy with high-dose cytosine arabinoside and Mitoxantrone. This combination has been shown to achieve high rates of complete remission in patients with newly diagnosed or relapsed ALL or AML (24, 25). Autologous peripheral blood stem cells will be collected following this chemotherapy and patients will then go on to autologous transplant. Following the transplant, they will all receive Imatinib until progression. Measurement of BCR-ABL by PCR will be carried out at multiple time points through the study to assess the quality of patients' remissions.

Rev. 7/04

2.0 OBJECTIVES

2.1 To compare CR duration and survival in ALL resulting from post-remission therapy with allogeneic vs autologous SCT versus intensive conventional chemotherapy.

2.2 To examine differences in outcome for allogeneic SCT versus intensive conventional chemotherapy or autologous SCT.

Rev. 5/06

2.3 To examine, in a non-randomized study, the effect of 4 weeks of Imatinib therapy on patients with Ph+ ALL during Phase II of induction therapy.

2.4 To assess the benefit of an allogeneic stem cell transplant post treatment with Imatinib for those Ph+ patients with an allogeneic sibling matched donor, a matched unrelated donor or a related single haplotype matched donor. For those Ph+ patients who have no donor the benefit of an autologous stem cell transplant will be assessed.

2.5 To assess the benefit of Imatinib therapy post transplant for all Ph+ autologous and Ph+ allogeneic patients.

2.6 Correlative Objectives

2.61 To measure minimal residual disease (MRD) in these Ph+ patients before the introduction of Imatinib and to follow minimal residual disease post treatment with Imatinib by PCR.

2.62 Assess clinical resistance to Imatinib therapy caused by BCR-ABL gene amplification or mutation.

Rev. 10/05 **3.0 SELECTION OF PATIENTS**

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG Patient No. _____
Patient's Initials (L, F, M) _____

Rev. 7/04 **NOTE:** All questions regarding eligibility should be directed to the ECOG Coordinating Center at (617) 632-3610.

Rev. 7/04 **NOTE:** Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Induction Eligibility Criteria

Patients must:

Rev. 7/04 _____ 3.11 Diagnosis of ALL must be made upon bone marrow immunophenotyping with > 25% lymphoblasts. Cases with myeloid antigen expression, but unequivocal lymphoid immunophenotype, are eligible (46).

Rev. 7/04 _____ 3.12 Central diagnostic reviews are mandatory.

3.121 Samples must be submitted as indicated in Sections 10 and 11. Reviews include immunophenotying, karyotypes, pathology review, and the establishment of Philadelphia chromosome status.

3.122 Philadelphia chromosome status will be determined by cytogenetics, FISH and/or RNA analysis. Patients negative for the Philadelphia chromosome by cytogenetics, but positive for BCR-ABL by FISH or PCR are considered Philadelphia chromosome positive (Ph+).

Rev. 5/99 **NOTE:** Rambam Medical Center in Israel is required to preserve samples as per protocol and submit them to ECOG's Reference Laboratory within 6 months of patient registration.

_____ 3.13 Be previously untreated for malignancy. (Exception: Previous therapy with corticosteroids alone will not exclude the patient.)

Rev. 7/04, 5/06
_____ 3.14 Be ≥ 20 and ≤ 65 years old. For patients < 20, pediatric treatment strategies are recommended.

Rev. 7/04 _____ 3.15 Have lab values obtained ≤ 1 week prior to registration. Serum direct bilirubin ≤ 2 mg/dl and serum creatinine < 2 mg/dl.
Serum bilirubin:_____ Serum creatinine:_____ Date of tests;_____

Rev. 7/04
_____ 3.16 Be HLA typed if ≤ 50 years of age (A, B, at least, C and DR if feasible) during induction therapy phase or a written explanation for not undergoing HLA typing on the flow sheet for patients ≤ 50 years of age.
NOTE: Ph+ patients can be ≤ 65 years old.

_____ 3.17 Have no intercurrent organ damage or medical problems that will jeopardize the outcome of therapy (i.e., psychiatric disorder, drug abuse, pregnancy).

_____ 3.18 Not be known to be HIV serum antibody positive.

_____ 3.19 Have no myelodysplasia or other antecedent hematologic disorder.

_____ 3.110 Have no significant cardiac disease (requiring digoxin and/or diuretics), or requiring antiarrhythmic for major ventricular dysrythmia, or antiangina medications for ischemic heart disease.

Rev. 2/96 _____ 3.111 Have given written signed, informed consent.

Rev. 7/04 3.2 Post-Induction Therapy Eligibility Criteria

All patients must meet the eligibility criteria in Section 3.21. Patients considered for allogeneic SCT must also meet the criteria in Section 3.22. Ph- patients without an appropriately matched HLA compatible donor will be randomized to autologous SCT or
Rev. 12/04 conventional consolidation/maintenance.

3.21 Eligibility Criteria

_____ Patients must:

_____ 3.211 Have performance status 0 or 1.

3.212 Have documented complete remission as defined in Sections 6.11, 6.12, and 6.13.
Rev. 7/04, 5/06

_____ 3.213 Be CNS (CSF) negative for leukemia.

_____ 3.214 Have absence of persisting infection (off all parenteral antibiotics).

Rev. 7/04 _____ 3.215 Have serum creatinine $\leq$ 2 mg/dl and creatinine clearance must be $\geq$ 60 ml/min.
Serum creatinine:_____Creatinine clearance:_____
Date of tests:_____

Rev. 7/04

3.216 Have serum direct bilirubin < 2 mg/dl, and SGPT (ALT) or SGOT (AST) < 3 x normal.
_____ Serum direct bilirubin:_____SGPT(ALT):_____
SGOT(AST)_____
3 x normal:_____ Date of tests:_____

3.217 Have normal cardiac ejection fraction ($\geq$ 50%).
EF:_____ Date of Test:__
Rev. 2/07 _____ **NOTE:** Only for patients considered for transplant.

3.218 Have pulmonary function with $FEV_1 \geq 60\%$ of predicted and DLCO $\geq$ 50% of predicted.
_____ FEV1:_____ DLCO:_____ Date of tests:_____
Rev. 2/07 **NOTE:** Only for patients considered for transplant.

3.219 Have no occult or overt leukemic meningitis at time of bone marrow harvesting.
_____

Rev. 7/04 3.2110 Ph status must have been established.
PH status Pos or Neg: _____

Rev. 7/04 _____ 3.22 Criteria for allogeneic transplants:

3.221An appropriate HLA histocompatible donor must be identified.

3.2211Ph- patients HLA identical sibling.

_____ 3.2212 Ph+ patients HLA identical, HLA matched unrelated donor (MUD) or haploidentical related donor.

_____ 3.222 Umbilical cord allogeneic transplants are **NOT** allowed.

_____

Rev. 7/04

4.0 REGISTRATION/RANDOMIZATION PROCEDURES

This study commences with a single induction arm.

All patients who have a negative Ph status and meet CR criteria in Section 6 are either:

Rev. 2/96

Assigned to allogeneic bone marrow or peripheral blood stem cell transplantation if they are ≤ 50 years old and have a histocompatible sibling;

OR

Randomized to receive autologous bone marrow or peripheral blood stem cell transplantation or consolidation/maintenance chemotherapy.

Rev. 5/06

Philadelphia chromosome positive ALL patients will receive Imatinib 600 mg po qd for one month during Phase II of induction therapy and then proceed to allogeneic SCT from a matched related, or unrelated donor or a related haploidentical donor. If no other donor is available or the patient is not felt to be a candidate for allogeneic transplant, an autologous SCT will be performed following collection of PBSC after mobilization with chemotherapy. After transplant, patients will receive Imatinib.

NOTE: Ph+ patients can be ≤ 65 years old.

Rev. 2/95

Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:
CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Rev. 12/04
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form

Or

B. HHS 310 Form

Or

C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB.**
- **Full protocol title and number.**

- **Version Date**
- **Type of review (full board vs. expedited).**
- **Date of review.**
- **Signature of IRB official.**

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2_page.asp. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com**. Monday through Friday, 9:00am - 6:00pm**.

Patients must not start protocol treatment prior to registration.
Treatment should start within three working days after registration.

Rev. 2/98
Rev. 7/04

4.1 Induction Registration

All patients must be registered within 24 hours before starting induction therapy or within 72 hours before starting treatment if a weekend or holiday intervenes. If therapy must be started when the Randomization Desk is closed, a telephone call must be made providing information about the patient to the answering device. A follow-up call when the Randomization Desk is open is then made as indicated below. Under no circumstances will non-registered patients be retrospectively eligible for the study.

Rev. 2/96, 2/03

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (https://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday through Friday 9:00am - 5:00pm Eastern Time. Please note that a password is required to use this program. The following information will be requested:

4.11 Protocol Number

4.12 Investigator Identification

4.121 Institution name and/or affiliate

4.122 Investigator's name

4.13 Patient Identification

4.131 Patient's initials and chart number

4.132 Patient's Social Security number

4.133 Patient Demographics

4.1331 Sex

Rev. 2/96

4.1332 Birth date (MM/DD/YY)

4.1333 Race

4.1335 9 digit zip code

4.1336 Type of insurance

Rev. 2/03

4.14 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.15 Additional Requirements

4.151 Patient must provide signed and dated written informed consent.

4.152 Pathology materials must be submitted as outlined in Section 10.

4.153 Correlative materials must be submitted as outlined in Section 11.

Rev. 7/04

NOTE: Patients should also be registered to E3903, *Ancillary Laboratory Protocol for Collecting Diagnostic Material on Patients Considered for ECOG Treatment Trials for Leukemia or Related Hematologic Disorders.* If the patient is already registered to E3903, then the ECOG sequence number must be provided.

Rev. 7/04

4.2 Post-Induction Therapy

All patients meeting CR criteria in Sections 6.11, 6.12, and 6.13 will register for post-induction therapy. This registration/randomization will be done by the referring institution.

Rev. 2/96

4.21 Registration for Allogeneic/MUD Bone Marrow Transplantation

Rev. 2/96

Patients ≤ 50 years old achieving a CR who have a histocompatible sibling or who are Philadelphia chromosome positive with an unrelated HLA matched donor identified will be treated with allogeneic/MUD bone marrow transplantation. Ph+ ALL patients are also eligible for autologous SCT outside the randomization arm as described in Section 4.

Rev. 2/96, 2/03

4.211 Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (https://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022. Please note that a password is required to use this program.

Verification for the following must be given by completing Step 2 checklist questions:

4.2111 Is the patient in complete remission as defined by criteria in Sections 6.11, 6.12, and 6.13?

4.2112 An MRC Bone Marrow Transplant Data Form is to be completed after the outcome of allogeneic bone marrow transplantation is known.

4.2113 Has the patient's Philadelphia chromosome status been determined?

4.2114 Protocol Number

4.2115 Investigator Identification

4.21151 Institution name and/or affiliate

4.21152 Investigator's name

4.2116 Patient Identification

4.21161 Patient's initials, chart number and protocol sequence number

4.21162 Patient's Social Security number

Rev. 2/03

4.2117 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.2118 Additional Requirements

4.21181 Pathology materials must be submitted as outlined in Section 10.

4.21182 Correlative materials must be submitted as outlined in Section 11.

4.22 Randomization for Autologous Bone Marrow Transplant versus Conventional Consolidation/Maintenance

Patients not eligible for allogeneic SCT and who are not Ph+ will be randomized to receive either autologous bone marrow or peripheral blood stem cell transplantation or conventional consolidation/maintenance. Marrow or PBSC harvesting and therapy will begin no sooner than 4 weeks and no later than 7 weeks from start of intensification therapy, i.e., between weeks 16 and 19. An additional 1 month delay is permissible to allow for resolution of post-intensification therapy toxicities, i.e., recovery from hepatitis. recovery of adequate renal function, or resolution of infection so that the patient meets the eligibility requirements specified in Section 3.2. To randomize a patient, the investigator will provide the name of the bone marrow transplantation center

Rev. 2/96

when registering patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (https://webreg.ecog.org).

NOTE: If the patient is randomized to autologous bone marrow transplantation, the procedure must be performed at an approved ECOG autologous bone marrow transplant center.

The following information will be requested:

4.221 Protocol Number

4.222 Investigator Identification

4.2221 Institution name and/or affiliate

4.2222 Investigator's name

4.223 Patient Identification

4.2231 Patient's initials, chart number and protocol sequence number

4.2232 Patient's Social Security number

Rev. 2/03

4.224 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.225 Additional Requirements

4.2251 Patient must provide signed and dated written informed consent.

4.2252 Pathology materials must be submitted as outlined in Section 10.

4.2253 Correlative materials must be submitted as outlined in Section 11.

4.226 Stratification Factors for Randomization

4.2251 Age

≤ 50
> 50

4.2252 Time to Achieve CR

≤ 4 weeks
> 4 weeks

Rev. 7/04

4.2253 Philadelphia Chromosome

Positive
Negative

Rev. 7/04

4.3 MRC Registration/Randomization

Participants entering patients through MRC will ring the Clinical Trial Service Unit (CTSU) in Oxford. MRC will be randomizing independent of ECOG.

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Rev. 7/04

4.4 Selection of Transplant Center

Eligible patients will be referred to one of the approved allogeneic Bone Marrow Transplant institutions. Haploidentical allogeneic SCT will be performed at ECOG Allogeneic Bone Marrow Transplant Centers with experience and commitment to this highly specialized procedure. Arrangements will be made by contacting the marrow transplant patient coordinator at the chosen institution. If necessary, contact the ECOG Coordinating Center, (617) 632-3610, to obtain a current listing of the BMT coordinators.

Rev. 7/04

4.5 Cancellation Guidelines

If a patient does not receive protocol therapy, the patient may be canceled. Reasons for cancellation should be submitted in writing to the ECOG Coordinating Center (ATTN: DATA) as soon as possible. Data will be collected on all canceled patients (see Section 12). Note: A patient may only be canceled if no protocol therapy is administered. Once a patient has been given protocol treatment all forms should be submitted.

Rev. 2/96
Rev. 2/98

5.0 TREATMENT PLAN

Rev. 7/04 **NOTE:** Both allogeneic and autologous stem cell transplant (SCT) will refer to peripheral blood or bone marrow transplant.

Rev. 12/04 **NOTE: As of Addendum #12, Alpha-interferon use during Allogeneic/MUD BMT, Autologous BMT, and Maintenance Therapy has been discontinued.**

Prior to Addendum #12, Alpha-interferon was administered to Ph + patients on Day +30 for Allogeneic/MUD BMT and Autologous BMT at a dose of 3 MU SC 3x week for 15 months. It was also administered to Ph+ patients during Maintenance Therapy at a dose of 3 MU SC 3x week for 15 months.

Rev. 12/04 **NOTE: As of Addendum #14, Erwinia Asparaginase use as a substitute for L-Asparaginase or PEG-Asparaginase has been discontinued as the drug is no longer available.**

Rev. 7/04 5.1 Overall Study Design

This trial will be a randomized Phase III study comparing autologous SCT (with unpurged Rev. 7/98 stem cells) versus conventional intensive consolidation/maintenance therapy, versus assignment to allogeneic SCT.

Rev. 12/04, 10/05 The study commences with a single induction arm and is administered in 2 phases. Note that Ph+ patients will also be given Imatinib in addition to chemotherapy in the second phase of induction treatment. Patients in CR will be assigned to one of three forms of consolidation. Rev. 10/05 Prior to consolidation, Ph- patients will undergo intensification with high-dose methotrexate. Prior to consolidation, patients will undergo intensification with high dose methotrexate.

All patients must be HLA typed as soon as possible, preferably in phase I (induction), to prevent delays in proceeding to transplant. The following patients will be registered to allogeneic SCT Philadelphia chromosome negative patients (≤ 50 years old) with a histocompatible sibling donor, and Philadelphia chromosome positive patients (≤ 65 years old) with histocompatible sibling, HLA matched unrelated, or haploidentical related donor. After the allogeneic SCT, Ph+ patients will take Imatinib until relapse. For Ph+ patients, the following options for donors should be explored in the sequence given:

1. The availability of a matched sibling donor.
2. The availability of a matched unrelated donor (MUD). Such transplants should be considered but should only be carried out in transplant centers with experience with this approach.
3. The availability of a related single haplotype match. Again the option should only be carried out in transplant centers with experience with this approach.

Patients lacking an appropriate donor who are Philadelphia chromosome negative and ≤ 50 years old will be randomized to received either intensification followed by autologous SCT intensification followed by conventional intensive consolidation/maintenance.

All patients not assigned to allogeneic/MUD SCT will undergo autologous marrow harvesting after intensification treatment.

Philadelphia chromosome positive patients lacking an appropriate donor will be registered to receive intensification followed by autologous SCT. Patients will then receive Imatinib until progression.

The preparative transplant regimen is the same for both autologous and sibling-matched related allogeneic SCT and uses etoposide and fractionated TBI (FTBI). Patients receiving matched unrelated or haploidentical SCT may receive preparative regimens utilized at the center where they are being transplanted. All patients undergoing SCT will receive IV GM-CSF to shorten the period of neutropenia.

5.2 Induction Therapy

5.21 Initial Considerations

5.211 All patients are begun on Allopurinol at least 300 mg/day orally between days 1 and 29, inclusive. Reversible abnormalities of renal or metabolic

function should be treated aggressively and corrected prior to institution of therapy.

5.212 Immediate measures to diagnose and begin treatment of infections should be instituted prior to induction therapy.

5.213 Spinal Fluid Examination

Regardless of spinal fluid sugar or protein concentrations or cell count, a concentrated properly stained sediment should be examined (preferably by cytospin technique) for the presence of blast forms.

If CNS leukemia is present at diagnosis, methotrexate 12.5 mg intrathecally or via an Omaya Reservoir should be given weekly until blasts are not present in the spinal fluid. 24 Gy cranial irradiation and 12 Gy to the spinal cord should then be administered concurrently with Phase II.

5.22 Induction Drug Administration Schedule

Two Phases (I and II) of induction therapy are used. Doses are calculated on ideal weight basis in obese patients and on actual weight basis for the other patients, whichever is less. (See Appendix II)

5.221 Phase I Induction

Daunorubicin	60 mg/m^2 IV push Day 1, 8, 15 and 22
Vincristine	1.4 mg/m^2 IV push Day 1, 8, 15 and 22 (maximum dose 2 mg)
Prednisone	60 mg/m^2 PO daily Day 1-28
L-Asparaginase	10,000 international units total IV in 100 ml D5W over 30 min or IM daily Day 17-28 (see Section 5.2231)
Methotrexate	12.5 mg intrathecally day 23 only unless the patient received treatment for CNS leukemia as per Section 5.213

Rev. 7/04

Rev. 2/96, 2/03, 7/04

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5.2211 HLA Typing and Donor Search

Rev. 7/04

This should be done as soon as possible where relevant before or during Phase I of induction chemotherapy for matched sibling donors of Ph negative patients, or matched sibling, unrelated

Rev. 7/04

donors, or related single haplotype match for Ph positive patients. Typing and search may need to be done during or after Phase II in patients without CR at day 28.

Rev. 2/95

5.2212 Twenty-eight days after start of the Phase I induction a bone marrow aspiration and biopsy is performed to assess remission status. Whatever the results, Phase II should then be initiated.

5.222 Phase II:

Rev. 7/04

5.2221 Phase II of the induction regimen begins on day 29 from start of Phase I induction. It should be postponed until WBC > 3 x 10^9/L in patients with delayed hematologic recovery. Phase II consists of the following:

Rev. 2/95	Cyclophosphamide	650 mg/m^2 IV in 250 cc normal saline over 30 min Day 1, 15, and 29 of the second phase
	Cytarabine	75 mg/m^2 IV in 100 cc D5W over 30 min per day, Day 1-4, 8-11, 15-18 and 22-25
Rev. 7/98	6-mercaptopurine	60 mg/m² orally Day 1-28 of the second phase
	Methotrexate	12.5 mg intrathecally days 1, 8, 15 and 22 of the second phase, unless the patient received treatment for occult disease in phase I
Rev. 10/05	Imatinib	**For Ph+ patients only:** 600 mg orally/day for a minimum of 28 consecutive days. Imatinib should be taken in the morning with breakfast in a sitting position with a large glass of water. It should not be taken with grapefruit products.
Rev. 5/06		Imatinib may be continued for an additional two months after phase II induction to allow time for patients to undergo BMT.

Rev. 10/05
Rev. 2/95

5.2222 Patients with CNS leukemia at diagnosis, who received weekly IT Methotrexate during Phase I induction receive irradiation concurrent with Phase II induction therapy as per Section 5.213.

5.223 Dose Modifications for Initial Induction

5.2231 L-Asparaginase Related Toxicities

Rev. 10/00

NOTE: If allergic reaction occurs, or if E. Coli Asparaginase (L-Asparaginase) is not available, PEG-Asparaginase may be substituted for L-Asparaginase. (See Section 5.2232 for PEG-Asparaginase administration.)

Rev. 10/00

NOTE: Institutions should check L-Asparaginase inventory prior to patient starting treatment. Investigators should only use L-Asparaginase if there is an adequate supply for the full (14-day) administration (Phase I and II of induction therapy). If there is an insufficient supply for this period, then PEG-Asparaginase should be given.

Rev. 10/00

NOTE: If the patient is allergic to PEG-Asparaginase or if PEG-Asparaginase is not available, Erwinia-Asparaginase may be substituted. (See Section 5.2233 for Erwinia-Asparaginase administration.)

Modifications of L-Asparaginase dosage in the initial Phase I induction treatment should be made as follows:

Rev. 5/93

Despite hyperglycemia, the drug should be continued in full doses with insulin administration as indicated. Patients being retreated (8 week gap between induction, Phase I and intensification) and those receiving infrequent dosing (i.e., weekly) are at increased risk of experiencing anaphylaxis.

Rev. 7/04, 12/04
Rev. 7/04

Rev. 5/93

USE ONLY PEG-ASPARAGINASE IN ALLERGIC PATIENTS. Wait 1 day after detection of allergic reaction to standard E.Coli Asparaginase to administer PEG-Asparaginase. The dose of PEG-

Rev. 7/04

ASPARAGINASE is 2,500 international units/m^2, by IM route only. During induction, this dose will be given only once every 21 days. For example, during the Induction Regimen if an allergic reaction occurs at any time to the standard Elspar (E.Coli) then only one dose of PEG-ASPARAGINASE will be given to complete the day 17-28 requirements for asparaginase. During the Intensification Regimen PEG-ASPARAGINASE will be given only on Days 2 and 23.

Rev. 5/93

PEG-ASPARAGINASE also contains E.Coli Asparaginase attached to Polyethylene Gycol. There is a possibility that an allergic reaction may also occur with this product. The plant pathogen

Rev. 2/96, 5/96
Rev. 7/04

derived form Erwinia Asparaginase, an investigational agent, is

Rev. 7/04

available through Ipsen Pharmaceuticals Ltd. (Refer to Section 8.0 and Appendix VIII for availability).

Hold: Patients with hypersensitivity should receive PEG-Asparaginase after E.Coli only. Additionally, all forms of Asparaginase should be held for any of the following reactions:

a. pancreatitis
b. grade 3 or 4 liver toxicity
c. deep venous thrombosis or pulmonary embolism
d. major hemorrhage

Rev. 10/00

5.2232 PEG-Asparaginase Administration

Rev. 7/04

Only one PEG-Asparaginase dose 2,500 international units/m^2 should be given for each two periods of L-Asparaginase.

Rev. 10/00

5.2233 Erwinia-Asparaginase Administration

Rev. 5/06

As of Addendum #14, Erwinia-Asparaginase use as a substitute for L-Asparaginase or PEG-Asparaginase has been discontinued as the drug is no longer available.

Rev. 10/00

5.2234 Hepatic Toxicity

Daunorubicin and Vincristine doses should be modified on a weekly basis.

Rev. 7/04

Direct Bilirubin	Dose of Vincristine to Give	Dose of Daunorubicin to Give
2 - 3 (mg/dL)	100% calculated	50% calculated
> 3	50% calculated	25% calculated

Rev. 10/00

5.2235 Neurotoxicity

The vincristine dose should be modified to 50% for paresthesia proximal to the DIP joints and stopped entirely for major muscle weakness, cranial nerve palsy or severe ileus.

Rev. 10/05 5.224 Dose Modifications for Phase II Induction

Rev. 10/05 5.2241 Dose Modifications for Toxicity Directly Attributable to Imatinib

Rev. 10/05 5.22411 Non-Hematologic Toxicity

If a patient experiences a grade 2 non-hematologic toxicity lasting for more than two days, Imatinib should be withheld until the toxicity is resolved to ≤ grade 1. Imatinib may then be resumed at a dose of 600 mg orally per day. If the grade 2 toxicity recurs, Imatinib must be withheld until the toxicity is resolved to < grade 1. Imatinib may then be resumed at a reduced dose of 400 mg orally q.d. If grade 2 toxicity recurs, further dose reduction to 300 mg daily can be performed using the above procedures.

If grade 3/4 toxicity occurs, Imatinib must be withheld until the toxicity is resolved to < grade 1. Imatinib may then be resumed at a reduced dose of 400 mg daily. If > grade 2 toxicity recurs, a further dose reduction to 300 mg orally daily can be performed using the above procedures.

Rev. 7/04, 10/05 5.22412 Hepatic Toxicity

Patients with a total serum bilirubin ≤ 1.5 x ULN at post-induction baseline who experience ≥ 2-4 elevation should be managed using the criteria detailed above for non-hematologic toxicity.

Rev. 7/04 In patients with total serum bilirubin > 1.5 - ≤ 3 x ULN at post- induction baseline who experience ≤ 2-fold increase in bilirubin, Imatinib must be held until the levels return to post-induction baseline values and then resumed at a dose of 600 mg orally daily. If a similar degree of toxicity recurs, the study drug must be held until the bilirubin levels return to post-induction baseline level values and study drug may be resumed at a dose of 400 mg daily. If a similar degree of toxicity recurs, a further dose reduction to 300 mg orally daily can be performed, using the above procedures.

If patients experience greater than 2-fold increase in total bilirubin levels, study drug must be withheld until the levels return to post-induction baseline values and study drug may then be resumed at a dose of 400 mg daily. If a similar degree of toxicity recurs, further dose reduction to 300 mg orally daily can be performed, using the above procedures.

Patients with SGOT (AST)/SGPT (ALT) ≤ 2.5 x ULN at a post-induction baseline who experience ≥ grade 2-4 elevations in one or both transaminases should be managed using the criteria detailed above for non-hematologic toxicity.

Rev. 7/04 In patients with SGOT (AST) or SGPT (ALT) > 2.5 - ≤ 5 x ULN at post-induction baseline who experience < 3-fold increase in the levels of the most elevated transaminase, Imatinib must be held until the transaminase levels return to post-induction baseline values and then resumed at a dose of 600 mg orally daily. If a similar degree of toxicity recurs, study drug must be held until transaminase levels return to post-induction baseline values and the study drug may then

be resumed at a dose of 400 mg orally daily. If a similar degree of toxicity recurs, further dose reduction to 300 mg orally daily can be performed using the above procedures.

If patients experience > 3-fold increase in the levels of the most elevated transaminase, study drug must be withheld until the transaminase levels return to baseline values and study drug may then be resumed at a dose of 400 mg orally daily. If a similar degree of toxicity recurs, a further dose reduction to 300 mg orally daily can be performed, using the above procedures.

Rev. 10/05

5.22413 Hematologic Toxicity

Patients developing anemia may be transfused at the discretion of the investigator. No dose reductions are needed for any degree of anemia or for grade 1-3 neutropenia or thrombocytopenia.

Similarly, if platelet counts can be maintained by the periodic administration of platelet transfusions, no dose reductions are foreseen for grade 4 thrombocytopenia.

Rev. 10/05

5.225 Supportive Care

Throughout both phases of induction therapy, cytokine therapy - either G-CSF or GM-CSF - may be used at the investigators discretion. Use of
Rev. 5/06 CSF during such therapy should be noted on the data forms.

Rev. 10/05

5.3 Post-Induction Therapy

Rev. 10/05

Note regarding donor search fpr Ph+ patients:

Rev. 5/06

If a donor search is still in progress at the time of registration for post-induction therapy for Ph+ patients, registration may be delayed for up to two months until a donor is found or it is decided to proceed to autologous BMT. If further delay to BMT is planned beyond two months, the patient will be taken off-study.

Rev. 7/04, 10/05

5.31 Intensification Therapy with High Dose Methotrexate for Ph- Patients: Arms B&C

Rev. 2/95, 7/04

Intensification commences 4 weeks after the completion of the second phase of induction, i.e., at the beginning of week 13 and ending on week 16.

Rev. 7/04

At this point, randomization for those who do not have a matched sibling AND for those patients < age 50 will take place between autologous SCT and standard consolidation/maintenance chemotherapy (Arm C or Arm D).

Rev. 7/04, 5/06

Ph+ patients will not receive intensification, conventional consolidation/maintenance (Arm D), but will proceed directly to either allogeneic or autologous SCT (Arm E or Arm F).

Rev. 2/96

Registration for patients allocated to allogeneic/MUD SCT (Arm B) will also take place at this time prior to intensification.

Rev. 7/04

Patients must have achieved CR in order to begin intensification therapy.

The intensification consists of three separate pairs of injection with methotrexate and L-asparaginase.

Methotrexate	3 g/m^2 in 500 ml NS IV over 2 hrs Day 1, 8 and 22 of the intensification course, i.e., at the beginning of week 13, 14 and 16.
Rev. 2/03,7/04, 12/04 L-Asparaginase	10,000 international units total IV in 100 ml D5W over 30 min Day 2, 9 and 23 of the intensification course.
Leucovorin Rescue	10 mg/m^2 IV in 50 ml D5W 22-24 hrs after completion of methotrexate infusion every 6 hrs for 4 doses, then 10 mg/m^2 orally every 6 hours for 72 hrs.

5.311 CNS Prophylaxis

Rev. 2/95, 2/96 For those not receiving allogeneic/MUD or autologous SCT (and who did not present with occult CNS disease) 24 Gy in 12 fractions in 2 to 3 weeks between intensification and the start of consolidation should be given. Intrathecal therapy with 50 mg cytarabine per dose should be given weekly x 4 during radiotherapy. Cytarabine 50 mg should then be given intrathecally on 4 occasions 3 months apart during maintenance therapy, i.e., for one year.

5.312 Patient Support

Warning: Investigators should be aware that nephrotoxicity and mucositis can occur with high-dose methotrexate in this protocol. To prevent this toxicity the following measures should be taken:

Rev. 7/04 5.3121 Urinary alkalinization (pH > 7) is achieved by administration of sodium bicarbonate, 3 g orally every 3-6 hours the night before methotrexate infusion and for 48 hours thereafter. Hydration with at least 3L of fluid per day is maintained before, during and after each course.

Rev.2/96 5.3122 Creatinine and methotrexate serum levels: If the serum creatinine increases by more than 50% above baseline at 24 hours and/or the methotrexate level is greater than 5 x 10^{-6}M, leucovorin factor is increased to 100 mg orally every 3 hours until the serum methotrexate level decreases to 1 x 10^{-8} M (28).

Rev. 7/04

Rev. 7/04, 10/05 5.32 Conventional Consolidation/Maintenance: Arm D

NOTE: Ph+ patients will not receive conventional consolidation/maintenance, but will proceed directly to either allogeneic or autologous SCT (Arm E or Arm F).

5.321 "Standard" Consolidation

Rev. 2/95 Four courses of conventional consolidation therapy will be administered following intensification therapy for patients who will not receive an allogeneic or autologous transplant.

Rev. 7/04 **NOTE**: It is strongly recommended that patients randomized to receive conventional consolidation/maintenance have marrow harvested or peripheral blood stem cells collected (for use in the event of subsequent relapse). Marrow harvesting or peripheral blood stem cell collection should be performed as per Section 5.33. Patients will receive all four courses of conventional consolidation therapy.

Rev. 10/05

5.3211 Cycle 1 Consolidation

Rev. 7/04 Begins after intensification or harvest when WBC > 3 x 10^9/L and platelets > 100 x 10^9/L

Rev. 10/05	Cytarabine	75 mg/m^2 in 100 ml D5W IV over 30 min, Day 1-5 inclusive
	Etoposide	100 mg/m^2 in 500 ml NS IV over 1 hr Day 1-5 inclusive
Rev 2/96	Vincristine	1.4 mg/m^2 IV push Day 1, 8, 15 and 22 of consolidation (maximum 2mg/dose)
	Dexamethasone	10 mg/m^2 PO Day 1-28 of consolidation

5.3212 Cycle 2 Consolidation

Rev. 7/04 Begins 4 weeks from day 1 of first cycle of consolidation or when WBC > 3 x 10^9/L

Rev. 10/05	Cytarabine	75 mg/m^2 in 100 ml D5W over 30 min Day 1-5 inclusive
	Etoposide	100 mg/m^2 in 500 ml NS IV over 1 hr Day 1-5 inclusive

5.3213 Cycle 3 Consolidation

Rev. 7/04 Begins 4 weeks from day 1 of second cycle of consolidation or when WBC > 3 x 10^9/L

	Daunorubicin	25 mg/m^2 IV push Day 1, 8, 15 and 22
	Cyclophosphamide	650 mg/m^2 in 250 ml NS IV over 30 min, Day 29 only
	Cytarabine	75 mg/m^2 in 100 ml D5W over 30 min on Day 31-34 and 38-41
	6-Thioguanine	60 mg/m^2 PO Day 29-42

5.3214 Cycle 4 Consolidation

Rev. 7/04 Begins 8 weeks following start of consolidation 3 or when WBC > 3 x 10^9/L.

Identical with consolidation 2.

5.322 Maintenance Chemotherapy

5.3221 Patients completing the four courses of consolidation will continue on maintenance chemotherapy consisting of:

	6-mercaptopurine	75 mg/m^2 PO daily
Rev. 2/95	Methotrexate	20 mg/m^2 po or IV once a week for 2 and 1/2 years
Rev. 2/95, 2/96	Vincristine	1.4 mg/m^2 IV every 3 months with prednisone (maximum 2mg/dose)
	Prednisone	60 mg/m^2 for 5 days PO every 3 months with Vincristine

Rev. 2/96, 7/04 5.3222 Maintenance chemotherapy will begin 4 weeks after day 1 of the

Rev. 7/04

fourth cycle of consolidation or when WBC >3 x 10(9)/L. Maintenance should continue for 2½ years from start of intensification therapy.

Rev. 2/96

5.323 Supportive Care

Throughout both phases of induction therapy, consolidation therapy and maintenance therapy, cytokine therapy - either G-CSF or GM-CSF - may be used at the investigators discretion. Use of CSF during such therapy should be noted on the data forms.

Rev. 7/98

5.324 Stem Cell Collection

Rev. 7/04

Bone marrow harvest or peripheral blood stem cell collection will be carried out as soon as possible after neutrophil recovery to 1000/uL and platelets to 100,000/uL from the third high dose methotrexate, i.e., week 14 course.

In recognition of prevailing worldwide practice, stem cells may be collected from the bone marrow, from the peripheral blood or from both. It is assumed that the transplant centers have expertise in the particular modality that is used and infuse no less than 2×10^8 nucleated marrow cells/kg or 2×10^6 CD34+ peripheral blood stem cells/kg.

Rev. 7/04

Administration of GM-CSF or G-CSF after the third high-dose methotrexate is the most appropriate way to mobilize peripheral blood stem cells.

Rev. 2/96, 7/04, 10/05

5.33 Allocation to Allogeneic SCT: Arms B & E

Rev. 7/04

5.331 Donors

Rev. 2/96

Donors must be aged 65 or less. Donors will be excluded for psychological or medical reasons if they are unable to tolerate the procedure or if HIV-positive or Hepatitis B or C positive.

Rev. 7/04

5.332 Preparative Regimen

Rev. 2/96

The preparative regimen for matched-related allogeneic SCT is identical to that for autologous BMT recipients and consists of fractionated total body
irradiation (FTBI) and high-dose etoposide. For Ph+ patients receiving matched unrelated donor or related haploidentical donor SCT, the preparative regimen will be as per local institutional guidelines.

FTBI is performed between days -6 and -4 as outlined in Appendix VI. The total dose is 1320 cGy. Males will receive an additional 400 cGy boost to the testes (47).

5.333 Fractionated TBI (FTBI) (for additional details see Appendix VI)

Rev. 2/95, 2/98

Fractionated Total Body Irradiation is only permissible at pre-approved ECOG facilities. Please contact the ECOG QARC Center for TBI approval information at:

Rev. 10/00, 7/04

Fran Laurie
Quality Assurance Review Center
Attention: ECOG Materials
272 West Exchange Street, Suite 101
Providence, RI 02903-1025
Tel: (401) 454-4301
FAX: (401) 454-4683

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Please call Dr. Richard Whittington at (215) 662-6515 for TBI treatment questions.

Prescription doses and fractionation: The single therapy session tumor dose of 220 cGy will be given twice daily, 5-10 hours apart, for three consecutive days (T-6 through T-4) for a total tumor dose of 1320 cGy (6 fractions) in 3 days. The point of dose prescription is a single point, midline in the body, at the level of the umbilicus. On day -6 a 400 cGy electron boost to the testes will be delivered for male patients.

5.3331 It is suggested that the patient be "NPO", or receive a diet consisting of only clear liquids beginning the day before and continuing throughout the 3 days of TBI.

5.3332 Dose rate: The dose rate will be 5-30cGy/ minute and should be clearly recorded for each treatment. Total elapsed time of treatment will be recorded to compute the effective dose rate per treatment field.

5.3333 Field arrangements: To improve uniformity of dose, parallel opposed fields (usually right and left lateral fields, though anterior -posterior fields are allowed with appropriate compensation for equivalent lung dose) will be used during each single therapy session. Hence, the tumor dose per treatment field per therapy session will be 110 cGy; treating each opposed field per therapy session will yield 220 cGy tumor dose per therapy session. Combinations of AP-PA and laterals are allowed if they will result in better dose uniformity in the patient.

5.3334 Treatment distance: The treatment distance, either source-to-skin distance (SSD) or source-to-axis distance (SAD), will be at least 3m greater dose uniformity will be achieved at increased distances.

5.3335 Field size: The treatment configuration shall be that the patient is entirely included within the treatment beam exclusive of the penumbra (i.e., the patient shall be situated well within the 90% decrement line at each depth). The 90% decrement line is defined as a line in each plane perpendicular to the central axis connecting points which are 90% of the central axis dose in that plane. It is essential that agreement between the light and radiation fields be established and verified for the extended TBI treatment distance.

5.3336 Beam energy: Treat only with megavoltage units, i.e., Cobalt-60 or Linacs of 4 MeV or greater energy.

Rev. 5/93

5.3337 Prescription dosimetry and dose calculations: Any conventional methods may be used, i.e., SSD-%DD, SAR-TAR, SMR-TMR calculations, etc., as long as the method is clearly specified and documented. Confirmation dosimetry in cubical phantoms and in anthropomorphic phantoms should be performed at the treatment distance to verify calculation doses. This confirmation is not required on each patient but must be done prior to treating the first patient in the protocol. "*In vivo*" dosimetry is optional, but should be performed initially to confirm the accuracy of the general method of radiation treatment.

5.3338 Tissue compensating filters: Tissue compensating filters may be required to keep the midline tumor dose to the head, neck and trunk to within 110% of the prescription tumor dose. Tissue conpensators usually are not required for the lower extremities; however, they should be used if the dose to the lower extremities exceeds 120% of the prescription of compensation technique and its effect on the prescription dose and dose distribution shall be reported and submitted as part of the quality control documentation.

5.3339 Skin dose: The dose to the skin should be as high as reasonably achievable and must be at least 90% of dose maximum at 5 mm depth. It may be necessary to incorporate bolus or a lucite scatterer placed near the patient to accomplish this for high energy beams.

Rev. 5/93

5.33310 Doses to points other than the prescription point: Due to the large volume treated, it is desirable to know the doses at several points other than the prescription point: Midline doses should be recorded for the head, neck, mid-mediastinum, umbilicus, pelvis, knee and ankle. The dose statements made may be based on "*in vivo*" dosimetry on each patient, anthropomorphic phantom dosimetry for the method of treatment, or by calculation. Two point dose profiles, using the sum of the entry and exit doses at D_{max}, and the midline dose, should be recorded for the mid-mediastinum and pelvis, as these are likely to be the thickest anatomical regions presenting to the beam in either AP-PA or right and left lateral treatments.

Rev. 5/93

5.33311 Lung doses: Heterogeneity corrections are <u>not</u> to be applied for dose prescription or to determine satisfaction of the dose homogeneity requirement of the reference points. For AP/PA fields, record the dose in the center of right or left lung at level of mid-mediastinum. For lateral fields, record the dose in the portion of the lung at mid-mediastinum not shielded by arms. If a correction factor is used, enter estimated thickness of lung and explain method of correction.

5.33312 Dose Modification: No dose modification of FTBI will be made.

5.33313 <u>Fractionated TBI Toxicities</u>

Fractionated TBI (FTBI) will be given as described above. The toxicities of FTBI given in this manner are as listed below.

1) <u>Early side effects</u> <u>(< 1 month)</u>: Most patients experience some degree of nausea, vomiting and diarrhea either during or immediately after treatment. Fever that develops soon after TBI is not uncommon, and lasts 12 to 24 hours after TBI. Other side effects include skin erythema, parotid gland swelling, diminished salivary gland function, stomatitis, and alopecia. Myelosuppression occurs promptly following TBI and doses of 1000 cGy or more are assumed to cause permanent bone marrow aplasia and would be lethal without bone marrow transplantation.

NOTE: A number of studies indicate that an empty bowel will experience significantly less damage during the TBI therapy; therefore, it is suggested that the

patient be "NPO" or receive a diet consisting of only clear liquids beginning the day before and continuing throughout the 3 days of TBI.

2) Intermediate Side Effects (1 to 4 months): Interstitial pneumonia is assumed to be related in various degrees to chemoradiotherapy - an incidence of up to 5 to 10% fatal interstitial pneumonitis may be anticipated; graft-versus-host disease will not be a factor in this study using autologous marrow (and irradiated blood component transfusions); prolonged immunoincompetence may predispose to opportunistic infections.

3) Late Effects (> 4 months):Available data are limited, but an increased incidence of cataracts and sterility is known; the risk of developing a second malignancy is unknown but may be increased. Additional complications may appear as more long-term survivors appear.

All doses calculated on basis of corrected ideal weight (see Appendix I, Table of Ideal Weight), which is the ideal weight plus 25% of the difference between the actual and ideal body weight.

5.334 Etoposide Treatment

Etoposide is administered as a single infusion on day -3 prior to marrow infusion. The dose of etoposide will be 60 mg/kg, delivered undiluted IV over 4 hours. Patients should be observed for anaphylactic type reactions during the infusion. Emergency medication must be available.

Rev. 7/04

5.335 Allogeneic Peripheral Blood Stem Cell (PBSC) or Marrow Collection and Infusion

Peripheral blood stem cells may be mobilized from allogeneic donors. A Suggested mobilization regimen is G-CSF 10 µg/kg SC daily for 4 days followed by initiation of peripheral blood stem cell collection on day 5 with continued G-CSF 10 µg/kg daily until collections are completed. Alternative mobilization regimens using higher doses of G-CSF or in combination with GM-CSF are allowed and can be strongly considered in donors, especially for haploidentical transplants. It is strongly encouraged that peripheral venous sites be utilized for the collection. However, if peripheral venous access is inadequate, a central vemous catheter can be placed for this purpose. The dose of peripheral blood stem cells collected should be preferably equal to or exceed 5×10^6 CD34+/kg (recipient weight) for matched related or unrelated donors. For haploidentical donors, a suggested minimum collection should be $10x\ 10^6$ CD34+/kg.

If allogeneic marrow collection opted for, it will be aspirated under spinal or general anesthesia, screened and infused IV 72 hours after the dose of etoposide. A dose of 3×10^8 nucleated cells/kg real body weight of the recipient is desirable. If an ABO incompatibility exists, immunoadsorption, plasmapheresis, or red cell depletion techniques will be acceptable (48-50).

5.336 GVHD Prophylaxis

Rev. 7/04

For matched-related and unrelated donors, any of several GVHD prophylaxis regimens will be acceptable. The following are suggested guidelines regarding GVHD prophylaxis. In general, we would recommend using Cyclosporine alone or with methylprednisolone at the doses noted below or Cyclosporine combined with Methotrexate. Methotrexate/Cyclosporine is superior to Cyclosporine alone, but may retard

Rev. 7/04

marrow reconstitution, even if hematopoietic growth factors are used (51).

5.3361 Cyclosporine Administration: In general, Cyclosporine is started on the day before marrow infusion (day -1) at a dose of 3 mg/kg/day intravenously in two divided doses (1.5 mg/kg each) and infused over a period of 1-4 hours. IV Cyclosporine can be discontinued when patients start to eat and PO Cyclosporine substituted at a dose of 12.5 mg/kg/day in two divided doses (6.25 mg/kg each). Unless toxicities are encountered, Cyclosporine can be continued at the same dose until day 50, after which the drug can be reduced by 5% per week and discontinued on day 180 after grafting.

5.3362 Methotrexate Administration: If Methotrexate is to be combined with Cyclosporine, doses of 15 mg/m^2 on day 1 followed by 10 mg/m^2 on days 3, 6, and 11 are recommended.

5.3363 Methylprednisone Administration: If Methylprednisolone is to be combined with Cyclosporine, a suggested regimen would be 0.5 mg/kg IV on days 8-14, increased to 1 mg/kg and maintained through day 28, and then tapered until discontinuation on day 72.

5.337 Recombinant Human GM-CSF (rhGM-CSF)

GM-CSF has been successfully used to shorten hematopoietic recovery time following conventional or high dose chemotherapy treatment following autologous and allogeneic BMT as well as to induce an increase in neutrophil count in aplastic anemia and myelodysplastic syndromes (35-40).

5.3371 GM-CSF: Dose, Route and Schedule

Rev. 2/96

Patients should receive GM-CSF each day subcutaneously, beginning 6 hours after bone marrow infusion. GM-CSF should be initiated at a dose of 250 mcg/m^2. Treatment should continue until the patient has achieved an absolute neutrophil count (ANC) of $\geq$ 1000 cells/µL on 3 consecutive days.

NOTE: The WBC count may fall by 25-60% within 24-72 hours after the GM-CSF is discontinued.

Rev. 2/96

5.3372 Dose Adjustments: GM-CSF

Complications and toxicity will be graded according to the Common Toxicity Criteria (Appendix III), except for bone marrow engraftment toxicities (Appendix IV) which will be based on duration of cytopenia rather than nadir. Additionally, Appendix V will be used for grading capillary or vascular leak syndrome.

Adjustments in the total daily dose of GM-CSF will NOT be made for changes in body weight. Dosing of an individual patient will be terminated if toxicity thought to be due to the drug is believed to be life-threatening (Grade 4). PATIENTS WITH GRADE 4 TOXICITY ATTRIBUTABLE TO GM-CSF MAY NOT RE-START THE MEDICATION.

Individual patients who experience moderate (Grade 3) major organ toxicity may continue on GM-CSF but the dosage will be reduced by 50%. If Grade 3 toxicity persists for 7 days or advances to grade 4 toxicity, then GM-CSF will be discontinued, and the patient may not re-start GM-CSF.

Discontinuation of GM-CSF for lesser grades of toxicity will be at the Investigator's discretion.

Should a patient develop infection while on treatment with GM-CSF the medication should be continued.

5.3373 Drug Administration

Following allogeneic bone marrow transplant GM-CSF therapy will
Rev. 2/96 commence. The first injection will be given within 6 hours after the completion of the bone marrow infusion.

5.338 Supportive Care

Other supportive care issues are similar to those described for autologous
Rev. 10/05 transplantation under Section 5.336.

Rev. 7/04, 10/05 5.34 Autologous Peripheral Blood or Bone Marrow Transplantation: Arms C and F

For Ph- patients (Arm C):

Peripheral blood or marrow harvesting and therapy will begin no sooner than 4 weeks and no later than 7 weeks from start of intensification treatment. All patients should be harvested whether they are randomized to transplant or not. An additional 1 month is permissible to allow for resolution of post-intensification therapy toxicities, i.e., recovery from hepatitis, recovery of adequate renal function, or resolution of infection so that the patient meets the eligibility requirements specified in Section 3.2.

See section 5.324 for details of stem cell collection for Ph- patients.

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For Ph+ patients (Arm F):

For Ph+ patients lacking a suitable allogeneic donor, autologous transplant will be
Rev. 10/05 offered immediately following Phase II Induction. These patients will receive a consolidation chemotherapy course with high-dose cytarabine and mitoxantrone. This combination has been shown to achieve high rates of remission in patients with newly diagnosed or relapsed AML or ALL (52, 53). As patients recover from this chemotherapy they will undergo collection of their peripheral blood stem cells followed by autologous transplant.

Rev. 7/04 5.341 Consolidation/Mobilization Chemotherapy for Ph+ patients

Cytarabine	2 g/m^2 IV over 3 hrs per day Day 1-3 inclusive.
Rev. 12/04 Mitoxantrone	30 mg/m^2 IV push following the cytarabine Days 1-2 inclusive only.
G-CSF	10 µg/kg rounded to the nearest vial size q. day until peripheral blood stem cell collection and hematopoietic recovery beginning on Day 5.

Rev. 7/04

5.342 Peripheral Blood Stem Cell Collection

Patients will be monitored frequently (suggested daily) following completion of the cytarabine and mitoxantrone chemotherapy. It is anticipated that these patients will develop severe pancytopenia and require transfusions and monitoring for neutropenic fever. At the first signs of hematopoietic recovery, measurement of peripheral blood CD34 counts should be initiated as per institutional protocol and peripheral blood stem cell collection initiated when the CD34 count is > 10/mL. Peripheral blood stem cell collections should continue daily until a preferred goal of 5×10^6 CD34+ cells/kg have been collected. However, a minimum of 2×10^6 CD34+ cells/kg is required.

If, after five consecutive collections, 2×10^6 CD34+ cells/kg is not achieved or if there is evidence prior to completion of five collections that this goal will not be achieved, then the dose of G-CSF can be increased to 16 µg/kg SC b.i.d. and after several days in conjunction with monitoring of peripheral blood CD34 counts if a peripheral blood CD34 count > 10/mL has been achieved, further collections can proceed.

If this maneuver is unsuccessful in mobilizing adequate peripheral blood stem cells, then consideration can be given to marrow harvesting.

5.343 Marrow Harvesting (if opted for instead of peripheral blood stem cell collection or if patient fails peripheral blood stem cell collection)

Within 2 weeks preceding harvesting, lumbar puncture and a bone marrow aspiration and biopsy are performed. The presence of occult leukemic meningitis, focal clusters of leukemic cells in the marrow, or a marrow that is less than normocellular excludes a patient from autologous or allogeneic transplantation.

Marrow is harvested under spinal or general anesthesia. A minimum of 1×10^8 nucleated bone marrow cells (total nucleated cells collected minus peripheral blood cell contamination)/kg of body weight must be collected, but an optimum of at least 3×10^8 nucleated bone marrow cells/kg of body weight is desirable. Cells harvested in excess of this amount may be frozen for backup. Blood removed during the procedure will be replaced by transfusion of irradiated blood, administered as packed cells.

5.344 Marrow Processing

After filtration through stainless steel mesh filters (0.33 mm and 0.2 mm pores) to remove particulate matter, the buffy coat is extracted. All manipulations of the bone marrow should be performed in a closed system to avoid bacterial contamination. Acceptable procedures to obtain the buffy coat include centrifugation in blood transfer packs in a blood bank centrifuge, or use of the COBE 2991 cell washer or Haemonetics cell separator. Heparinized plasma from the marrow is saved for use in the processing and freezing, and should be irradiated to $\geq$ 1500 rad or filtered to remove any viable leukemic cells. The buffy coat is washed using normal saline + 2% irradiated autologous plasma and resuspended at 4-5 x 10^7 cells/ml in 10% final concentration DMSO and 10% final concentration of autologous plasma for cryopreservation in liquid nitrogen. The frozen cells are stored in the vapor or liquid phase if liquid nitrogen. All processing of bone marrow will be in accordance with good blood bank practices and use a method approved by the BMT Committee. The Standard Operating Procedure for the buffy coat may not vary for each institution and should be approved by the study chairman prior to patient enrollment.

5.345 Preparative Regimen

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See Section 5.332.

5.346 Peripheral Blood Stem Cell or Marrow Reinfusion

Rev. 7/04

Peripheral blood or marrow is thawed in close proximity to the patient's room and infused without using additional filtering or washing steps. Only one marrow bag must be thawed at a time.

The cells not washed before reinfusion, and the osmolality of the cell suspension requires the use of a flowing central venous catheter.

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Twelve hours before reinfusion of autologous peripheral blood stem cells or bone marrow, hydration should be initiated with crystalloid infusion such as 1/2 normal saline to insure urine output of at least 2L/m^2/day. Sodium bicarbonate should be added to the hydration fluids to ensure an alkaline urine (pH > 5). Emergency drugs (Benadryl, epinephrine, Solu-Medrol) in appropriate doses must be at the bedside. Baseline vital signs, forced vital capacity and EKG are recorded. It is suggested the patient is connected to a telemetry monitor for 4 hours during and after reinfusion. Fifteen minutes prior to administration of the thawed bone marrow, the patient is to receive:

50 ml of 25% Mannitol solution IV
50 mg of Benadryl IV
250 mg of Solu-Cortef IV
The anti-emetic drug of choice (optional)

These drugs are to ensure good urine flow and to minimize the effects of DMSO and DMSO mediated histamine release such as abdominal cramping, flushing, and hemoglobinuria. The bags of bone marrow will be quickly thawed in a 37°C water bath (in close proximity to the patient room to minimize transit time) and pulled into 50 ml syringes. These syringes will be infused IV without an in-line filter over 3-5 minutes each. If the patient develops chest tightness or other symptoms, a short rest may be required. Usually a 30-60 minute rest is required after 6-8 syringes. No additional premedications necessarily need be given after this short rest period. Only one bag of marrow should be thawed at a time, and not until the preceding bag has been completely infused. A physician MUST be present during the marrow infusion and for 1 hour afterwards. A nurse familiar with adverse signs of blood transfusion should monitor vital signs between each marrow infusion and every 15 minutes until 1 hour after the marrow infusion is completed. The patient's urine may be red for 12 hours after the infusion because of red cell hemolysis and the pH indicator in the tissue culture media. Orange scent may help mask the DMSO odor which will be present for about 24 hours after the marrow reinfusion.

5.347 Recombinant Human GM-CSF (RhGM-CSF)

GM-CSF has been successfully used to shorten hematopoietic recovery time following conventional or high dose chemotherapy treatment following autologous and allogeneic SCT as well as to induce increase in neutrophil count in aplastic anemia and myelodysplastic syndromes (54-59).

5.3471 GM-CSF: Dose, Route and Schedule

Rev. 2/96

Patients should receive GM-CSF each day subcutaneously, beginning 6 hours after bone marrow infusion. GM-CSF should be initiated at a dose of 250 mcg/m^2. Treatment should continue until the patient has achieved an absolute neutrophil count (ANC) of $\geq$ 1000 cells/µL on 3 consecutive days.

NOTE: The WBC count may fall by 25-60% within 24-72 hours after the GM-CSF is discontinued.

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5.3472 Dose Adjustments: GM-CSF

Complications and toxicity will be graded according to the Common Toxicity Criteria (Appendix III), except for bone marrow engraftment toxicities (Appendix IV) which will be based on duration of cytopenia rather than nadir. Additionally, Appendix V will be used for grading capillary or vascular leak syndrome.

Adjustments in the total daily dose of GM-CSF will NOT be made for changes in body weight. Dosing of an individual patient will be terminated if toxicity thought to be due to the drug is believed to be life-threatening (Grade 4). PATIENTS WITH GRADE 4 TOXICITY ATTRIBUTABLE TO GM-CSF MAY NOT RE-START THE MEDICATION.

Individual patients who experience moderate (Grade 3) major organ toxicity may continue on GM-CSF but the dosage will be reduced by 50%. If Grade 3 toxicity persists for 7 days or advances to grade 4 toxicity, then GM-CSF will be discontinued, and the patient may not re-start GM-CSF.

Discontinuation of GM-CSF for lesser grades of toxicity will be at the Investigator's discretion.

Should a patient develop infection while on treatment with GM-CSF the medication should be continued.

5.3473 Drug Administration

Rev. 2/96

Following autologous bone marrow reinfusion GM-CSF therapy will commence. The first injection will be given within 6 hours after the completion of the bone marrow reinfusion.

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5.348 Post-Autologous/Allogeneic/MUD SCT Imatinib Therapy for Ph+ patients only

Rev. 7/04, 5/06

After recovery of the WBC to 3 x 10(9)/L and platelets to 50 x 10 (9) L post-SCT, Imatinib at a dose of 200 mg po qd will be commenced and dose escalated to 600 mg po qd as soon as possible, if tolerated hematologically and generally by the patient, and will be continued indefinitely or until disease progression.

5.3481 Dose Modifications for Toxicity

5.34811 Non-Hematologic Toxicity

If a patient experiences a grade 2 non-hematologic toxicity lasting for more than two days, Imatinib should be withheld until the toxicity is resolved to $\leq$ grade 1. Imatinib may then be resumed at a dose of 600 mg orally per day. If the grade 2 toxicity recurs, Imatinib must be withheld until the toxicity is resolved to $\leq$ grade 1. Imatinib may then be resumed at a reduced dose of 400 mg orally q.d. If grade 2 toxicity recurs, further dose reduction to 300 mg daily can be performed using the above procedures.

If grade 3/4 toxicity occurs, Imatinib must be withheld until the toxicity is resolved to $\leq$ grade 1. Imatinib may then be resumed at a reduced dose of 400 mg daily. If $\geq$ grade 2 toxicity recurs, a further dose reduction to 300 mg orally daily can be performed using the above procedures.

5.34812 Hepatic Toxicity

Patients with a total serum bilirubin ≤ 1.5 x ULN at baseline who experience ≥ grade 2-4 elevation should be managed using the criteria detailed above for non-hematologic toxicity.

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In patients with serum total bilirubin > 1.5 - ≤ 3 x ULN at baseline who experience ≤ 2-fold increase in bilirubin, Imatinib must be held until the levels return to baseline values and then resumed at a dose of 600 mg orally daily. If a similar degree of toxicity recurs, the study drug must be held until the bilirubin levels return to baseline level values and study drug may then be resumed at a dose of 400 mg daily. If a similar degree of toxicity recurs, a further dose reduction to 300 mg orally daily can be performed, using the above procedures.

If patients experience greater than 2-fold increase in total bilirubin levels, study drug must be withheld until the levels return to baseline values and study drug may then be resumed at a dose of 400 mg daily. If a similar degree of toxicity recurs, further dose reduction to 300 mg orally daily can be performed, using the above procedures.

Patients with SGOT (AST)/SGPT (ALT) < 2.5 x ULN at baseline who experience > grade 2-4 elevations in one or both transaminases should be managed using the criteria detailed above for non-hematologic toxicity.

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In patients with SGOT (AST) or SGPT (ALT) > 2.5 - ≤ 5 x ULN at baseline who experience ≤ 3-fold increase in the levels of the most elevated transaminase, Imatinib must be held until the transaminase levels return to baseline values and then resumed at a dose of 600 mg orally daily. If a similar degree of toxicity recurs, study drug must be held until transaminase levels return to baseline values and the study drug may then be resumed at a dose of 400 mg orally daily. If a similar degree of toxicity recurs, further dose reduction to 300 mg orally daily can be performed, using the above procedures.

If patients experience > 3-fold increase in the levels of the most elevated transaminase, study drug must be withheld until the transaminase levels return to baseline values and study drug may then be resumed at a dose of 400 mg orally daily. If a similar degree of toxicity recurs, a further dose reduction to 300 mg orally daily can be performed, using the above procedures.

5.34813 Hematologic Toxicity

Patients developing anemia may be transfused at the discretion of the investigator. No dose reductions are needed for any degree of anemia or for grade 1-3 neutropenia or thrombocytopenia.

Similarly, if platelet counts can be maintained by the periodic administration of platelet transfusions, no dose reductions are foreseen for grade 4 thrombocytopenia. In the event that platelet support is either unavailable or ineffective, dose reductions for grade 4 thrombocytopenia are described below.

5.34814 Grade 4 Neutropenia and/or Thrombocytopenia (for patients when platelet support is unavailable/ineffective)

No dose modification will be performed during the first 28 days of therapy.

To assess cellularity and percentage of blasts, a bone marrow aspirate will be performed after a minimum of 28 days of therapy with Imatinib in patients with grade 4 neutropenia (ANC < 0.5 x 10^9/L) and/or thrombocytopenia (platelets < 10 x 10^9/L) that has lasted for $\geq$ 2 weeks.

If the bone marrow cellularity is < 10% and blasts < 10%, dose reduced to 400 mg orally daily. (If grade 4 neutropenia and/or thrombocytopenia persists for an additional two weeks, repeat the bone marrow aspirate to assess cellularity and percentage blasts. If the bone marrow is hypocellular and blasts < 10%, dose reduced to 300 mg per day.

If grade 4 neutropenia and/or thrombocytopenia persists for an additional two weeks and a repeat bone marrow is hypocellular and with blasts <

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10%, study drug will be held until ANC $\geq$ 1 x 10^9/L and platelets > 20 x 10^9/L at which time study drug will be resumed at 300 mg orally daily.

If bone marrow cellularity is > 10% and blasts are > 10%, patient is off study.

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5.349 Supportive Care Considerations

5.3491 Venous Access

Multilumen indwelling Silastic central venous catheters are required before initiating therapy. Triple lumen or quadruple lumen catheter are suggested.

5.3492 Mucosal Evaluation and Care

Mucositis is expected to be severe. In patients with poor oral hygiene, consultation by Oral Surgery is recommended prior to initiating therapy since multiple dental extractions may be necessary. Stomatitis and esophagitis due to herpes virus may be confused with drug-induced mucositis and viral cultures should be obtained frequently.

5.3493 Acyclovir Prophylaxis

All patients will receive Acyclovir Prophylaxis (250 mg/m^2 IV every 8 hours) from day -3 until day +17; it is suggested all patients receive IV acyclovir, until discharge.

5.3494 Nutritional Evaluation and Therapy

Malnutrition is expected due to lack of food intake after treatment. Intravenous alimentation should be initiated until oral food intake becomes adequate as recovery ensues.

5.3495 Blood Component Support

5.34951 All blood products will be irradiated (> 1500 rads) to prevent GVHD.

Packed red cell transfusions (leukocyte-poor) will be given as needed to keep the hemoglobin level > 9 grams % or Hct > 30%.

5.34952 Single donor (or pooled if unavailable) platelets will be given as needed in attempt to maintain the platelet count above 20,000/µl. For patients who are refractory to pooled platelets (increment < 5000/µl/m^2/10^{11} platelets/1 hour) considerations of the use of HLA-matched platelet transfusions should be given.

5.34953 Neutrophil transfusions may (only) be given to patients with granulocytes < 500/µl who also have gram negative bacteremia, or a local infection (fungal or bacterial) that has progressed after 48 hours of antibiotic therapy.

5.3496 Candida Prophylaxis

From the start of therapy, patients will receive oral Mycostatin (1 million units "swish and swallow", qid), Clotrimazole troches (5 x daily) or oral Fluconazole 200 mg every day or bid to reduce gastrointestinal colonization with Candida.

5.3497 Management of Fever/Infections

5.34971 Patients with neutropenia (< 500 granulocytes/µl) will be started on broad-spectrum antibiotics empirically for fever (> 38.2°C) after appropriate cultures (blood x 3 sets, urine, and any sites with signs or symptoms of infections) have been obtained. Selection of antibiotics should be based on the pattern of sensitivity of organisms at each institution. It is suggested antibacterials should include as a minimum, an aminoglycoside (e.g., tobramycin or Amikacin) and a cephalosporin or semi-synthetic penicillin (e.g., Mezlocillin, ticarcillin, or Piperacillin). Nafcillin or Vancomycin may be added for coverage of resistant S. Epidermidis which is a potential problem in patients with indwelling venous catheters. To avoid toxicity and provide maximum therapeutic benefit, serum levels of aminoglycoside and Vancomycin must be obtained and doses adjusted accordingly.

5.34972 P. Carinii prophylaxis should be accomplished with TMP/SMZ (Bactrim) DS I tab PO bid starting on day -10 and continuing until day +90. It may be the practice to administer TMP/SMZ 2-3 times per week at some institutions and this is permissible. For those exhibiting allergy to TMP/SMZ use of pentamidine 300 mg aerosol inhaled monthly for 6 months is recommended.

5.34973 Patients with documented fungal infections or with persistent unexplained fever that is unresponsive to 4-7 days of broad-spectrum antibiotics will receive intravenous Amphotericin B, 0.6 mg/kg/day. Rev. 7/04 Patients shown to have aspergillosis should receive 1-1.5 mg/kg/day amphotericin B.

5.34974 CMV prophylaxis for CMV seronegative patients is suggested with use of CMV seronegative blood products.

5.34975 Diffuse pulmonary infiltrates occur frequently and can present difficult diagnostic problems. Whenever possible a tissue diagnosis should be obtained by bronchoscopy or open lung biopsy. In the absence of a tissue diagnosis, empiric antibiotic therapy should be expanded to include potentially treatable etiologies, including Erythromycin (for Legionnaire's), TMP/SMZ (high dose regimen for presumed pneumocystis) as well as Acyclovir and Amphotericin B, if these agents are not already in use.

5.3498 Management of Acute Pulmonary Dysfunction

It has been recognized with increased frequency that patients undergoing autologous bone marrow transplantation are at high risk for the development of a syndrome of acute pulmonary dysfunction characterized by the sudden onset of severe dyspnea, tachypnea, and hypoxia (with or without roentgenographic findings)

Rev. 7/04 which may progress rapidly to dependence on mechanical ventilation (60-63). This syndrome, when it occurs, usually has its onset within 3 weeks of marrow transplant, and is fatal in a high percentage of patients. At present, the etiology is unknown. This syndrome may respond to high-dose corticosteroid therapy (e.g., methylprednisolone doses > 1-2 mg/kg/day in divided doses) IF THERAPY IS INITIATED WITHIN 12-24 HOURS OF THE ONSET OF SIGNS AND SYMPTOMS.

Patients who develop acute pulmonary dysfunction should receive corticosteroid therapy as well as undergo rapid invasive diagnostic procedures during the initial time period to rule out other etiologies (e.g., infection, fluid overload, etc.). Corticosteroid therapy can be tapered gradually over 4-6 weeks.

Patients who develop the above syndrome of acute pulmonary dysfunction should discontinue the use of GM-CSF.

5.3499 Management of Fluid Accumulation

After marrow transplant and hematopoietic growth factor therapy, patients may experience a "capillary-leak" syndrome leading to extravascular fluid retention. The peak of weight gain, if it develops, occurs 2 weeks after therapy and then resolves with supportive care. Careful attention to the patient's weight is necessary and intensive forced diuresis should be used to prevent excess fluid retention.

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5.4 ADVERSE EVENT REPORTING REQUIREMENTS

5.41 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please follow directions for routine reporting provided in the Records to be Kept Section). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.42 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

* *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events which occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Toxicity Criteria (CTC).* The CTC provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTC can be downloaded from the CTEP home page (**http://ctep.cancer.gov**). Additionally, if assistance is needed, the NCI has an Index to the CTC that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTC.

Step 2: *Grade the event using the NCI CTC.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial)*. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4 *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

If your patient received E. Coli Asparaginase (L-Asparaginase) or PEG-LAsparaginase

* **Arms A, B, C, D, E, and F** - the drug package insert or protocol

If your patient received Erwinia L-Asparaginase

* **Arms A, B, C, D, E, and F** - the investigator's brochure (for Erwinia L-Asparaginase), drug package insert or protocol

Step 5: *Review Tables 5.46 and 5.47 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

5.43 Reporting methods

* **For patients who received Erwinia L-Asparaginase - (Arms A, B, C, D, E, and F) or patients who received the bone marrow transplant (Arms B, C, E, and F)** - This study arm requires that expedited adverse event reporting use the NCI's Adverse Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http//ctep.cancer.gov

An AdEERS report must be submitted to ECOG by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http//ctep.cancer.gov, or

- Fax the completed NCI Adverse Event Expedited Report - Single Agent or Multiple Agents paper template located at http//ctep.cancer.gov to 617-632-2990, AttentionAE

NOTE: Paper copies of AdEERS reports will only be accepted if the AdEERS system is down.

Fax supporting documentation to ECOG (617-632-2990), Attention: AE.

* **For patients receiving E. Coli Asparaginase (L-Asparaginase) or PEG-L-Asparaginase) - Arms A and D**- This study arm requires that expedited adverse event reporting use the MedWatch system.

The FDA MedWatch 3500 Reporting Form can be obtained electronically at http//www.fda. gov/medwatch/safety/3500.pdf /3500.pdf

5.44 When to report an event in an expedited manner

* Some adverse events require 24-hour notification (refer to Table 5.46 to NCI and ECOG. Please complete a 24 Hour Notification Report via the NCI AdEERS website (http://ctep.cancer.gov/reporting/adeers.html).

* When the adverse event requires expedited reporting, submit the report within 7 working days of learning of the event.
* There may be protocol-specific timelines for expedited reporting-refer to Tables 5.46 and 5.47 for instruction.

NOTE: Adverse events that meet the reporting requirements in tables 5.46 or 5.47 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using AdEERS or MedWatch). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in tables 5.46 or 5.47 must be reported on an expedited adverse event report form (using AdEERS or MedWatch).

5.45 Other recipients of adverse event reports

ECOG will forward AdEERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

Adverse events determined to be reportable must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

The drug sponsor is obliged to forward reported AEs to the FDA. A drug sponsor representative may call a site for additional information regarding a serious adverse event. Any additional written AE information requested by the drug sponsor MUST be submitted to ECOG and not directly to the drug sponsor. ECOG will then forward the information to the drug sponsor.

Institutions are responsible for submitting MedWatch reports to ECOG, the NCI, and FDA.

ECOG Fax Number: (617) 632-2990
ECOG Mailing Address:
ECOG Coordinating Center
FSTRF
Attention: Adverse Event
900 Commonwealth Avenue
Boston, MA 02215

NCI Fax Number: (301) 230-0159
NCI Mailing Address:
Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824

FDA Fax Number: (800)-332-0178
FDA Mailing Address:

MedWatch
5600 Fishers Lane
Rockville, MD 20852-9787

5.46 Expedited reporting for investigational agents

Expedited reporting is required if the patient has received at least one dose of the investigational agents as part of the trial. Reporting requirements are provided in Table 5.46. The investigational agent used in arms A, B, C, D, E, and F of this study is Erwinia L-Asparaginase. Patients who receive the bone marrow transplant must also follow the reporting guidelines in this section.

Table 5.46.

Expedited reporting requirements for adverse events experienced by patients on study arm(s) who have received at least one dose of Erwinia L-Asparaginase in this study (Arms A, B, C, D, E, and F) or received the bone marrow transplant (Arms B, C, E, and F).

Attribution	**Grade 2**	**Grade 3**		**Grade 4**		**Grade 5[b]**		**Protocol Specific Requirements/ Exceptions**
	Unexpected	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected	See footnote (c) for special requirements. See footnote (d) for special exceptions.
Unrelated or Unlikely		AdEERS if Hospitalized	AdEERS if Hospitalized	24-Hr Report and AdEERS	AdEERS	24-Hr Report and AdEERS	AdEERS	
Possible, Probable, Definite	AdEERS[a]	AdEERS[a]	AdEERS if Hospitalized					

24-Hr Report: Please complete a 24 Hour Notification Report via the NCI AdEERS website (http//ctep.cancer.gov/reporting/adeers/html).

AdEERS: Indicates an expedited report is to be submitted within 7 working days of learning of the event.

Hospitalization: Any grade 3, 4, or 5 adverse event which precipitates a hospitalization lasting $\geq$ 24 hours or prolongs hospitalization must be submitted via AdEERS within 7 working days of learning of the event, regardless of requirements of the study phase, grade, the attribution, or whether the event is expected or unexpected.

a AdEERs reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

b This includes all deaths within 30 days of the last dose of treatment with an investigational agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with an investigational agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported via AdEERS.

c **Protocol-specific expedited reporting requirements**: The adverse events listed below also require expedited monitoring for this trial:

Hospitalization: Any grade 1 or 2 adverse event which precipitates a hospitalization lasting $\geq$ 24 hours or prolongs hospitalization must be submitted via AdEERS within 7 working days of learning of the event, regardless of requirements of the study phase, grade, the attribution, or whether the event is expected or unexpected.

d For study arms A, B, C, D, E, and F, the adverse events listed below do **not** require expedited reporting via AdEERS:

* AdEERs reporting is only required if the event is related to the bone marrow transplant or investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

5.47 Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 5.47. The commercial agents used in arms A, B, C, D, E, and F of this study are Daunorubicine, Vincristine, Prednisone, L-Asparaginase, Methotrexate, Cyclophosphamide, Cytarabine, 6-Mercaptopurine, Mitoxantrone, and Imatinib.

Table 5.47

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only - Arms A and D. **If the patient received Erwinia L-Asparaginase, follow the reporting guidelines in section 5.46.**

Attribution	**Grade 4**		**Grade 5[a]**		
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely					
Possible, Probable, Definite	MedWatch		MedWatch		

FDA MedWatch Form 3500: Indicates that an expedited report is to be submitted to ECOG, NCI, and FDA within 7 working days.

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

5.48 Reporting secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to ECOG. Submit the following information within 30 days of an AML/MDS diagnosis occurring after treatment for cancer on NCI-sponsored trials:

* a completed NCI/CTEP Secondary AML/MDS Report Form (*do not use AdEERS*);
* a copy of the pathology report confirming the AML/MDS; and
* a copy of the cytogenetics report (if available).

ECOG will forward copies to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP).

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS Report Form must be submitted for the most recent trial. ECOG must be provided with a copy of the report even if ECOG was not the patient's most recent trial.

5.49 Reporting of other second primary cancers

All cases of new primary cancers that occur on ECOG protocols during or after protocol must be reported to ECOG, according to the follow up schedule outlined in the protocol, on the ECOG Second Primary Form within 30 days of diagnosis, regardless of relationship to protocol treatment. Once data regarding survival and remission status are no longer required by the protocol, only second primaries thought to be possibly related to protocol treatment should be reported. Not for use for reporting recurrence or metastatic disease. A copy of the pathology report should be sent, if available.

Submit AML/MDS and Second Primary information to:

ECOG Coordinating Center
FSTRF
900 Commonwealth Avenue
Boston, MA 02215

6.0 MEASUREMENT OF EFFECT

6.1 Complete Remission (CR)

Please note: patients may register for Step 2 any time after the onset of CR.

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6.11 Peripheral Blood Counts

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6.111 Neutrophil count $\geq 1 \times 10^9$/L.

6.112 Platelet count $\geq 100 \times 10^9$/L.

6.113 Reduced hemoglobin concentration or hematocrit has no bearing on remission status.

6.114 Leukemic blasts must not be present in the peripheral blood.

6.12 Bone Marrow Aspirate and Biopsy

6.121 Cellularity of bone marrow biopsy must be > 20% with maturation of all cell lines.

6.122 $\leq$ 5% blasts.

6.13 Extramedullary leukemia, such as CNS or soft tissue involvement, must not be present.

6.2 Partial Remission (PR)

6.21 Requires that all of the criteria for complete remission be satisfied except that the bone marrow may contain > 5% blasts but < 25% blasts.

6.3 Relapse

Relapse following complete remission is defined as:

6.31 Peripheral Blood Counts

6.311 Reappearance of blasts in the blood.

6.32 Bone Marrow Aspirate & Biopsy

6.321 Presence of ≥ 5% blasts, not attributable to another cause (e.g., bone marrow regeneration).

6.322 If there are no circulating blasts and the bone marrow contains 5% to 20% blasts, then a repeat bone marrow performed ≥ 1 week later documenting more than 5% blasts is necessary to meet the criteria for relapse.

7.0 STUDY PARAMETERS

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7.1 Therapeutic Parameters

a) All scans and x-rays should be done ≤ 6 weeks before registration.

b) CBC with differential, all chemistries, clotting assessments, bone marrow aspirate and biopsy, and LP should be done ≤ 1 week before registration.

NOTE: When filling out these pre study results on the ECOG flow sheets, please make sure that ALL relevant dates are clearly given. Do NOT put all the results under the date for Day 1 of protocol treatment unless they were actually done that day. Record the actual dates.

For follow up Hgb, Hct, WBC, Plt, these tests should be done within 48 hours of the day of treatment.

Rev. 7/04

Table 1: Study Parameters for Ph- patients

	Induction		Transplant - Intensification/Consolidation/Maintenance		
	Prior to Phase I	Prior to Phase II	Prior	Prior	Follow-up
Physical Examination	X	X	X	X	X
Weight	X	X	X	X	
Hgb, Hct, WBC, Differential, Platelet	X	X	X	X	X
Creatinine, Uric Acid	X	X	X	X	
Bilirubin, SGOT/SGPT, LDH, ALK, Phosphatase	X	X	X	X	X
Chest X-ray	X[1]				
EKG	X				
Rev 2/96, 2/07 Cardiac Ejection Fraction [8]	X[7]		X	X	
PT, PTT, Fibrinogen	X	X	X	X	
Lumbar Puncture	X[2]	X[2]	X[2]	X[2]	
Rev 2/95 Bone Marrow Aspirate & Biopsy	X	X[3]	X	X[3]	X[4]
Samples for PCR analysis	X		X	X	X
HLA Type	X[5]				
Local cytogenetics	X[6]				
Rev 2/95, 2/96 Creatinine Clearance	X		X		
Rev 2/95, 2/96, 2/07 PFT (FEV, DLCO)[8]			X		

[1] As indicated.

[2] Schedule depends on whether or not occult disease is present at diagnosis. See Section 5.213 for phase I; Section 5.2222 for phase II; and Section 5.311 for intensification, consolidation and maintenance. Rev. 10/00, 10/05

[3] Repeat on Day 28 of phase I, Day 28 phase II. See Section 5.2221. Rev. 2/95

[4] During follow-up, every 6 months for 24 months. Rev. 7/98

[5] HLA type patient and siblings, or provide written explanation on flow sheet for not performing HLA typing. Search for donors during induction.

[6] Surface markers and karyotype studies should be done on entry. See Sections 7.2 and 11, Leukemia Correlative Studies Section for routing information. Rev. 2/98

[7] When pre-therapy Cardiac Ejection Fraction cannot be obtained (i.e. weekend or holiday intervenes), a 2-D echo or a MUGA within 5 days of initiation of therapy may be done. Rev. 7/98, 2/07

[8] Only for patients considered for transplant.

Rev. 7/04, 12/04, 10/05

Table 2: Study Parameters for Ph + Patients

	Induction							
	Prior to Phase I		Prior to Phase II		Prior to Autologous or Allogeneic Transplant		Follow-up	
Physical Examination		X		X		X		X
Weight		X		X		X		
Hgb, Hct, WBC, Differential, Platelet		X		X		X		X
Creatinine, Uric Acid		X		X		X		
Bilirubin, SGOT/SGPT, LDH, ALK, Phosphatase		X		X		X		X
Chest X-ray		X[1]						
EKG		X						
Cardiac Ejection Fraction		X[7]				X		
PT, PTT, Fibrinogen		X		X		X		
Lumbar Puncture		X[2]		X[2]		X		
Bone Marrow Aspirate & Biopsy		X		X[3]		X		X[4]
HLA Type		X[5]						
Surface Antigenic Markers & Karyotype Studies		X[6]						
Creatinine Clearance		X				X		
PFT (FEV, DLCO)						X		
Minimal Residual Disease (PCR for BCR-ABL)[7]	Please see footnote 8 for specific time points.							

1 As indicated.

2 Schedule depends on whether or not occult disease is present at diagnosis. See Section 5.213 for phase I; Section 5.2222 for phase II.

3 Repeat on Day 28 of phase I, Day 28 phase II. See Section 5.2221.

4 During follow-up, every 6 months for 24 months.

5 HLA type patient and siblings, or provide written explanation on flow sheet for not performing HLA typing. Search for donors during induction.

6 Surface markers and karyotype studies should be done on entry. See Sections 7.2 and 11, Leukemia Correlative Studies Section for routing information.

7 When pre-therapy Cardiac Ejection Fraction cannot be obtained (i.e. weekend or holiday intervenes), a 2-D echo or a MUGA within 5 days of initiation of therapy may be done.

8 PCR for BCR-ABL will be done at the following time points: baseline, after induction chemotherapy, after CR, after the four weeks of Imatinib administration, during stem cell harvest for autotransplant patients, every 3 months for 2 years and every 6 months in the third year for autotransplant and allogeneic transplant patients. Both bone marrow and peripheral blood will be tested depending on what is collected.

Rev. 7/04

7.2 Biological Material Submission

Baseline samples must be submitted from all patients upon study entry. Samples must also be submitted from baseline Ph+ patients upon recovery from transplant.

1. Central cytogenetic analysis for the presence of the Ph+ chromosome must be perfomed. Baseline karyotypes must be submitted for central analysis within one week following patient registration (see Section 11 for submission requirements).

2. Bone marrow and peripheral blood must be collected and submitted for central immunophenotyping and PCR analysis for the BCR-ABL oncogene (see Section 11 for submission requirements).

NOTE: South African institutions are not required to submit fresh samples because of the costs and problems associated with international shipping. Eligibility and treatment assignments will be based on local cytogenetic determination of Ph status only.

NOTE: Submission of biological materials from institutions participating through the MRC are outlined in section 10 and the MRC protocol UKALL XII.

7.2.1 Ph negative patients

	INDUCTION	3 Months Post-Induction	Every 6 months thereafter for 24 months
	Baseline[1]	First bone marrow Post-induction	
Rev. 7/04 BM biopsy slides[2]	X		
Peripheral Blood (EDTA or ACD)[3]	X	X	X x
BM aspirate (EDTA or ACD)[3]	X	X	X X
Karyotype[4]	X	X	

[1] Baseline samples must be collected prior to beginning Induction Phase I therapy.

Rev. 7/04 [2] Bone marrow biopsy slides are to be submitted as indicated in Section 10.

[3] Submit materials to the Leukemia Translational Studies Laboratory as indicated in Section 11.1.

[4] Submit materials to the Cytogenetics Laboratory as indicated in Section 11.2.

7.2.2 Ph Positive Patients

	Induction	At CR, Prior to Imatinib	Post-Imatinib, Pre-transplant	Harvest (Autologous Only)	Post-transplant[2]	Q 6 Months until Relapse	Relapse
	Baseline[1]	Prior to Induction Phase II				Prior to Imatinib	Q 3 Mons X4
BM Biopsy[2] slides	X						
Peripheral Blood (EDTA or ACD)[3]	X		X	X			X X X
Bm Aspirate (EDTA or ACD)[3]	X	X	X	X		X	X X X
Karyotype[4]	X		X		X		
Autologous Harvest					X[3]		

Rev. 7/04 Rev. 10/05

[1] Baseline samples must be collected and submitted prior to beginning Phase I induction therapy.

Rev. 7/04 [2] Bone marrow biopsy slides are to be submitted as indicated in Section 10.

[3] Submit materials to the Leukemia Translational Studies Laboratory as indicated in Section 11.1.

[4] Submit materials to the Cytogenetics Laboratory as indicated in Section 11.2.

8.0 DRUG FORMULATION AND PROCUREMENT

8.1 Asparaginase

Rev. 12/04 ***As of Addendum #14, Erwinia Asparaginase use as a substitute for L-Asparaginase or PEG-Asparaginase has been discontinued as the drug is no longer available.***

8.11 Other Names

Elspar®, L-Asparaginase, Erwinia Asparaginase

8.12 Classification

Enzyme.

8.13 Mode of Action

Inhibits protein synthesis by depriving tumor cells dependent on exogenous asparagine of this amino acid by hydrolyzing extracellular asparaginase.

8.14 Storage and Stability

Intact vials are stored under refrigeration. Reconstituted solutions and those further diluted are stable for 8 hours in the refrigerator. Cloudy solutions should not be used. Erwinia asparaginase is incompatible with the rubber stopper on the vial. Therefore the reconstituted solution should be used within 15 minutes.

8.15 Dose Specifics

See Section 5.

Rev. 2/03 #### 8.16 Preparation

For IV injection Add 5 ml of sterile water or sodium chloride injection without preservative to each 10,000 unit vial of drug, which results in a concentration of 2,000 units/mL, which may be further diluted in normal saline or 5% dextrose.

For IM injection Add 2mL of sterile water for injection or normal saline to a 10,000u vial for a concentration of 5,000u/mL.

To prepare a test dose Reconstitute a 10,000 unit vial with 5mL of sterile water for injection, which yields a concentration of 2,000units/mL. Withdraw 0.1mL and add 9.9mL of diluent in a new vial yielding a concentration of 20units/mL. Withdraw 0.1mL containing 2units which is used for the test dose.

Vigorous shaking of the vial may cause excessive foaming. A small number of gelatinous fiber-like particles which occasionally develop may be removed using a 5 micron filter. A 0.2 micron filter may decrease potency of the preparation. The preparation should be used within 8 hours of reconstitution.

Reconstitute the 10,000 unit vial of Erwinia preparation with 2 ml normal saline without preservative.

8.17 Administration

May be given IM or by infusion. Recommended route of administration is IM. For intravenous administration, an infusion through the sidearm of a freely running IV is preferred. Rev. 12/04

8.18 Incompatibilities

Use of a 0.2 micron filter results in a loss of potency.

Rev. 7/04

8.19 Availability

Rev. 2/96, 5/96

Available in 10,000 international units vials as lyophilized cake material from two natural sources. The E. coli preparation is commercially available. Erwinia L-Asparaginase is an investigational agent available through Ipsen Pharmaceuticals, Ltd.. Distribution services of Erwinia L-Asparaginase, on behalf of Ipsen Pharmaceutical Ltd., will be provided by McKesson

Rev. 7/04

BioServices Corporation. To obtain drug, institutions must complete the Erwinia L-Asparaginase shipment Request Form in Appendix VIII, and fax to:

McKesson BioServices Corporation
14665 Rothgeb Drive
Rockville, Maryland 20850
Tel: (301) 315-8460
Fax: (301) 738-2478

8.110 Side Effects

1. Hematologic: Prolonged thrombin, prothrombin times. Decrease in protein synthesis (decreased fibrinogen and depression of clotting factors, in particular antithrombin III deficiency), resulting in thrombosis and/or pulmonary embolism.
2. Gastrointestinal: Nausea and vomiting, usually controlled with antiemetics; anorexia, abdominal cramps, weight loss; rare diarrhea, mucositis, malabsorption.
3. Hepatic: Elevations in liver enzymes, depression of serum albumin, cholesterol and plasma fibrinogen.
4. Neurologic: EEG changes, depression, somnolence, lethargy, fatigue, convulsions, seizures, coma, headache, confusion, irritability, agitation, dizziness, and hallucinations, ranging from mild to severe.
5. Hypersensitivity reactions: Urticarial eruptions (may be controlled with antihistamines); symptoms of anaphylactoid reactions: laryngeal constriction, hypotension, diaphoresis, edema, asthma, and loss of consciousness. The most serious hypersensitivity reactions occur after several doses have been administered, but reactions have been reported on first administration. PEG-asparaginase will be used for allergic patients (see Section 8.2).
6. Other: Pancreatitis, sometimes fulminant; hyperglycemia; chills, fever; rare hyperthermia.
7. Renal: Azotemia, usually prerenal; rarely, severe renal failure.

Rev. 2/03

8.111 Nursing/Patient Implications

(See Section 5.2221 for dose modifications.)

Rev. 7/04

1. Limit IM volume at a single injection site to 2 ml.
2. IV route give over 30 minutes or more through the side arm of infusing IV.
3. Administer acetaminophen 1/2 to 1 hour before infusion.
4. Obtain baseline vital signs.

Rev. 12/04

5. During infusion - assess for anaphylaxis.
6. Have emergency meds (diphenydramine, epinephrine 1:1000, hydrocortisone) on hand.
7. Monitor liver function tests.
8. Assess for bleeding.

8.2 PEG-L-Asparaginase (NSC #644954)

8.21 Other Names

Polyethylene Glycol Conjugated L-Asparaginase - KH

8.22 Source and Pharmacology

The drug is an L-Asparaginase combination (L-Asparaginase amidohydrolase, EC 3.5.1.1), covalently attached to strands of monomethoxypolyethylene glycol of 5,000 daltons (PEG); by means of a coupling moiety. The source of the L-Asparaginase is Escherichia coli (L-asparaginasse). This conjugate is named PEG-L-Asparaginase EC.

The plasma half-life is 96-672 hours. The half-life of PEG-L-Asparaginase is significantly longer than that of the native enzyme.

8.23 Mode of Action

Inhibits protein synthesis by depriving tumor cells dependent on exogenous asparagine of this amino acid by hydrolyzing extracellular asparaginase.

8.24 Formulation and Stability

Rev. 5/93
Rev. 7/04

PEG-L asparaginase will be provided in vials containing 5 ml of an injectable solution (protein concentration of 3.5-5 mg/ml). Usual concentration provided is 750 international units/ml. Though potency information will be provided on the label of each vial and also with each drug shipment. Keep under refrigeration at 2-8°C (36-40°F). DO NOT FREEZE.

8.25 Dose Specifics

See Section 5.

8.26 Route of Administration

Rev. 5/93

IM. Special Precautions: Because of potential for anaphylaxis, the patient should be kept under observation for 30 minutes with resuscitative equipment available. Delayed hypersensitivity can be seen > 24 hours after the drug administration.

8.27 Availability

Rev. 2/95

Commercially available.

8.28 Side Effects

Acute toxicity includes hypersensitivity reaction with anaphylaxis (laryngeal constriction, hypotension, diaphoresis, fever, chills, edema, asthma and loss of consciousness), and rarely, life-threatening complications or even death. Use Erwinia chrysanthemi asparaginase for patients allergic to PEG-L-Asparaginase. Other acute toxicities which require discontinuation of the drug include pancreatitis, hyperglycemia and convulsions. On rare occasions hemorrhage may occur secondary to L-Asparaginase-induced decreased coagulation factor synthesis or, more commonly, thrombosis due to decreased antithrombin III production. Hyperammonemia may also occur. Other side effects include immunosuppression, decreased protein synthesis (including fibrinogen and other coagulation factors), malaise, anorexia, mild nausea and vomiting. Hepatic complications with abnormal LFT's are common but are rapidly reversible. CNS complications include somnolence and lethargy with possible coma. CNS ischemic attacks, possibly coma, are associated with long-term therapy. Renal complications are rare.

8.3 Cyclophosphamide

8.31 Other Names

Cytoxan®, CTX, CPM, Neosar®

8.32 Classification

Alkylating agent.

8.33 Mode of Action

Cyclophosphamide prevents cell division primarily by cross-linking DNA strands. The cell continues to synthesize other cell constituents (RNA and protein), an imbalance occurs and the cell dies. Cyclophosphamide is considered cell cycle phase non-specific.

8.34 Storage and Stability

Tablets and injectable powder are stored at room temperature. The temperature is not to exceed 90°F. Reconstituted parenteral solutions are stable for 24 hours at room temperature or 14 days if refrigerated.

8.35 Dose Specifics

See Section 5.

8.36 Preparation

Dissolve the 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm vials in 5, 10, 25, 50, and 100 ml of sterile water, respectively, resulting in a solution of 20 mg/ml. Shake vials vigorously and warm slightly in lukewarm water to facilitate dissolution. The lyophilized form is more easily solubilized.

8.37 Administration

IV infusion.

8.38 Incompatibilities

1. Barbiturates, phenytoin, and chloral hydrate may increase the rate of hepatic conversion of cyclophosphamide to active metabolites, although the clinical importance of these interactions have not been established.
2. Corticosteroids may inhibit metabolism and reduce the effect of cyclophosphamide, although the clinical importance of this interaction has not been established.
3. May prolong the neuromuscular blocking activity of succinylcholine.
4. Allopurinol, imipramine, and phenothiazines may reduce cyclophosphamide metabolism, increasing bone marrow suppression.
5. Possible potentiation of doxorubicin and daunorubicin cardiotoxicity.

8.39 Availability

Available for injection in 100, 200, 500 mg, 1 gm and 2 gm vials.

8.310 Side Effects

1. Hematologic: Leukopenia, with nadirs about 8-14 days after administration and recovery in 18-25 days; spares platelets.
2. Dermatologic: Alopecia.
3. Gastrointestinal: Nausea and vomiting (begins 6-10 hours after administration).
4. Hepatic: Increased SGOT (AST), SGPT (ALT).
5. Neurologic: Headache, dizziness.
6. Pulmonary: Interstitial pulmonary fibrosis (rare).
7. Cardiovascular: Cardiac necrosis with high-dose cyclophosphamide.
8. Renal: Hemorrhagic cystitis (onset of cystitis may be delayed from 24 hours to several weeks); SIADH, dose related, more common with single large doses greater than 2 gm/m^2.

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9. Other: Metallic taste during injection; nasal congestion; testicular atrophy, amenorrhea, may be long-term; rarely, anaphylaxis; teratogenic; may cause secondary neoplasms. Secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an anthracycline, especially if one or both drugs are given at higher than standard doses); secondary tumors (rare).

Rev. 2/03 8.311 Nursing/Patient Implications

1. Monitor CBC, platelet counts.
2. Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters/day for 72 hr. after administration. Patient should void q 2-3 hours to facilitate emptying of bladder.
3. For high-dose therapy, a Foley may be placed and CBI administered. Systematic mesna may be used to prevent cystitis.
4. A baseline 12 lead ECG may be obtained prior to high-dose therapy.
5. Premedicate with antiemetics.
6. Advise patient of potential "metallic taste". Hard candy with a strong flavor may alleviate this side effect.
7. Instruct patient as to when oral cyclophosphamide should be taken, often best tolerated after meals. When taken in the AM, fluids can "flush" the dose through, meaning less drug will be in the bladder at night, when fluid intake decreases.

8.4 Cytarabine

8.41 Other Names

Cytosar-U®, Ara-C, Arabinosyl, Cytosine Arabinoside

8.42 Classification

Antimetabolite.

8.43 Mode of Action

Converted to cytarabine triphosphate (Ara-CTP), a competitive inhibitor of DNA polymerase. The drug is also incorporated into cellular DNA and RNA. It is active against cells in S-phase and is considered to be phase specific.

8.44 Storage and Stability

The dry powder is stored at room temperature. After reconstitution, cytarabine is stable for 7 days at room temperature and 15 days refrigerated. Solutions with a slight haze should be discarded.

8.45 Dose Specifics

See Section 5.

8.46 Preparation

For IV use, reconstitute the 100 vial with 5 ml bacteriostatic water for injection to achieve a concentration of 20 mg/ml. Add 10 ml of bacteriostatic water to the 500 mg vial to achieve a final concentration of 50 mg/ml. Add 10 and 20 ml of bacteriostatic water to the 1 and 2 gm vials respectively to achieve a final concentration of 100 mg/ml. For subcutaneous use, reconstitute the powder with sterile water or saline to a concentration of 50-100 mg/ml. For IT use, mix with lactated Ringer's solution or normal saline without preservatives, rather than the bacteriostatic water that is included with some products.

8.47 Administration

IV over 30 minutes.

8.48 Incompatibilities

Possible interaction with fluorouracil.

8.49 Compatibilities

Cytarabine (0.25 mg/ml), daunorubicin (0.03 mg/ml) and etoposide (0.4 mg/ml) are stable in D5/0.45% NaCl for 72 hours at room temperature. Cytarabine is also compatible with sodium chloride, potassium chloride, calcium, and magnesium sulfate.

8.410 Availability

Commercially available in 100 mg, 500 mg, 1 gm, and 2 gm vials.

8.411 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia, anemia, and phlebitis. Nadir occurs in 5-7 days with recovery in 2-3 weeks.
2. Dermatologic: Rash, alopecia.
3. Gastrointestinal: Nausea, vomiting, diarrhea, dysphagia, mucositis, anorexia.
4. Hepatic: Transient increase in liver enzymes.

5. Renal: Urinary retention.
6. Other: Flu-like syndrome, fever. Profound hyperuricemia may occur in leukemia patients with high white blood counts.
7. After intrathecal administration, the most common side effects are nausea, vomiting, fever, and headache, usually mild and self-limiting. Meningism, paresthesia, paraplegia, seizures, blindness, necrotizing encephalopathy have occurred.

Rev. 2/03

8.412 Nursing/Patient Implications

1. Monitor CBC, platelet counts.
2. Patient education related to prolonged myelosuppression.
3. Monitor for nausea, vomiting, diarrhea, stomatitis and treat symptomatically.
4. Patient/family may need to be taught subcutaneous injection technique.

8.5 Daunorubicin

8.51 Other Names

Daunomycin, Rubidomycin, Cerubidine®

8.52 Classification

Anthracycline antibiotic.

8.53 Mode of Action

Anthracycline mechanism of action results in a very tight binding of the drug to the DNA molecule. The ultimate effect is interference with nucleic acid synthesis, both RNA and DNA.

8.54 Storage and Stability

Intact vials are stored at room temperature and protected from direct sunlight. Reconstituted solutions are stable for 48 hours when refrigerated and 24 hours at room temperature, when protected from sunlight.

8.55 Dose Specifics

See Section 5.

8.56 Preparation

Each 20 mg vial is reconstituted with 4 ml of sterile water to give a final concentration of 5 mg/ml. The desired dose may be drawn into a syringe containing 10-15 ml of normal saline. Protect from sunlight.

8.57 Administration

Injected into a recently established patent IV site through the side arm of a running IV over 2-5 minutes.

8.58 Incompatibilities

Sodium heparin. Direct admixture with dexamethasone.

8.59 Availability

Commercially available in 20 mg glass vials of red colored lyophilized drug.

8.510 Side Effects

1. Hematologic: Myelosuppression (leukopenia with a nadir between 1-2 weeks).

2. Dermatologic: Rash; alopecia; chemical thrombophlebitis or local necrosis if extravasation occurs.
3. Gastrointestinal: Nausea, vomiting, commonly occurring one hour after a dose and lasting for several hours; diarrhea, stomatitis.
4. Cardiovascular: Arrhythmias, usually transient; congestive cardiomyopathy; maximum total (lifetime) dose of 500-600 mg/m^2 is recommended because of cumulative cardiotoxicity.
5. Renal: Red urine; not hematuria.

Rev. 2/95

6. Other: Fever; transient elevations in serum bilirubin, SGOT, alkaline phosphatase. Secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an alkylating agent, especially if one or both drugs are given at higher than standard doses).

Rev. 2/03

8.511 Nursing/Patient Implications

1. Vesicant - avoid extravasation. Refer to extravasation protocol if inadvertent infiltration occurs.
2. Monitor CBC, platelet counts.
3. Advise patient of red coloration of urine.
4. Administer antiemetics as needed.

8.6 Dexamethasone

8.61 Other Names

Decadron®, Hexadrol®, Dexameth, Dexone®, DXM

8.62 Classification

Adrenal corticosteroid.

8.63 Mode of Action

Dexamethasone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, antineoplastic, and antiemetic properties and very little mineralocorticoid activity. As an antineoplastic agent, dexamethasone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.64 Storage and Stability

Rev. 7/04

The drug is stored at room temperature in a dry place.

8.65 Dose Specifics

See Section 5.

8.66 Preparation

Rev. 7/04

None.

Rev. 2/95

8.67 Administration

10 mg/m^2 PO days 1-28 of consolidation.

Rev. 2/95

8.68 Availability

Rev. 7/04
Rev. 7/04

Commercially available in 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets and 0.1 mg/ml oral solution or syrup.

8.69 Side Effects

1. Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain; aggravation of peptic ulcers.
2. Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.
3. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).
4. Neurologic: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures. muscle weakness.
5. Cardiovascular: Fluid retention and edema, hypertension; rarely, thrombophlebitis.
6. Ocular: Cataracts, increased intraocular pressure, exophthalmos.
7. Metabolic: Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.
8. Hematologic: Leukocytosis.
9. Other: Osteoporosis (and resulting back pain), appearance of serious infections including herpes zoster, varicella zoster, fungal infections, *pneumocystis carinii*, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

Rev. 2/03

8.610 Nursing/Patient Implications

1. May cause perineal burning/itching when given IVP. Slowing the infusion will decrease this side effect.
2. When administered orally, give with food or milk.
3. Observe for signs of hyperglycemia.
4. Observe for subtle signs of infection (fever, pain).

8.7 Etoposide

8.71 Other Names

VP-16, VePesid®, VP-16-213, EPEG, epipodophyllotoxin, NSC # 141540

8.72 Classification

Podophyllotoxin derivative.

8.73 Mode of Action

Etoposide inhibits the enzyme topoisomerase II, nucleoside transport, and incorporation, and causes DNA breakage.

8.74 Storage and Stability

The injection should be stored at room temperature; the capsules must be refrigerated (2-8°C). Following dilution in 0.9% sodium chloride or 5% dextrose to concentrations of 0.2-0.4 mg/ml the drug is chemically stable for 96 and 48 hours at room temperature, respectively. Bristol-Myers in-house data indicate that etoposide may be stable in 5% dextrose or normal saline for 24 hours (0.6 mg/ml), 4 hours (1 mg/ml), and 2 hours (2 mg/ml).

8.75 Dose Specifics

See Section 5.

8.76 Preparation

The desired dose is usually diluted to a concentration of £ 0.4 mg/ml) in normal saline or 5% dextrose. More concentrated solutions may be used but have shorter stability (and may precipitate).

Rev. 2/95 8.77 Administration

Slow IV infusion over at least 30 minutes for consolidation. Capsules are administered orally. Patients receiving Etoposide prior to bone marrow transplant receive IV infusion over 4 hours (64, 65).

8.78 Compatibilities

Compatible with cisplatin 200 mg/µl in D5$^{1}/_{2}$NS or NS for 24 hours when protected from light. Addition of mannitol and/or potassium chloride reduces stability to 8 hours in NS, but remains stable for 24 hours in D5$^{1}/_{2}$NS; also compatible with cytarabine and daunorubicin.

Rev. 2/95 8.79 Availability

Commercially available as an injection in 100 mg (20 mg/ml) multiple dose vials and in 50 mg pink capsules for oral use.

8.710 Side Effects

1. Hematologic: Leukopenia, dose-related, primarily granulocytopenia; nadirs within 7-14 days and recovery within 20 days of administration; thrombocytopenia, uncommon; anemia.
2. Dermatologic: Alopecia is generally mild, reversible and is reported to occur in 20-66% of the patients, although some patients develop total baldness; rash (rare), severe pruritus (rare), radiation recall reaction (rare), phlebitis, local pain at injection site, pigmentation (rare).
3. Gastrointestinal: Nausea and vomiting, relatively uncommon, but more frequent with oral dosing; anorexia in 10-13% of patients; stomatitis, rare with conventional doses, more common and more severe in patients who have received radiation to the head and neck and with high doses (e.g., bone marrow transplantation); abdominal pain, diarrhea, aftertaste, parotitis, dysphagia, and constipation occur rarely.
4. Hypersensitivity: Anaphylaxis (rare).
5. Hepatic: Hyperbilirubinemia and increased transaminase levels, usually mild, transient and more common in high dose protocols.
6. Cardiovascular: Transient hypotension, associated with rapid administration; transient hypertension (rare); other cardiovascular events (e.g. congestive heart failure) thought to be related to large amounts of sodium chloride administered with the drug.
7. Neurologic: Peripheral neuropathy, somnolence, fatigue, headache, vertigo, transient cortical blindness (all rare); transient confusion with high doses, perhaps due to the alcohol-containing vehicle.
8. Other: Rarely, fever, muscle cramps, metabolic acidosis, hyperuricemia, secondary AML/MDS: high risk with large cumulative doses, other drugs in same family add to risk (i.e., teniposide).

Rev. 2/95

Rev. 2/03

8.711 Nursing/Patient Implications

1. Monitor CBC, platelet count.
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Infuse drug over at least 30 minutes. A more rapid infusion may cause hypotension.
4. Observe for possible phlebitis at injection site or burning pain with infusion.
5. Monitor for anaphylactoid reaction (rare).
6. Administer antiemetics as indicated.
7. Track cumulative doses, particularly in pediatrics, adolescents.

Rev. 2/96, 7/04, 2/07

8.8 Granulocyte Macrophage-Colony Stimulating Factor

Refer to the FDA-approved package insert for complete product information.

8.81 Other Names

Sargramostim, GM-CSF, Rhu GM-CSF, Leukine®

8.82 Classification

Colony Stimulating Factor - Cytokine.

8.83 Mode of Action

Stimulates granulocytes and macrophage production by bone marrow hematoprogenitor cells and activates mature neutrophils and monocytes.

8.84 How Supplied

GM-CSF (sargramostim) is a commercially available drug manufactured by Berlex Laboratories. The liquid formulation is a sterile, preserved (containing 1.1% benzyl alcohol) solution containing 500 mcg/mL, 1 mL per vial. The lyophilized formulation is a sterile, white preservative-free powder containing 250 mcg per vial. Each mL of the preserved solution and reconstituted lyophilized formulation contains 40 mg/mL mannitol, USP, 10 mg/mL sucrose, NF, and 1.2 mg/mL tromethamine, USP.

8.85 Storage and Stability

Store intact vials of the liquid and lyophilized formulations refrigerated at 2-8oC. Each vial bears an expiration date. The liquid formulations may be stored for up to 20 days at 2-8oC once the vial has been entered. Any remaining solution should be discarded after 20 days. The lyophilized formulation reconstituted with Sterile Water for Injection, USP should be discarded within 6 hours of preparation. The lyophilized formulation reconstituted with Bacteriostatic Sterile Water for Injection, USP (containing 0.9% benzyl alcohol) may be stored for up to 20 days at 2-8oC once the vial has been reconstituted. Any remaining solution should be discarded after 20 days.

8.86 Dose Specifics

See Section 5.

8.87 Preparation

Reconstitute each 250 mcg lyophilized vial with 1 mL of Sterile Water for Injection, USP or 1 mL of Bacteriostatic Sterile Water for Injection, USP containing 0.9% benzyl alcohol to yield a 250 mcg/mL solution. The diluent should be directed against the side of the vial to avoid excess foaming. Avoid vigorous agitation of the vial; do not shake.

8.88 Administration

Subcutaneous injection.

Rev. 2/07

8.89 Availability

Commercially available in 250 mcg lyophilized vials and 500 mcg multi-dose vials (500 mcg/mL, 1 mL vial).

Rev. 2/07

8.810 Side Effects

1. Dermatologic: Local erythema, rash.
2. Gastrointestinal: Anorexia, nausea, vomiting, abnormal taste.
3. Hepatic: Elevated serum AST/ALT; hyperbilirubinemia; elevated serum alkaline phosphatase, hepatic enzymes, abnormal clotting times.
4. Neurologic: Headache, confusion, neuropathies.
5. Pulmonary: Dyspnea (due to fluid retention and capillary leak syndrome), pleuritis.
6. Cardiovascular: Cardiac arrhythmias, atrial fibrillation, pericarditis.
7. Other: Fever, flu-like syndrome (chills, rigors, myalgias), asthenia, malaise, fatigue, arthralgias, bone pain, hypersensitivity reactions, thromboembolic phenomena.

Rev. 2/07

8.811 Nursing/Patient Implications

1. Monitor for central venous catheter occlusion, or generalized thrombosis.
2. Administer antipyretics, antiemetics, and analgesics as needed.
3. Inform patient of possible side effects. Answer any questions.
4. Patients may need instructions on subcutaneous drug administration.
5. Leukocytosis - monitor CBC with differential + liver enzymes.
6. Acetaminophen administered prior to treatment and every 4 hours following initial injections may decrease severity of symptoms. Diphenhydramine PO may decrease erythema at subcutaneous injection sites.
7. Monitor for acute reactions. Outpatients may need to be observed for 1-2 hours after receiving first dose.

8.9 Leucovorin Calcium

8.91 Other Names

Leucovorin®, Wellcovorin ®, Citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV

8.92 Classification

Tetrahydrofolic acid derivative.

Rev. 2/95

8.93 Mode of Action

Leucovorin acts as a biochemical cofactor for 1- carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin.

Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

8.94 Storage and Stability

All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10 mg/ml, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/ml the drug is chemically stable for at least 24 hours at room temperature under normal laboratory light. The oral solution, 1 mg/ml, is stable for 14 days refrigerated and 7 days at room temperature.

8.95 Dose Specifics

See Section 5.

8.96 Preparation

The 50 and 100 mg vials for injection are reconstituted with 5 and 10 ml of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/ml solution. The 350 mg vial is reconstituted with 17 ml of sterile water resulting in a 20 mg/ml solution. The 60 mg bottle for oral solution is reconstituted with 60 ml of aromatic elixir provided, resulting in a 1 mg/ml oral solution.

8.97 Administration

Leucovorin is given orally and by IV.

8.98 Compatibilities

Leucovorin (0.5-0.9 mg/ml) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin (0.03, 0.24 and 0.96 mg/ml) is stable for 48 hours at room and refrigeration temperatures when admixed with floxuridine (FUDR, 1, 2 and 4 mg/ml) in normal saline. Leucovorin is also compatible with fluorouracil.

8.99 Availability

Commercially available as a tablet (5, 10, 15, 25 mg), cryodessicated powder for oral solution, and in parenteral formulations (3 and 5 mg ampule; 50 mg, 100 mg and 350 mg vial).

8.910 Side Effects

1. Hematologic: Thrombocytosis.
2. Dermatologic: Skin rash.
3. Gastrointestinal: Nausea, upset stomach, diarrhea.
4. Allergic: Skin rash, hives, pruritus.
5. Pulmonary: Wheezing (possibly allergic in origin).
6. Other: Headache; may potentiate the toxic effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

Rev. 2/03 8.911 Nursing/Patient Implications

1. Observe for sensitization reactions.
2. Dose timing is often critical. The schedule should be understood thoroughly.

Rev. 2/95

3. When given with fluoropyrimidines monitor closely for diarrhea and stomatitis.

8.10 Mercaptopurine

8.101 Other Names

6-Mercaptopurine, 6-MP, Purinethol®.

8.102 Classification

Antimetabolite.

8.103 Mode of Action

Mercaptopurine is converted intracellularly to the ribonucleotide derivative 6MP ribose phosphate (6-thioinosinic acid) which may be incorporated into RNA, thus inhibiting its effects; it also blocks several steps in the synthesis of purines.

8.104 Storage and Stability

Rev. 7/04

Tablets are stored at room temperature.

8.105 Dose Specifics

See Section 5.

Rev. 7/04

8.106 Preparation

None.

8.107 Administration

Oral.

8.108 Incompatibilities

When administered with allopurinol, the dose of mercaptopurine should be reduced to 25-33% of the usual dose; allopurinol inhibits xanthine oxidase which metabolizes mercaptopurine.

Rev. 2/95

8.109 Availability

Rev. 7/04

Commercially available in 50 mg tablets.

8.1010 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia, anemia; agranulocytosis and pancytopenia may occur.
2. Dermatologic: Causes necrosis when extravasated. Hyperpigmentation, rash are both rare.
3. Gastrointestinal: Occasionally, nausea, vomiting, anorexia, abdominal pain, mucositis.
4. Hepatic: Jaundice, elevated hepatic enzymes, cholestasis, ascites, hepatic encephalopathy associated with hepatic necrosis and severe fibrosis. Onset variable, usually in 1-2 months. Deaths have occurred; associated with doses over 2.5 mg/kg/day more frequently.
5. Neurologic: Fever, headache.

Rev. 2/03

8.1011 Nursing/Patient Implications

1. Monitor CBC, platelet count, liver function tests.
2. Monitor for GI toxicities and drug fever and treat symptomatically.
3. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs.
4. Blood levels not currently used clinically, but may be of use in patients felt to be poor absorbers.

8.11 Methotrexate

8.111 Other Names

Methotrexate sodium, MTX, Mexate®, Mexate-AQ®, Folex®, Folex PFS®, Abitrexate®, Rheumatrex®, Amethopterin

8.112 Classification

Antimetabolite.

8.113 Mode of Action

Methotrexate inhibits the enzyme dihydrofolate reductase, thereby blocking the conversion of folic acid to its active form, tetrahydrofolic acid. Inhibition of this enzyme reduces purine synthesis and the conversion of deoxyuridylate to thymidylate which inhibits the synthesis of DNA, RNA and proteins.

8.114 Storage and Stability

Store at room temperature protected from light. Reconstituted solutions are stable at room temperature for at least 1 week. Solutions (50 mg/100 ml) in PVC bags of 5% dextrose may be frozen at -20°C for at least 30 days when thawed in 2 minutes by microwave radiation. There is no loss of potency after 5 freeze-thaw cycles.

8.115 Dose Specifics

See Section 5.

8.116 Preparation

Lyophilized 20, 50, 100, and 250 mg vials are reconstituted with sterile water, normal saline or 5% dextrose to a concentration no greater than 25 mg/ml. The 1000 mg vials are reconstituted with 19.4 ml to provide a concentration of 50 mg/ml. Higher doses (> 100 mg) are often further diluted with 100 ml or more of 0.45%-0.9% sodium chloride or 5% dextrose.

Rev. 2/95

8.117 Administration

Usually administered by IV bolus (< 100 mg), or slow IV infusion over 30 minutes or longer (> 100 mg). The drug is given orally and intrathecally as well.

8.118 Compatibilities

Compatible with sodium bicarbonate, cytarabine, cephalothin, mercaptopurine, vincristine sulfate, hydrocortisone, leucovorin, furosemide, and amino acids. At the "Y-site," compatible with fluorouracil, cisplatin and heparin.

8.119 Incompatibilities

Incompatible in solution with bleomycin, fluorouracil, prednisolone sodium phosphate, droperidol, metoclopramide, and ranitidine. Aspirin, probenecid, and nonsteroidal anti-inflammatory drugs may prolong methotrexate clearance and increase toxicity. They should not be given to patients receiving larger doses of methotrexate (for 48 hours after a dose).

8.1110 Availability

Commercially available as a lyophilized powder for injection (20, 50, 100, 250, and 1000 mg/vial), as a 25 mg/ml preservative free isotonic solution for injection (50, 100, 200 and 250 mg/vial), as a 2.5 mg/ml (5 mg vial) and 25 mg/ml (50 and 250 mg vials) preservative protected isotonic solution for injection and as a 2.5 mg tablet.

8.1111 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia: dose-related, more likely with prolonged drug exposure; anemia.
2. Dermatologic: Skin erythema and/or rash, sometimes pruritic; alopecia; photosensitivity; furunculosis; depigmentation or hyperpigmentation; acne; telangiectasia; skin desquamation (exfoliative dermatitis) and bullae formation; folliculitis.
3. Gastrointestinal: Nausea and vomiting, uncommon with conventional doses, and usually mild; stomatitis, common, dose- and infusion duration-related and highly variable; diarrhea; anorexia; hematemesis; melena.
4. Genitourinary: Renal dysfunction: dose-related, more likely to occur in patients with already compromised renal function, dehydration, or on other nephrotoxic drugs, manifested by increased creatinine, hematuria.
5. Hepatic: Increased SGOT (AST), mild and transient; hepatic fibrosis and cirrhosis, more likely to occur in patients receiving long-term continuous or daily methotrexate treatment.
6. Neurologic: Encephalopathy, more commonly with multiple intrathecal doses and in patients who have received cranial irradiation; tiredness, weakness, confusion, ataxia, tremors, irritability, seizures, coma. Acute side effects of intrathecal methotrexate may include: dizziness, blurred vision, headache, back pain, nuchal rigidity, seizures, paralysis, hemiparesis.
7. Allergic: Fever and chills; rash; urticaria; anaphylaxis.
8. Ocular: Conjunctivitis; excessive lacrimation; cortical blindness has occurred with high doses.
9. Pulmonary: Pneumonitis, pulmonary fibrosis, cough, dyspnea.
10. Other: Malaise; osteoporosis (aseptic necrosis of the femoral head); hyperuricemia; reversible oligospermia.

Rev. 2/03

8.1112 Nursing/Patient Implications

1. Administer antiemetics as indicated.
2. Monitor for hematologic toxicity.
3. Observe for gastrointestinal toxicity (stomatitis, diarrhea); offer symptomatic care.
4. For patients who are to begin methotrexate therapy at a dose of 1 gm/m^2 or greater: Proper functioning of kidneys must be documented. Proper hydration and alkalinization of urine must be maintained.
5. Instruct patient to use sunscreen lotion or cream when exposed to the sun.
6. Scheduling for methotrexate serum levels may be necessary in high dose situations.

7. Time of administration of infusions may be critical - should be carefully monitored. An infusion pump may be necessary.
8. High dose methotrexate (see route of administration) must be given with leucovorin rescue. Educate patient and significant other about importance of compliance with medication schedule. There may be financial implications due to the high cost of the drug.

8.12 Prednisone

8.121 Other Names

Deltasone, Orasone, Medicortone, Panasol-S, Liquid-Pred, others

8.122 Classification

Adrenal corticosteroid.

8.123 Mode of Action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralo- corticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.124 Storage and Stability

The drug is stored at room temperature in a dry place.

8.125 Dose Specifics

See Section 5.

8.126 Administration

Prednisone is taken orally

8.127 Availability

Commercially available in 1, 2.5, 5, 10, 20, 25 and 50 mg tablets. Also available as a 1 mg/ml oral solution or syrup and as a 5 mg/ml oral solution.

8.128 Side Effects

1. Hematologic: Leukocytosis.
2. Gastrointestinal: Nausea, vomiting, anorexia; increased appetite and weight gain; peptic ulceration.
3. Dermatologic: Rash; skin atrophy; facial hair growth, acne, facial erythema; ecchymoses.
4. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).
5. Neurologic: Insomnia; muscle weakness; euphoria, psychosis, depression; headache, vertigo, seizures.
6. Cardiovascular: Fluid retention and edema; hypertension; hyperkalemia.
7. Ocular: Cataracts; increased intraocular pressure; exophthalmos.
8. Metabolic: Hyperglycemia; decreased glucose tolerance; aggravation or precipitation of diabetes mellitus; adrenal suppression.

9. Other: Osteoporosis (and resulting back pain); serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis; muscle wasting.

Rev. 2/03

8.129 Nursing/Patient Implications

1. Instruct patients to take prednisone after meals. Should not be taken too close to bedtime to avoid insomnia. A mild sedative may be required.
2. GI symptoms should be treated symptomatically.
3. Monitor blood glucose levels.
4. Educate patient concerning potential mood swings.
5. Gradual tapering of doses after long-term use should be employed.

8.13 Vincristine

8.131 Other Names

Oncovin®, Vincasar PFS®, vincristine sulphate, VCR, leucocristine, LCR

8.132 Classification

Vinca alkaloid (tubulin inhibitor).

8.133 Mode of Action

Vincristine binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and causing cessation of cellular mitosis.

8.134 Storage and Stability

Vincristine is stored in the refrigerator.

8.135 Dose Specifics

See Section 5.

8.136 Preparation

Doses for continuous infusion are further diluted with normal saline or 5% dextrose in water.

8.137 Administration

IV push using extravasation precautions.

8.138 Incompatibilities

Furosemide; some in-line filters; polysiloxan containers used in portable delivery devices.

8.139 Compatibilities

Chemically stable in normal saline or 5% dextrose for at least 4 days, alone or mixed with doxorubicin, at room temperature in either glass or PVC containers.

Also compatible with bleomycin, cytarabine, fluorouracil, methotrexate, and metoclopramide.

8.1310 Availability

Vincristine is commercially available in a concentration of 1 mg/ml in 1, 2, and 5 mg vials and 1 mg and 2 mg syringes (Hyporets).

8.1311 Side Effects

1. Hematologic: Leukopenia (mild and rare), thrombocytopenia (rare), anemia.
2. Dermatologic: Alopecia; skin and soft tissue damage if extravasated (the manufacturer recommends subcutaneous injection of hyaluronidase and application of heat to help disperse the drug); rash.
3. Gastrointestinal: Nausea, vomiting (rare); constipation (see neurological side effects); abdominal pain (cramps); anorexia; diarrhea. Fatal ascending paralysis follows intrathecal administration.
4. Hepatic: Elevations of SGOT (AST), SGPT (ALT), (mild and transient).
5. Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis); autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis); ataxia; myalgias; cortical blindness; headache; seizures.
6. Pulmonary: Bronchospasm (acute shortness of breath), more common when administered with mitomycin.
7. Ocular: Diplopia; ptosis; photophobia; cortical blindness (see neurologic); optic atrophy.
8. Other: Severe pain in the jaw, pharynx, bones, back and limbs following injection; syndrome of inappropriate antidiuretic hormone (SIADH); fever; pancreatitis (rare).

Rev. 2/95, 2/03

8.1312 Nursing/Patient Implications

1. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs.
2. Monitor for neurotoxicities - numbness, tingling, ataxia, loss of deep tendon reflexes, etc. - doses may be decreased or eliminated (see Section 5.2233).
3. Monitor for constipation and treat promptly. May require prophylactic laxatives.
4. Precautions should be taken to prevent inadvertent intrathecal injection.

8.14 Thioguanine

8.141 Other Names

6-Thioguanine, 6TG, Aminopurine-6-thiol-hemihydrate, NSC 752

8.142 Classification

Purine antimetabolite.

8.143 Mode of Action

Thioguanine is a chemical analog of the natural purine, guanine. The drug is enzymatically incorporated into purine synthesis reactions and is S-phase specific. Thioguanine competes with hypoxanthine and guanine for the enzyme hypoxanthine-guanine-phosphoribosyltransferase (HGPRTase) and is converted to 6-thioguanylic acid (TGMP). TGMP interferes at several points with the synthesis of guanine nucleotides. Thioguanine nucleotides are incorporated into both RNA and DNA by phosphodiester linkages and incorporation of such fraudulent bases may contribute to its cytotoxic effects.

8.144 Storage and Stability

Tablets are stored at room temperature. Unreconstituted drug vials are stable for at least 4 years under refrigeration and 3 years at room temperature.

At a concentration of 15 mg/ml the drug is chemically stable for at least 24 hours at refrigeration temperatures. Following further dilution in 5% dextrose or normal saline, thioguanine is chemically stable for at least 24 hours at room and refrigeration temperatures.

8.145 Dose Specifics

See Section 5.

8.146 Preparation

The 75 mg/vial is reconstituted with 5 ml of normal saline, resulting in a 15 mg/ml solution. The desired dose may be further diluted with 500 ml of 5% dextrose or normal saline. An oral suspension of thioguanine can be made from the tablets. Consult your pharmacist for details.

8.147 Administration

Thioguanine is taken orally, between meals if possible.

8.148 Incompatibilities

None known.

Rev. 2/95

8.149 Compatibilities

A 1 mg/ml solution containing 0.5 mEq of sodium bicarbonate for every 75 mg of thioguanine is stable for 8 hours in 5% dextrose or normal saline.

Rev. 2/95

8.1410 Availability

Rev. 7/04

Thioguanine 40 mg tablets are commercially available.

8.1411 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia, with nadirs occuring 10-14 days after administration; anemia.
2. Dermatologic: Rash, dermatitis.
3. Gastrointestinal: Nausea (infrequent), vomiting (infrequent), stomatitis, diarrhea.
4. Hepatic: Hyperbilirubinemia, jaundice, increased SGOT (AST), veno-occlusive disease.
5. Neurologic: Loss of vibratory sensation, unsteady gait.
6. Renal: Elevated BUN, elevated serum creatinine, hyperuricemia (due to tumor cell lysis).

Rev. 2/03

8.1412 Nursing/Patient Implications

1. Monitor CBC, platelet count, renal and liver function tests.
2. Monitor for GI toxicities and treat symptomatically.
3. Observe for neurologic symptoms (changes in sensation, gait).

Rev. 7/04

8.15 Mitoxantrone

8.151 Other Names

Mitoxantrone hydrochloride, Novantrone, dihydroxyanthracenedione, DHAD, DHAQ.

8.152 Classification

Antitumor antibiotic (anthracenedione derivative).

8.153 Mode of Action

Mitoxantrone's precise mechanism of action is not fully known. The drug has been shown to intercalate between DNA base pairs. Mitoxantrone interacts with DNA and RNA through other mechanisms, including inhibitions of topoisomerase II, which may account for its cytocidal activity.

8.154 Storage and Stability

Intact vials are stored at room temperature. Storage under refrigeration may cause formation of a precipitate that redissolves upon warming to room temperature. Once mixed with normal saline or 5% dextrose, the drug is chemically stable for at least 48 hours at room temperature. Concentrations of 0.02-0.5 mg/ml in normal saline or 5% dextrose are chemically stable for at least 1 week at room temperature.

8.155 Dose Specifics

See Section 5.

8.156 Preparation

Dilute in at least 50 ml normal saline or 5% dextrose prior to administration.

8.157 Administration

IV push.

8.158 Incompatibilities

Heparin (1-10 u/ml with mitoxantrone 50-200 mg/ml) causes an immediate precipitate. Hydrocortisone sodium phosphate (2 mg/ml with mitoxantrone 50 mg/ml) causes an immediate precipitate.

8.159 Availability

Commercially available as a 2 mg/ml solution (20, 25, and 30 mg/vial).

8.1510 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia, anemia.
2. Dermatologic: Alopecia (mild), pruritus, dry skin.
3. Gastrointestinal: Nausea and vomiting (usually preventable); diarrhea, mucositis, abdominal pain.
4. Cardiovascular: Cumulative cardiomyopathy (congestive heart failure); arrhythmias; tachycardia; chest pain. Please note that the lifetime dose should not exceed 140-160mg/m^2 .

Rev. 7/04

5. Allergic: Hypotension, urticaria, rash.
6. Hepatic: Transient increases in AST; rarely jaundice; hyperbilirubinemia.
7. Neurologic: Headache; rarely seizures.
8. Pulmonary: Cough, dyspnea.
9. Other: Blue discoloration of sclerae, veins; blue discoloration of the urine and stool, may persist for 24 to 48 hours after administration; fever; conjunctivitis; phlebitis; amenorrhea; rarely tissue ulceration and necrosis upon extravasation; urinary tract infection.

Rev. 7/04

8.1511 Nursing Implications

1. Monitor CBC, platelet count, AST, bilirubin.
2. Administer antiemetics as indicated.
3. Advise patient that blue/green discoloration of urine and stool may occur for 24-48 hours.
4. Monitor for signs and symptoms of cardiomyopathy and calculate total cumulative dose with each administration.
5. Monitor IV site for signs of phlebitis or extravasation.
6. Monitor for GI symptoms (diarrhea, stomatitis, abdominal pain) and treat symptomatically.
7. Advise patient that mild alopecia may occur.

8.1512 References

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Rev. 7/04

8.16 Imatinib Mesylate

8.161 Other Names

Gleevec©, STI571

8.162 Classification

Tyrosine kinase inhibitor

8.163 Mode of Action

Imatinib mesylate is protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemia cells from Philadelphia chromosome positive chronic myeloid leukemia.

In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, Imatinib slows inhibition of BCR-ABL positive colonies from CML patients. *In vivo*, it inhibits tumor growth of BCR-ABL transfected murine myeloid cells as well as BCR-ABL positive leukemia cell lines derived from CML patients in blast crisis. *In vitro* studies demonstrate Imatinib is not entirely selective; it also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

8.164 Storage and Stability

Rev. 10/07

Store tablets at room temperature not to exceed 30o (86°F) in the original package. Shelf life testing of the intact bottles is on-going. Current data support a shelf life of five years.

8.165 Dose Specifics

See Section 5.

8.166 Preparation

Rev. 10/07

Tablets.

8.167 Administration

Oral.

8.168 Incompatibilities

No information available.

8.169 How Supplied

Rev. 7/04, 10/07

Imatinib (STI571) is commercially available in very dark yellow to brownish orange, round, biconvex tablets with NVR on one side and SA and a score on the other. They contain 100 mg imatinib with microcrystalline cellulose, crospovidine, hypomellose, colloidial silicone dioxide and magnesium stearate. Each bottle contains 100 tablets.

8.1610 Drug Interactions

The major human cytochrome P-450 isoenzyme that metabolizes Imatinib is CYP3A4. In addition, in vitro studies demonstrated that Imatinib is a competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4. Drugs that are substrates for these isoenzymes may have increased plasma levels when co-administered together with Imatinib, and drugs that are enzyme inhibitors or inducers may increase or decrease, respectively, the plasma levels of Imatinib. The following table summarizes the interactions known to date:

Isoenzyme	Substrates	Inhibitors	Inducers
CYP2D6	Beta-blockers, antidepressants, antipsychotics, $5HT_3$ - antagonists, codeine, dextromethorphan, ethylmorphine	Fluoxetine, paroxetine, quinidine, ritonavir, celecoxib	None known
CYP3A4	Acetaminophen, codeine, select calcium channel antagonists, select HMG-CoA reductase inhibitors, immune modulators (e.g. cyclosporine), oral contraceptives, warfarin	Ketoconazole, itraconazole, erythromycin, clarithromycin, grapefruit juice	Phenytoin, dexamethasone, carbamazepine, rifampin, phenobarbital, St. John's wort
CYP2C9	Ibuprofen, diclofenac, select angiotensin blockers, phenytoin, cimetidine, digoxin, warfarin	Amiodarone, lovastatin, teniposide	Rifampin, secobarbital

Rev. 2/07

8.1611 Side Effects

Allergy/Immunology: Allergic reaction/hypersensitivity
Blood/bone marrow: Anemia, leukopenia, neutropenia, thrombocytopenia
Cardiac (general): Pericardial effusion, left ventricular systolic dysfunction
Constitutional symptoms: Fatigue, asthenia, lethargy, malaise, fever, rigors, diaphoresis, weight gain
Dermatology/skin: Alopecia, hyperpigmentation, hypopigmentation, pruritis/itching, desquamating rash, Stevens-Johnson syndrome
Gastroenterology: Anorexia, ascites, constipation, dehydration, flatulence, heartburn/dyspepsia, mucositis/stomatitis, nausea/vomiting, dysguesia
Hemorrhage/bleeding: Hemorrhage - CNS, GI, intratumoral
Infection: Neutropenic fever, infection without neutropenia
Lymphatics: Head/neck edema, peripheral edema
Metabolic/laboratory: Increased alkaline phosphatase, AST, ALT, total Bilirubin, serum creatinine; hypophosphatemia, hyponatremia, hypokalemia
Musculoskeletal/soft tissue: Arthritis, avascular necrosis
Neurology: Dizziness, encephalopathy, hydrocephalus, anxiety, motor and sensory neuropathy,
Ocular/vision: Optic disk, edema, watery eyes
Pain: Abdominal, back , chest, headache, throat, joint, muscle
Pulmonary/upper respiratory: Cough, dyspnea, pleural effusion, pulmonary edema
Renal/genitourinary: Renal failure
Syndromes: Flu-like syndrome
Vascular: Thrombosis/thromboembolism

Also reported on STI571 trials but with the relationship to STI571 still undetermined:
ALLERGY/IMMUNOLOGY - autoimmune reaction; vasculitis
CARDIAC GENERAL - cardiac ischemia/infarction; cardiopulmonary arrest
COAGULATION - DIC
CONSTITUTIONAL SYMPTOMS - insomnia
DERMATOLOGY/SKIN - dry skin
GASTROINTESTINAL - duodenal perforation; esophageal fistula; gastritis; GI ulcer; ileus
HEMORRHAGE/BLEEDING - respiratory tract hemorrhage; urinary hemorrhage
HEPATOBILIARY/PANCREAS - liver dysfunction/failure
INFECTION - febrile neutropenia
METABOLIC/LABORATORY - hypercalcemia; hypomagnesemia; lipase
NEUROLOGY - seizure
OCULAR/VISUAL - blurred vision; ocular surface disease
PULMONARY/UPPER RESPIRATORY - voice changes
RENAL/GENITOURINARY - kidney stones
SYNDROMES - Guillain-Barre syndrome

NOTE: STI571 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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Studies on rats in long-term imatinib therapy have demonstrated the development of benign and malignant tumors of the kidneys, urinary and genital tracts. The significance of this finding for humans on imatinib therapy is unknown at this time.

8.1612 Nursing Implications

1. Administer with food and large glass of water to lessen nausea and vomiting.
2. Notify physician of any signs or symptoms suggesting liver dysfunction (e.g., unusual fatigue, anorexia, nausea, vomiting, jaundice, dark urine, pale stools), or if abdominal pain, fever, or diarrhea become pronounced.
3. May produce headache, dizziness, and drowsiness; observe caution while driving or performed other tasks requiring alertness, coordination or physical dexterity.

8.1613 References

American Hospital Formulary Service 2001 Drug Information. American Society of Health-Systems Pharmacists.

Drug Facts and Comparisons. 2001.

Imatinib mesylate (Gleevec) package insert, Novartis Pharmaceuticals 2001.

Imatinib mesylate (Gleevec) clinical monograph, Novartis Pharmaceuticals 2001.

Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. New Engl J Med 2001; 344: 1031-7.

Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. New Engl J Med 2001; 344: 1038-42.

Rev. 7/04 8.17 Interferon Alfa

Rev. 12/04 ***INTERFERON ALPHA WAS PART OF TREATMENT FOR PH+ PATIENTS DURING ALLOGENEIC/MUD BMT TRANSPLANT, AUTOLOGOUS TRANSPLANT, AND MAINTENANCE THERAPY. AS OF ADDENDUM #12, INTERFERON ALPHA TREATMENT USE HAS BEEN DISCONTINUED.***

8.171 Other Names

Interferon alfa-2b: Intron-A ®, IFN-alpha 2b NSC #377523

8.172 Classification

Biologic response modifier.

8.173 Mode of Action

Interferon alfa has antiviral, antiproliferative (cytostatic), and immunomodulatory properties. Its direct antiproliferative properties (e.g., inhibition of cell growth) may explain its activity in certain malignancies.

8.174 Storage and Stability

Intact vials of interferon alpha 2b are stored under refrigeration. Reconstituted solutions of interferon alfa-2b are stable for 1 month at refrigeration temperatures and for 2 weeks at room temperature when reconstituted as directed by the manufacturer. It is also stable for 1 month in the freezer and through 4 freeze-thaw cycles when left in the original vial. In plastic or glass syringes the drug is stable for 1 month frozen
Rev. 7/04 and for 2 freeze-thaw cycles. When reconstituted to a concentration of ≥ 100,000 units/ml in normal saline, it is stable for only 24 hours at room temperature.

8.176 Dose Specifics

See Section 5.

8.177 Preparation

Rev. 7/04 The lyophilized product is reconstituted as directed by the manufacturer.

Rev. 2/95 8.178 Administration

Administer subcutaneously.

8.179 Incompatabilities

Rev. 7/04 Please refer to Intron A's Commercial Package Insert at http://www.spfiles.com/piintrona.pdf for more information.

8.1710 Compatibilities

Rev. 7/04 Please refer to Intron A's Commercial Package Insert at http://www.spfiles.com/piintrona.pdf for more information.

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8.1711 Availability

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INTERFERON ALPHA WAS PART OF TREATMENT FOR PH+ PATIENTS DURING ALLOGENEIC/MUD BMT TRANSPLANT, AUTOLOGOUS TRANSPLANT, AND MAINTENANCE THERAPY. AS OF ADDENDUM #12, INTERFERON ALPHA TREATMENT USE HAS BEEN DISCONTINUED.

Interferon alfa-2b is available from the NCI in vials containing 10 million unit only.

Rev. 5/06

[Ordering information deleted, Addendum #16]

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form.

(See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1712 Side Effects

1. Flu-like symptoms: Fever, chills, diaphoresis, and rigors occur universally regardless of dose, route, or schedule. Usual onset is in 1-2 hours, peak within 4-8 hours, and duration less than 18 hours, and tend to lessen with continued dosing.
2. Constitutional Symptoms: Fatigue, malaise, anorexia, weight loss, muscle pain, arthralgias, headaches; may be dose-limiting, usually occurring during the first or second week of treatment.
3. Hematologic: Leukopenia, thrombocytopenia, and anemia (uncommon).
4. Hepatic: Increased bilirubin; increased alkaline phosphatase, increased transaminases occasionally; hepatitis (uncommon).
5. Cardiovascular: Hypotension, hypertension, dizziness, syncope, arrhythmia (atrial or ventricular), tachycardia, congestive heart failure, and myocardial infarction have been reported.
6. Neurologic: Somnolence, confusion with high doses; numbness, paresthesia, neuropathy; depression, personality disorder, psychomoter retardation, acute paranoid reactions, hallucinations, inability to concentrate, agitation, anxiety; visual disturbances, eye pain, hemianopsia, retinal infarction with vision loss (1 patient); sleep disturbances, insomnia; tremor, seizures, acute aphasia, coma.
7. Gastrointestinal: Mild nausea, vomiting, diarrhea, dysphagia, anorexia, taste change, flatulence, constipation, and gastric distress have been reported.
8. Dermatologic: Alopecia, rash, pain at injection site, dry skin, flushing, urticaria, epidural necrosis.
9. Renal: Proteinuria, microscopic hematuria, pyuria, azotemia, acute renal failure, nephrotic syndrome (1 patient), glycosuria, albuminuria, polyuria.
10. Pulmonary: Orthopnea, dyspnea, bronchospasm (Schering), caugh, pulmonary edema/acute respiratory distress syndrome, pharyngitis.
11. Metabolic: Hyperglycemia, hypertriglyceridemia, hypothyroidism.
12. Coagulation: Increased PT, PTT.

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8.1713 Nursing/Patient Implications

1. Inform patient of expected side effects and reassure him that symptoms are not necessarily related to tumor progression.
2. Instruct patient in keeping a daily record of temperature, symptoms, and activity level. Review and document type, character, and duration of side effects.
3. Fever, rigors, and other flu-like symptoms: Acetaminophen administered prior to treatments and every four hours following the initial injections may decrease severity of symptoms. Nonsteroidal or steroidal anti-inflammatory agents should be avoided since their effect on the immune system is not known.
4. Fatigue and CNS toxicity: Patient performance status and mental status should be assessed regularly and appropriate dose adjustments made per protocol. Instruct patient to arrange most important activities in the morning, and allow for frequent rest periods.
5. Anorexia: Monitor weight regularly. Encourage patient to maintain adequate fluid, caloric, and protein intake. Antiemetics as needed.
6. Granulocytopenia, thrombocytopenia, liver enzyme elevations: Monitor blood counts closely and modify dosage per protocol. Advise patient of special precautions regarding infection and/or bleeding when appropriate.

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8.18 G-CSF

8.181 Other Names

Filgrastim, Neupogen, recombinant-rnethionyl human granulocyte-colony stimulating factor, granulocyte colony-stimulating factor, r-metHuG-CSF.

8.182 Classification

Colony stimulating factor; cytokine.

8.183 Mode of Action

Hematopoietic regulator with effects on both immature bone marrow progenitors and mature myeloid cells; it acts by supporting growth of human bone marrow-derived colony forming units and enhancing neutrophil-mediated antibody dependent cellular toxicity.

8.184 Storage and Stability

Filgrastim should be refrigerated and not allowed to freeze. It is stable for 24 hours at room temperature if the solution remains clear. At a concentration of *5* mcg/mL or greater in D5W, filgrastim is stable for 7 days at room or refrigerator temperatures. At dilutions from 5 to 14 mcg/mL, albumin in a final concentration of 2 mcg/mL should be added to protect against adsorption. Addition of albumin is unnecessary when the drug is diluted to a concentration greater than or equal to 15 mcg/mL in D5W. Concentrations of less than 5 mcg/mL should not be used. Dilutions in D5W are stable in glass bottles, polyvinyl chloride, polyolefin, or polypropylene bags and IV sets, and Travenol Infusors.

Undiluted filgrastim injection is stable in BD tuberculin syringes for up to 24 hours at 15-30^{o}C or for up to 7 days when refrigerated at 2-8^{o}C.

8.185 Dose Specifics

See Section 5.

8.186 Preparation

Draw appropriate dose into syringe for subcutaneous injection. May be further diluted in DSW for continuous infusion. Albumin, if required, is added before filgrastim.

8.187 Route of Administration

Subcutaneously or intravenous bolus. Has also been given by intravenous or subcutaneous continuous infusion.

8.188 Incompatibilities

Normal saline.

8.189 Availability

Commercially available as a 300 mcg/mL solution in 1 mL and 1.6 mL vials.

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8.1810 Side Effects

1. Musculoskeletal: Mild to moderate medullary bone pain in 20% to 25% of patients.
2. Dermatologic and hypersensitivity: Redness, swelling, itching, and pain may occur at the injection site. Transient, generalized rash has been reported occasionally. Anaphylactoid and allergic reactions have been reported rarely.

3. Hematologic: Leukocytosis occurs occasionally.

4. Other: Less frequently reported side effects include transient supraventricular arrhythmia, splenomegaly, and vasculitis. Transient increases in serum concentrations of uric acid, LDH, alkaline phosphatase and leucocyte alkaline phosphatase have been reported after cytotoxic chemotherapy.

8.1811 Nursing Implications

Patients may need help to deal with financial concerns due to the expense of this drug.

Patients or care givers must be instructed and be able to demonstrate their ability to properly measure and administer the drug parenterally. Filgrastim should be kept in the refrigerator until needed and the vials should not be shaken.

Instruct patients to administer the drug at the same time each day. Vials of filgrastim are single-dose and remaining drug should be discarded.

Refer to protocol for information regarding requirements for patient documentation of doses administered, temperatures, side effects, etc.

Administration of filgrastim is usually started 24 hours after the end of chemotherapy. Refer to protocol for specific information.

Acetaminophen is the recommended analgesic for mild bone pain.

Duration of therapy will be determined by the return of blood counts (WBC/ANC) to specified values. Refer to protocol for specific information regarding duration of therapy.

Discuss with the patient proper methods of disposal of syringes, needles, vials, etc.

8.112 References

Takads M, *et al*. Recombinant human G-CSF (rGt-CSF) in patients with non-small cell lung cancer (NSCLC) treated with combination chemotherapy (CT) of mitomycin, vindesine and cisplatin (MVP). Proc Am Soc Clin Oncol 1990.; 9:224.

Crawford J, *et al.* G-CSF: Prevention of chemotherapy induced febrile neutropenia in patients with small cell lung cancer. Proc Am Soc Clin Oncol 1990; 9:229.

Sheridan W, Morstyn G. Phase II study of granulocyte colony-stimulating factor in autologous bone marrow transplantation. Proc Am Soc Clin Oncol 1989; 8:178.

Morstyn G, *et al*. Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. Lancet 1988; 1:667-72.

Neidhart J, *et al*. (Granulocyte colony-stimulating factor stimulates recovery of granulocytes in patients receiving dose-intensive chemotherapy without bone marrow transplantation. J Clin Oncol 1989; 7:1685-92.

Gabrilove JL, *et al.* Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. N Engl J Med 1988; 318:1414-22.

Morstyn G, *et al*. Treatment of chemotherapy-induced neutropenia by subcutaneously administered granulocyte colony-stimulating factor with optimization of dose and duration of therapy, J Clin Oncol 1989; 7:1554-62.

Personal communication, Michael Pecsok, Pharm. D. Amgen, May 25, 1994.

9.0 STATISTICAL CONSIDERATIONS

9.1 Patient Numbers

The numbers of patients required in a trial depends chiefly on the difference in survival between treatment arms that is to be detected reliably. For example, to demonstrate at 2P=0.05 a 60% improvement in 5-year survival from 25% on one treatment to 40% on the other requires approximately 500 patients to have a 95% chance of detecting this difference. If, however, a smaller - but still worthwhile - 40% improvement in survival from 25% to 35% is to be detected, this would require approximately 1000 patients to have a 95% chance of detecting this difference. With only 600 patients there would be a 20% chance of missing a survival improvement of this size.

There are approximately 170 cases of ALL between the ages of 15 and 59 diagnosed each year in the British Isles. Half of these patients are aged 15-24 and only 20% aged 45-59. So, nearly all should be considered suitable for intensive chemotherapy. It is hoped that over 75% of all ALL patients aged 15-59 will be entered into the trial and that about 80% of them will subsequently achieve remission and so be eligible for randomization between auto-BMT and chemotherapy. However, about 25% of patients will have HLA-matched donors and a further 10% may have contraindications to BMT or refuse consent to randomization. The annual intake of patients is projected, therefore, to be about 130 registrations and about 70 randomizations. Since this trial is joint with ECOG, at least an additional 70 patients per year should be recruited, increasing the randomization rate to about 110 per year.

Thus, if the trial proceeds successfully for 5 years, some 550 patients could be randomized, which would give a 70% chance of detecting (at a 2-tailed P-value of 0.05) an absolute difference of 10% survival at 5 years, and a 95% chance of detecting a 15% difference. About 40 patients a year can be expected to have a donor. Thus the comparison between these patients and those without a donor will have approximately 75% power to detect an absolute survival difference of 10% and over 95% power to detect a 15% difference. The numbers would be increased substantially if SWOG and other trial groups also participate, increasing the power of the study.

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Up to September 2005, the actual recruitment and randomisation rates have been approximately 160 and 25, respectively, per year. The proportion of registered patients who reach randomisation has been lower than anticipated, and this means that the target number randomised of 500 will require a total of 2200 patients to be registered.

9.2 Data Analysis

Interim analyses of the main endpoints will be supplied approximately annually, in strict confidence, to a data monitoring committee (DMC). In the light of these interim analyses, the DMC will advise the MRC Leukemia Steering Committee if, in their view, the randomized comparisons in the trial have provided proof beyond reasonable doubt (2 P <0.001) that for all or for some types of patient one treatment is clearly indicated or clearly contraindicated. The main subsets to be analyzed separately will be Ph+ve/-ve.

The main analyses will be performed using standard log-rank methods based on the intention to treat, i.e., all patients believed to be eligible at the time of randomization will be included in the analysis, irrespective of protocol compliance, early relapse, etc.

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Final analyses will be performed when the last patient randomized has been followed up for 2 years, i.e., after all patients have finished their initial treatment.

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9.3 Statistical analysis of Philadelphia positive patients

In the interim results from a large cooperative group trial from MRC and ECOG, (MRC UKALL XII/E2993), the 2 year failure rate was approximately 40% in the allogeneic transplant group and approximately 80% in the autologous transplant group. With Imatinib we wish to achieve a 20% reduction in failure rate in each transplant group. Failure in this study is defined as death or relapse, whichever occurs first.

A total of 140 eligible patients will be entered and followed for an additional 2 years to evaluate the primary endpoint. Of these 140, it is assumed that 75% of patients (or 105 patients) will achieve complete remission (CR). Of these 105 patients who achieve CR, approximately 10% will either refuse to continue to post-remission therapy or drop out of the study after administration of Imatinib. Thus, it is assumed that the remaining 94 patients will receive either allogeneic or autologous transplant. Of these 94, it is anticipated that about 50% of patients will be allocated to the allogeneic transplant group. This is because in this study, there will be more haplo and unrelated donor patients than in the Ph- cohort of this study. With 94 patients, we will have approximately 98% power to detect a 20% reduction of the 2 year failure rate. With 47 patients in each transplant group, we will have at least 84% power to detect a 20% reduction in the allogeneic or autologous transplant group. This power calculation is based on the exact binomial distribution at 0.05 two-sided level of significance.

Feasibility Allowing for 10% ineligibility, the overall accrual goal will be 154 patients. Based on the past accrual to MRC UKALL XII and ECOG 2993 in this patient population, the projected accrual rate is about 35 patients per year. Therefore, the accrual will be completed in approximately 4.4 years.

9.4 Data Management and Monitoring Agreements

This is a joint MRC/ECOG clinical trial. The data will be computerized by CTSU (MRC) in England. Interim reports on accrual and toxicity for all entered patients will be available periodically for review. AE monitoring of ECOG cases will be performed by ECOG according to NCI guidelines (see Section 5). Interim monitoring and all outcome analyses will be performed in conjunction with a working committee comprised of representatives from all contributing groups.

Rev. 7/04 **10.0 PATHOLOGY REVIEW**

10.1 Instructions for Institutions Participating Through ECOG

The clinical investigator and the submitting pathologist have the responsibility for submitting representative diagnostic material for review and classification.

10.11 At study entry the materials are to be submitted:

10.12 A copy of the pathology report.

In addition to the pathology report, if immunologic studies have been performed at the home institution, it is necessary that these be forwarded as well.

10.13 Two (2) unstained bone marrow biopsy slide

If bone marrow biopsy slides are unavailable, please forward 2 peripheral blood smears.

NOTE: Submission of pathologic materials is mandatory in order for the patient to be considered evaluable. Failure to submit these samples may render the patient inevalualable.

10.14 Routing

The required materials must be submitted within 1 month of patient registration to:

Elisabeth Paietta, Ph.D.
Our Lady of Mercy Cancer Center
600 East 233rd Street
6th Floor, Immunology Laboratory
Bronx, NY 10466-2697
Tel: (718) 920-9992

10.2 Instructions for Institutions Participating Through MRC

10.21 The materials required for pathology review are:

Six (6) unstained unfixed bone marrow slides
Forty (40) ml (4 x 10 ml) heparinized blood
Three (3) ml of bone marrow in tissue culture medium containing preservative-free heparin for cytogenetics and immunophenotyping

10.22 Submit material to:

Professor G. Janossy
Department of Immunology
Royal Free Hospital Medical School
London NW 3 2PF

Rev. 7/04 **11.0 LEUKEMIA CORRELATIVE STUDIES**

NOTE: For all patients at study entry, karyotypes (11.2) and biological samples (11.1) must be submitted for central review and analysis for the **presence of the Ph+ chromosome by cytogenetics analysis and by PCR for the BCR-ABL oncogene**.

NOTE: South African institutions are not required to submit fresh samples because of the costs and problems associated with international shipping. Eligibility and treatment assignments will be based on local cytogenetic determination of Ph status only. All other institutions must submit materials for central review.

11.1 Immunophenotype

Immunophenotyping has become an essential part of the diagnostic work-up of all leukemia patients. In fact, the diagnosis of leukemia without immunophenotypic characterization is no longer acceptable. ECOG has, therefore, developed a model system for antigenic data collection that requests specimens from all patients entered on ECOG leukemia treatment trials be studied by ECOG's Leukemia Translational Studies Laboratory. In addition to establishing the leukemia subtype, this centralized testing and data collection has allowed that research questions of clinical relevance to be applied to a growing database (e.g., definition of prognostically significant antigen expression levels to eventually yield specific treatment subcategories). Depending on the study protocol and tissue availability, anti-coagulated (heparin, EDTA, ACD) peripheral blood or bone marrow or both are to be submitted to Leukemia Translational Science Laboratory.

Cells from peripheral blood or bone marrow from patients entered on studies of hematologic malignancies are stored in ECOG's Leukemia Tissue Bank for future laboratory studies. The bank provides the scientific community a source of leukemia specimens that are collected, processed, and maintained following quality control and quality assurance guidelines. The bank will accommodate requests from investigators within and outside ECOG in a timely and efficient manner, with respect to tissue type, tissue preparation, and most importantly, biologic characteristics of specimens.

NOTE: Samples submitted will be used for the studies indicated in sections 11.1, 11.3, 11.4, and 11.5.

11.11 Specimen Submission Schedule

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Peripheral blood and bone marrow aspirate sample submissions are required at the following timepoints:

11.111 For Ph- patients

- Pretreatment
- Post-induction chemotherapy: the first marrow performed
- 3 months after the completion of induction chemotherapy
- Every 6 months thereafter for 24 months

11.112 From Ph+ patients

1. Induction:

   - Prior to study entry (prior to induction Phase I).
   - Prior to Induction Phase II
   - Prior to Imatinib if in CR

2. Autologous transplant patients

   - Post Imatinib, prior to SCT
   - Aliquot of the PBSC collection
   - After SCT, prior to Imatinib therapy

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   - Every 6 months thereafter until relapse.
   - Relapse

3. Allogeneic transplant patients

   - Post Imatinib, prior to SCT
   - After SCT, prior to Imatinib therapy

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   - Every 6 months thereafter until relapse.
   - Relapse

Samples are to be shipped on the day they are drawn. If this is not possible, call the Immunophenotyping Reference Laboratory.

If you have questions, contact the Leukemia Translational Science Laboratory (718) 920-9992.

11.12 Submission Guidelines

11.121 The following must be faxed (718-920-1161) or submitted with the pretreatment samples:

1. A copy of the signed section of the E2993 consent that relates to Tissue Banking for future research.

2. A copy of the signed HIPAA authorization form

11.122 Biological materials:

The ECOG Material Submission Form (#709) must be submitted with each specimen type (peripheral blood or bone marrow) at each time of submission.

a. Anti-coagulated bone marrow aspirate (as much as possible, but minimum 0.5mL of bone marrow) must be submitted. As anti-coagulant use EDTA (purple top) or ACD (yellow top).

NOTE: Heparin (green top) to be used ONLY if EDTA or ACD tubes are not available.

NOTE: In patients with inaspirable bone marrow ("dry tap"), call ECOG's Leukemia Translational Studies Laboratory to discuss submission of peripheral blood only. Be prepared to provide the WBC and blast count at the time of the telephone call.

b. Anti-coagulated peripheral blood (30 - 40 mL) must be submitted. As anti-coagulant use EDTA (purple top) or ACD (yellow top).

NOTE: Heparin (green top) to be used ONLY if EDTA or ACD tubes are not available.

c. PBSC Harvest (Ph+ autologous patients) 5 mL of the PBSC harvest is to be submitted at time of harvest.

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NOTE: Samples must be submitted for purposes of diagnostic review and classification and determination of Ph status. Submission of these materials is mandatory to determine appropriate allocation to treatment and for the patient to be considered evaluable. Failure to submit these samples may render the patient inevalualable.

11.13 Shipping Procedures

The Immunophenotyping Reference Laboratory **must** be notified by telephone, 24 hours prior to the arrival of a sample. **Fax is not acceptable**.

Telephone: (718) 920-9992 Beeper (off hours): (917) 729-7231

Samples must be sent fresh (on the day of collection) **on wet/cool packs** (do not freeze) by overnight courier (preferably Federal Express) to arrive within 24 hours to

Elisabeth Paietta, Ph.D.
Our Lady of Mercy Cancer Center
600 East 233rd Street
6th Floor, Immunology Laboratory
Bronx, NY 10466-2697
Tel: (718) 920-9992
FAX: (718) 920-1161

The laboratory is open to receive shipments Monday through Saturday. Shipments on Fridays for Saturday delivery must have “Saturday Delivery” marked on the overnight courier slip.

If you need to advise the laboratory of a sample shipment after hours, please leave a message on the laboratory’s answering machine. Page Dr. Paietta only if there are questions about the sample submission.

11.14 Banking

The residuals and/or derivatives of samples collected for this study will be retained at the Immunophenotyping Reference Laboratory for possible use in ECOG approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.2 Cytogenetics Review

Cytogenetics for the presence of the Ph+ chromosome will be performed at study entry and at recovery from allogeneic transplant. Determination of Ph status is required for the assignment to the appropriate treatment arm.

Submission of original karyotypes is mandatory.

11.21 Submission Schedule

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Two original karyotypes must be submitted at the following timepoints:

11.211 For Ph- patients:
- Baseline (within one week after registration)
- 3-months post-induction

11.212 For Ph+ patients:
- Baseline (within one week after registration)
- Post-Imatinib, Pre-transplant, Post-transplant

11.22 The clinical research associate (CRA) must complete the Institution section of both the ECOG Material Submission Form (#709) and the ECOG Leukemia Cytogenetics Form (#365R). These forms should then be forwarded to their local Cytogenetics Laboratory for further completion. The local Cytogenetics lab, following completion of their designated section of the ECOG Leukemia Cytogenetics Form (#365R), must forward the two forms, two original karyotypes and a copy of the lab report to:

Gary Hicks
Mayo Clinic Cytogenetics Laboratory
970 Hilton
200 First Street., S.W.
Rochester, MN 55905
Ph: (507) 284-2950
Fax: (507) 284-0043

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Original karyotypes will be returned upon written request when review and analysis are complete.

11.3 Analysis of BCR-ABL Using PCR

PCR will be utilized for measurement of BCR-ABL at various timepoints through the study in the subset of patients with Ph+ ALL to determine the ability of chemotherapy, Gleevec, and the transplant to decrease the level of MRD through the course of treatment.

Baseline and post-transplant evaluations are mandatory. These evaluations will be used to verify the cytogenetic reveiw. Past evaluations of E2993 patients have shown about 10% of BCR/ABL+ patients are Ph negative by standard cytogenetics. Thus, both evaluations are required. If a patient is Ph negative by standard cytogenetics and BCR/ABL+ by molecular PCR, the patient will be considered Ph+.

These analyses will be performed in Dr. Elisabeth Paietta's laboratory.

11.31 Sample Submissions

Blood and bone marrow specimens submitted as described in Section 11.1 will be used for this study. No additional samples are requested for this study.

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Rev. 7/04 11.4 Sample Inventory Submission Guidelines

Inventories of all samples collected and the respective aliquots made and used on the above mentioned laboratory study(ies) will be submitted to the ECOG Coordinating Center on a monthly basis. Inventories will be submitted electronically or by diskette by any laboratory holding and/or using any specimens associated with this study. Electronic submissions should be submitted to 303.lab@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

Rev. 7/04 11.5 Lab Data Transfer Guidelines

The data collected from the performance of the laboratory studies outlined in this protocol will be submitted to the ECOG Coordinating Center by the Central Laboratories on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30 and December 31. Data is due at the Coordinating Center 1 week after these cut-off dates. Electronic submissions should be submitted to 303.lab@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

12.0 RECORDS TO BE KEPT

Rev. 2/96, 2/03 12.1 The following forms must be submitted to the ECOG Coordinating Center, Frontier Science, Attn: Data, 900 Commonwealth Avenue, Boston, MA 02215. A copy of the forms, completed by the referring institution, should also be sent to the transplant center once the patient is transferred.

Rev. 2/96 The ECOG Coordinating Center will forward completed forms to CTSU in Oxford, England after reviewing for legibility and completeness.

	Form	To Be Submitted
	ALL	
	* Notification - Form1	Within 2 weeks of registration
	Induction - Form 2	At completion of induction phase II
	Intensification - Form 3	At completion of intensification
Rev. 2/96	* ECOG Follow-Up Form Parts A & B	Every 3 months for 2 years, every 6 months years 2-5, every 12 months > 5 years
	Notification Relapse or Death - Form 8	When relapse or death occurs
Rev. 2/96	Adverse Event Expedited Reports (AdEERS) or MedWatch (FDA Form 3500) (refer to Section 5.4)	Within 7 days of reportable toxic event as defined in Section 5.4
Rev. 2/96, 3/03	ECOG Second Primary Form	Within 30 days of diagnosis of a new primary cancer.
Rev. 2/96, 3/03	NCI/CTEP Secondary AML/MDS Report From	Within 30 days of diagnosis of AML/MDS
	BMT ARMS (Autologous or Allogeneic)	
	Bone Marrow Transplant - Form 4	When BMT has been completed and evaluated (autologous or allogeneic)
	CHEMOTHERAPY CONSOLIDATION ARM	
	Chemotherapy Consolidation - Form 5	At completion of 4 cycles consolidation
	Maintenance Chemotherapy - Form 6	At two years from entry

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* These forms are to be submitted for all canceled patients according to the above schedule.

If treatment starts more than 3 days after registration, please document the reason for the delay on the flow sheets.

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12.2 Correlative Science Study Forms - See Section 11 for mailing instructions.

Form	To Be Submitted
ECOG Material Submission Form (#709)	Submit with each sample (see Section 11 for sample submission schedule).
ECOG Leukemia Cytogenetics Report Form (#365R)	Submit within 1 month of registration (see Section 11 for complete details).

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Rev. 2/95, 2/98

13.0 PATIENT CONSENT AND PEER JUDGMENT

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

Rev. 2/98

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Phase III Randomized Trial of Autologous and Allogeneic Bone Marrow Transplantation versus Intensive Conventional Chemotherapy in Acute Lymphoblastic Leukemia in First Remission

APPENDIX I

Suggested Patient Consent Form

RESEARCH STUDY

I, _____, willingly agree to participate in this research study which has been explained to me by Dr. _____. This study is being conducted by the Eastern Cooperative Oncology Group, the Medical Research Council of Great Britian and by_____ (Institution).

PURPOSE OF THE STUDY

Rev. 12/04 It has been explained to you that you have acute lymphoblastic leukemia. You have been invited to participate in this research study. This study involves the use of chemotherapy to obtain remission, followed by either conventional treatment with more chemotherapy or either autologous bone marrow transplant or allogeneic transplant if a suitable donor is available. The purpose of this study is to: 1) slow or stop the growth of your leukemia; 2) gain information about your disease; and 3) evaluate the safety and effectiveness of drugs and procedures which have been shown to be effective in other patients with this disease.

DESCRIPTION OF PROCEDURES

This study involves a combination of five drugs for initial treatment: a combination of Daunorubicin (given intravenously once each week over 15-30 minutes), Vincristine (given intravenously once each week over 3-5 minutes), Prednisone (taken by mouth daily for 28 days), L-asparaginase (given intravenously or intramuscularly once daily for the last 12 days of the 28), and Methotrexate (given once into the spinal column). If leukemia cells are present in the spinal fluid, Methotrexate will be given into the spinal column weekly, through a special reservoir installed surgically for this purpose, until no abnormal cells appear. Along with these treatments, patients with leukemia cells in the spinal fluid will receive radiation treatments to the cranium and spine during the next phase.

Rev. 10/05 The second phase of treatment involves five drugs: a combination of Cyclophosphamide (given intravenously over 30 minutes every 2 weeks), Cytarabine (given intravenously over 30 minutes for 4 days each week for 4 weeks), 6-Mercaptopurine (taken by mouth daily for 28 days), and Methotrexate (given into the spinal column weekly) unless this therapy had already been given for abnormal cells. The fifth drug called Imatinib (also
Rev. 5/06 known as Gleevec), will be given only if you have a subtype of acute lymphoblastic leukemia known as Philadelphia chromosome or BCR-ABL positive acute lymphoblastic leukemia (Ph+). Imatinib works by blocking the abnormal protein, BCR-ABL, and preventing this protein from stimulating growth of the Ph+ leukemia cells. You will take Imatinib by mouth for a minimum of 28 days, but may take it for an additional 2 months depending on the course of your treatment.

Rev. 7/04, 10/05, 5/06 If you have Ph+ acute lymphocytic leukemia and achieve a good response to this initial 2-part therapy, you will no longer follow the treatment program outlined below, but instead will be offered one of several types of transplants depending on the availability of a suitable donor (a family member or unrelated donor) or you may use your own cells for an autologous transplant. Depending on whether you will use donor cells or your own cells for the transplant, you will receive certain kinds of chemotherapy before the transplant.

Rev. 12/04, 5/06 For instance, if you use your own cells, you will receive Cytarabine (intravenously over 3 hours/day for 3 days), Mitoxantrone (2 days over IV push), and G-CSF daily. G-CSF is a protein growth factor produced by our bodies that is used as a drug here to stimulate the bone marrow to produce blood stem cells that will be collected from your blood when your blood counts recover after the chemotherapy. These blood stem cells will be frozen and used later for transplant. Whether you use your own stem cells or donor stem cells, you will take Etopside (intravenously over 4 hours for 1 day) followed by total body irradiation (TBI) twice a day for three days or a different combination of chemotherapy and/or radiation therapy chosen by the blood and marrow transplant physician and your cells or the donor cells will then be given to you by vein. Following the transplant, when your doctor feels you are ready, you will resume Imatinib and take it for as long as your leukemia remains in remission (less intense or serious).

Rev. 7/04 If your leukemia is not Philadelphia chromosome or BCR-ABL positive and if there is a good response to this initial 2-part therapy, more therapy is needed to kill any leukemia that may remain. There are three possible treatments. It is not known which is the best at this time. If you are 50 years or younger and have a suitable donor, you will receive an allogeneic bone marrow transplant. If this is not an option, one of two other treatments will be offered. The one that is offered to you will be chosen at random by a computer.

You will first receive a three drug combination called "intensification therapy". Methotrexate (intravenously over 2 hours for 3 doses, one, then two weeks apart), L-asparaginase (intravenously over 30 minutes, for 3 doses, one then two weeks apart) and Leucovorin (some intravenous and some oral doses every 6 hours for 4 days) will be used. Following this you will then receive treatment according to the program selected for you.

Rev. 5/99 In one program an autologous stem cell transplant will be performed, in which your own stem cells will be used. While you are asleep, multiple bone marrow samples will be taken from your pelvic bones and stored frozen until you need to use it. Alternatively, stem cells may be collected from the blood after removal from a peripheral vein. You will then be treated with radiation treatments over 3 days along with the drug Etoposide (given intravenously over 2-3 hours).Several days later, your bone marrow or peripheral blood will be thawed and infused over 15-30 minutes into a vein. Following transplantation, you will receive GM-CSF
Rev. 2/96, 12/04 injected underneath the skin (subcutaneously) until your white blood cell count is normal.

In the other randomly chosen program, a series of combinations of chemotherapy are given called "consolidation" and "maintenance". These drugs include Cytarabine (intravenously over 30 minutes), Etoposide (intravenously over 1 hour daily for 5 days), Vincristine (intravenously over 3-5 minutes each
Rev. 10/05 week), and Dexamethasone (orally for 28 days). The other drugs in consolidation are drugs that you have
Rev. 12/04 already received during the treatment, although the consolidation schedule varies from previous treatment schedules. Maintenance also involves drugs that you have received previously.

If you receive an allogeneic transplant, you will receive chemotherapy, radiation therapy, and GM-CSF just like in the autologous transplant. However, the bone marrow that you receive will be from your donor, rather than from your own bone marrow.

Rev. 2/98 Small amounts (less than 10% of that required for standard evaluation and treatment) of your blood and bone marrow samples will be used for research purposes, and sent to outside laboratories for review of some of the characteristics of your blood cells including their appearance under a microscope, their chromosomes and surface markers. These studies could be helpful for better determining the nature of your disease.

RISKS AND DISCOMFORTS

Drugs often have side effects. The drugs used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Rev. 5/93 & 2/95 Asparaginase can cause allergic reactions that can be mild (rash) and rarely severe (shortness of breath), bleeding abnormalities, nausea and vomiting, abdominal pain, loss of appetite, diarrheas, mouth sores, depression, dizziness, hallucinations, ranging from mild to severe, headaches, irritability, throat constriction, fluid retention, a decrease in blood pressure, chills, fever, an increase in certain gasses in the kidney, fatigue, liver test abnormalities, and inflammation of the pancreas. Patients who become pregnant while receiving this drug risk the possibility of genetic damage to the fetus. If an allergic reaction occurs PEG-Asparaginase IM Rev. 12/04may be used. PEG-Asparaginase is commercially available.

Side effects to PEG-Asparaginase IM include: low blood pressure, fever, chills, fluid retension, difficulty in breathing, loss of consciousness, and rarely complications that could result in death.

Rev. 7/04, 12/04

Rev. 2/95 Cyclophosphamide can cause nausea, vomiting, hair loss, nasal congestion and headache, dizziness, watery eyes, metallic taste in the mouth, decrease in the size of the testicals, bladder irritation and inflammation which may produce burning or bleeding on urination, lowering of the blood counts, which can lead to fatigue; respiratory kidney, and liver abnormalities, heart damage, and permanently impair your ability to have children. If taken while pregnant, cyclophosphamide can cause damage to an unborn baby. Rarely, allergic reactions have been reported. In rare cases, acute leukemia or other cancers may develop after treatment with cyclophosphamide, especially when it is given along with other anticancer drugs.

Rev. 2/95 Daunorubicin can cause nausea and vomiting, total hair loss, a lowering of the blood counts which leads to an increased risk of infection, easy bruising and bleeding, formation of ulcers and soreness in the mouth, fever and local skin rash, diarrhea, irregular heart beat, kidney and liver problems, temporary red urine, and potential heart damage. Tissue damage may occur if it leaks outside the vein. In rare cases, acute leukemia may develop after treatment with Daunorubicin, especially when it is given along with other anticancer drugs.

Higher dose therapy involving drugs like Daunorubicin and Cyclophosphamide (which are part of the treatment you may receive in this study) is associated with a range of increased side effects compared to standard therapy. Some of the increased side effects may occur during therapy (such as low blood counts). Other side effects that could occur later might also be life threatening, or even fatal. An example of such a delayed side effect is acute leukemia, which can occur as a result of treatment given in this study. Just as the potential benefit to you of higher dose therapy compared to standard dose therapy is not known at this time, the precise increase in risk of leukemia is not known, but the risk is thought to be small (less than 1%). This estimate is based on the information from a large, North American study of women with breast cancer who received higher than standard doses of cyclophosphamide (Cytoxan) combined with standard doses of doxorubicin (Adriamycin) and tamoxifen. Patients on this study also received granulocyte-colony stimulating factor (GM-CSF) and antibiotics to prevent infections. The few leukemia cases that occurred in this study usually developed within two years from the start of treatment.

Rev. 2/95 Etoposide can cause a lowering of the blood counts which leads to an increased risk of infection, and easy bruising and bleeding, decreased energy, hair loss, skin rash, pain at location of where drug is administered, including inflammation of the vein, a drop in the blood pressure if infused too fast. There is a potential of a building up of fluid around the heart. Vision problems, including blindness, headache, dizziness, confusion (all are rare). Fever, muscle cramps, a decrease in the function of your nervous system, a buildup of uric acid, related to problems in the kidney, an increase in blood pressure, excess acidity throughout the body due to abnormal metabolism, allergic reactions, weight loss, abdominal pain, diarrhea, constipation, mouth sores, aftertaste, difficulty in swallowing, swollen glands, increased levels of certain chemicals in the liver, nausea and vomiting, a change in the color or your skin; a rash could develop in the area where radiation was given. In rare cases, acute leukemia may develop after treatment with Etoposide.

Rev. 2/95 Cytarabine can cause a lowering of the blood counts which leads to an increased risk of infection, easy bruising and bleeding and loss of energy (anemia); hair loss, loss of appetite, nausea and vomiting, diarrhea, mouth sores, weight loss, difficulty in swallowing, kidney problems including a buildup of urine, fever, flu-like symptoms, rash, headache, blindness, seizures, the sensation of pricking, tingling, or creeping on the skin, inflammation of the eye, skin rash, and mild liver damage. Loss of balance and coordination is usually temporary when it occurs, but is occasionally more long-term. Higher doses can cause significant nausea. Death to brain tissue is also a possibility.

Rev. 2/07 Imatinib

Risks

Likely

Lowered white blood cell count (may make you more likely to get infections)
Lowered platelets (may make you more likely to bruise or bleed)
Fatigue that could make you feel lethargic, weak and tired
Rash with skin peeling
Nausea and vomiting
Diarrhea
Swelling in your hands and/or feet
Pain in the joints or muscles

Less Likely

Lowered red blood cell count (may make you feel tired or weak, may require blood transfusions)
Allergic reaction (shortness of breath; closing of the throat; difficulty breathing; swelling of the lips, face, or tongue; or hives)
Build up of fluid in the membrane that surrounds the heart which could prevent the heart from pumping normally. This could be a life-threatening situation.
Fever
Chills
Sweating
Weight gain
Hair loss on the scalp or other parts of the body
Redness and/or itching of the skin
Either lightening or darkening of areas of the skin
A skin rash that can progress to skin ulcerations or the skin may peel off. This can become progressively worse and be life-threatening.
Loss of appetite

Fluid accumulation around the abdomen
Dehydration
Constipation
Passing gas
Heartburn or upset stomach
Mouth sores
Taste changes
Bleeding into the stomach, brain, or site of cancer that can be life-threatening
Infection with either normal immunity or when the white blood cells that fight infection are low which could become life-threatening
Swelling with fluid around the head or neck
Abnormalities of the laboratory values that measure the function of the liver. When elevated, these findings suggest damage to the liver
Abnormality of the laboratory value that measures the function of the kidneys. When elevated, these findings suggest damage to the kidneys
Abnormalities of certain electrolytes in the blood such as sodium or potassium
Arthritis
Destruction of bone tissue that could become severe enough to require surgical replacement of a joint
Dizziness
Swelling of the tissue that lines the brain
Anxiety
Sensations of tingling in the hands and feet that makes tasks such as buttoning shirts and pants more difficult
Tearing of the eyes
Swelling the optic disk in the eye that could impair normal vision
Pain in the abdomen, back, chest, head or throat
Cough
Shortness of breath
Collection of fluid in the membrane that surrounds the lungs which could cause difficulty breathing
Collection of fluid in the lungs that causes difficulty in breathing
Kidney damage
Flu-like symptoms
Blood clots

<u>Rare, but serious</u>

Damage to the heart muscle that impairs the heart's ability to pump blood normally. In more severe cases the loss of heart function can result in the diagnosis of heart failure, which will require treatment with additional medications. Symptoms include increased fluid in the arms and legs, shortness of breath, or inability to exercise or carry out normal activities without fatigue.

Rev. 12/04 Studies on rats in long-term imatinib therapy show growth of benign (non-cancerous tumors) and malignant tumors (tumors that can spread to other parts of the body) in the kidneys, urinary and genital tracts. Researchers are still determining how this finding affects humans who are on imatinib therapy.

Rev. 2/95 GM-CSF: Patients receiving GM-CSF have experienced fever; chills; nausea; vomiting; diarrhea; fatigue; weakness; headache; abnormal taste, decreased appetite; irritation of the vein; rapid or irregular heartbeat or other heart problems; feeling of faintness; facial flushing; pain in the bones, muscles, chest, abdomen, or joints; lung inflammation and difficulty breathing, local reaction at the site of injection; rashes; and kidney, liver and nervous system dysfunction. Blood component abnormalities or infections may occur.

Rev. 2/95, 12/04

Rev. 2/95 Leucovorin can cause allergic reactions (skin rash), nausea, vomiting, diarrhea, wheezing, headache, mouth sores, hives, an increase in the number of cells that cause clotting.

Rev. 2/95 Dexamethasone Nausea and vomiting, loss or increase of appetite, weight gain, aggravation of ulcers, rash, facial hair growth, acne, bruising of the skin, redness of the face, menstrual changes, headache, loss of sleep, dizziness, depression, psychosis, a sense of well being, seizures, muscle weakness, fluid retention, an increase in blood pressure, irritation or inflammation of the veins, increased pressure in the eyes, cataracts, a change in metabolism, an increase in white blood cells, back pain, osteoporosis, viral, bacterial and fungal infections, including herpes, delayed wound healing, muscle wasting. This drug could cause abnormal reactions to skin tests. Other side effects include a pertusion of the eyes and skin cell death.

Rev. 2/95 Prednisone can cause weight gain, fluid retention, high blood pressure, inflammation of the veins, an increase in white blood cells, low blood sugar, an increase in potassium in the blood, vision problems, including pertusion of the eyes, a change in metabolism that could lead to diabetes, back pain, osteoporosis, loss of muscle, loss of calcium from the bone, feeling of well being, changes in hair and skin, rash, acne, facial hair growth, bruising of the skin, herpes, fungal infections, tuberculosis, menstrual irregularities, insomnia, headache, a sense of well being, psychosis, depression, seizures, muscle weakness, loss of muscle, dizziness, nausea and vomiting, loss or increase of appetite, ulcers, and aggravation of peptic ulcers, viral, bacterial and fungal infections, including herpes and tuberculosis. More common with short-term use are stomach upset and insomnia.

Rev. 2/95 Mercaptopurine can cause a lowering of the counts, resulting in increased risk of infection, loss of energy, and increased risk of bleeding, skin problems include rash, irritation can result if the drug leaks on to the top layer of the skin, yellowing of the skin and eyes, a change in the color of the skin, death to skin cells; nausea, vomiting, loss of appetite, abdominal pain, mouth sores, changes in liver tests, fever and headache.

Rev. 2/95 Thioguanine can cause a lowering of the blood counts which leads to an increased risk of infection, loss of energy, and increased risk of bleeding, nausea, vomiting, diarrhea, sores and soreness in the mouth, liver damage, fever, and loss of appetite, changes in liver tests, kidney problems, disease of the veins, yellowing of the eyes and skin, other skin problems including rash, loss of sensation, and difficulty in walking.

Rev. 2/95 Methotrexate can cause nausea, vomiting, diarrhea, decrease in the blood counts leading to fatigue, infection and bleeding; inflammation of the mouth and throat, mouth sores, dilation of blood vessels, loss of appetite, vomiting blood, dark tarry stools, lung problems and coughing, malaise, blurred vision, watery eyes and eye inflammation, cortical blindness, chills, fever, liver injury, kidney damage, hair loss, inflammation of the lung, osteoporosis, excess acid in the urine, and allergic reactions. Methotrexate may also cause various skin problems, which may include skin redness, irritation, and rashes, changes in the color of your skin, acne, blisters, and swelling and inflammation of the skin and/or hair follicles. It also may cause a peculiar sensitivity to sunlight. Neurologically, methotrexate may cause alterations in brain structure (though this is less common with intrathecal administration), tiredness, dizziness, weakness, confusion, difficulty in coordination, tremors, irritability, seizures, headache, back pain, stiff neck, paralysis, and coma. Other side-effects include decreased levels of sperm that never increases to normal levels and a decrease in bone mass in the leg.

Rev. 7/04 Mitoxantrone can cause low blood cell counts, dry skin, rash, hair loss, nausea, vomiting, diarrhea, abdominal pain, inflamation of mucous membrane, congestive heart failure, chest pain, irregular heart beat, high blood pressure, itchy skin, increased liver enzymes, headache, cough, shortness of breath, fever, red eye, inflamation Rev. 7/04 and discoloration of veins, discoloration of urine and stool, urinary tract infection and abnormal menstruation.

Rev.2/95 Vincristine can cause numbness and tingling in the hands and feet, with possible difficulty walking and performing fine motor tasks, lowering of the blood counts, resulting in increased susceptibility to infection, bruising or uncontrollable bleeding; weakness (anemia), fever, hair loss, rash, nausea, vomiting (rarely), abdominal pain, diarrhea, constipation, loss of appetite, increased liver chemicals possibly indicating liver damage, seizures, headaches, blindness, severe pain in the jaw, face, throat, extremities, bones, back and limbs, muscle weakness. Other side effects include coughing, skin and soft tissue damage, vision problems and kidney problems.

Rev. 10/05 G-CSF can cause mild to moderate bone pain; redness, swelling, itching, and pain at the injection site; rash; allergic reactions; high white blood cell count; heart problems; enlargement of the spleen; inflammation of blood vessels; and increase of uric acid, LDH, alkaline phosphatase and leucocyte alkaline phosphatase in the blood.

As with chemotherapy, there are a number of potential hazards with bone marrow transplantation: There is a minimal risk of death, infection and brain damage from any procedure involving general anesthesia. Your pelvic bones will be sore and your skin bruised from the multiple punctures involved in taking the marrow samples. These symptoms are usually mild, can be controlled with aspirin-like pain killers, and subside over 5 to 7 days.

Nausea, vomiting, hair loss, mouth sores, rash, anemia, lung or liver or kidney damage, heart failure, bloody urine, cataracts, diarrhea, allergic reactions and possible sterility may be associated with the high-dose chemotherapy (Etoposide) and radiation used for treatment. Darkening of the skin, lung injury and inflammation of the salivary glands may also occur. One of the major side effects of high-dose chemotherapy and radiation therapy is the effect on the bone marrow and the bleeding and infection problems that can follow because of the low platelet and white blood cell counts.

The purpose of giving your frozen bone marrow back (bone marrow transplant) is to minimize these problems. Receiving your stored bone marrow is necessary for recovery of bone marrow function following drug therapy at this high dose level. These side effects may, alone or in combination, be severe enough to cause death.

You may die from the complications of this treatment or if the reinfused bone marrow fails to function normally. A further potential problem is that in spite of our best efforts to make certain the bone marrow is free of leukemia cells, when it is stored, there is the possibility that if tumor cells were present, they would be reinfused. There may be other side effects which cannot be determined.

Rev. 5/99

The transplanted bone marrow or peripheral blood, obtained from any other source than your own body (allogeneic bone marrow) may react against you, causing graft-versus-host disease. This may produce symptoms of skin rash, diarrhea or jaundice. Usually these symptoms respond to increased immune suppression with prednisone, although sometimes other experimental therapies are necessary. Sometimes despite these interventions, the disease persists causing chronic illness and/or death.

The immune system is profoundly suppressed especially allogeneic bone marrow transplanted for 6 months to 1 year. Therefore, there is increased risk of infection, particularly from viral pneumonia due to cytomegalovirus. While new antiviral medications are available, there is still risk of a fatal lung infection during this period.

Rev. 5/99

Other major complications expected following bone marrow or peripheral blood transplantation are: 1) infection(s) with bacteria, fungi or different viruses; 2) recurrent leukemia; 3) risk of failure to accept the bone marrow graft, resulting in loss of the bone marrow function. These problems may result in a risk of death within 6 months following bone marrow transplantation.

Your physician will be checking you closely to see if side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Many side effects disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control. Other side effects may be long lasting or permanent. These include effects on fertility. You understand that the use of medications to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study drugs.

Rev. 2/07
Rev. 12/04

CONTACT PERSONS

In the event that physical injury occurs as a result of this research, facilities for treatment of injury will be available. You understand, however, you will not automatically be provided with reimbursement for medical care or other compensation. For more information concerning the research and research-related risks or injuries, you can notify Dr. _____, the investigator in charge at

_____. In addition, you may contact _____
(Telephone)

at _____ for information regarding patients' rights in research studies.
(Telephone)

ALTERNATIVES

Alternatives which could be considered in your case include treatment with the same or different drugs used in different doses or combinations, given for differing periods of time. An additional alternative is no further therapy. You understand that your doctor can provide detailed information about your disease and the benefits of the various treatments available. You have been told that you should feel free to discuss your disease and prognosis with your doctor.

You understand that your physician will be available to answer any questions you may have at any time concerning this study. In addition, you understand that you are free to ask your physician any questions concerning this program that you wish in the future. You should be aware that added costs may arise and some of these costs may not be covered by your insurance. Your doctor will discuss these with you.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from participation in this study. You have been told that should your disease become worse, side effects become very severe, should new scientific developments occur that indicate the treatment is not in your best interest, or your doctor feels that this treatment is no longer in your best interest, the treatment would be stopped. Further treatment would be discussed.

VOLUNTARY PARTICIPATION

You are aware that the bone marrow transplantation is an option on this study. You agree to allow samples of your blood to be taken for typing for possible bone marrow transplantation.

Participation in this study is voluntary. No compensation for participation will be given. You understand that you are free to withdraw your consent to participate in this treatment program at any time without prejudice to your subsequent care. However, if you are randomized to received autologous bone marrow transplant and you go on to receive high-dose chemotherapy, if you then withdraw from the study before reinfusion of your previously stored marrow it would likely prove fatal. You are free to seek care from a physician of your choice at any time. If you do not take part in or withdraw from the study, you will continue to receive care. In the event that you withdraw from the study, you will continue to be followed and clinical data will continue to be collected from your medical records.

CONFIDENTIALITY

You understand that a record of your progress while on the study will be kept in a confidential form at _____ and also in a computer file at the statistical headquarters of the
(Institution)
Eastern Cooperative Oncology Group.

The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA) and the National Cancer Institute (NCI) and sponsoring agencies may have access to medical records which contain your identity. However, no information by which you can be identified will be released or published. Histopathologic material, including slides, may be sent to a central office for review.

* *

I have read all of the above, asked questions, received answers concerning areas I did not understand and I willingly give your consent to participate in this program. Upon signing this form, I will receive a copy.

(Patient Signature) (Date)

(Witness Signature) (Date)

(Parent or Guardian Signature [if applicable]) (Date)

(Physician Signature) (Date)

Rev. 2/98, 5/99 **I, _____, willingly agree that any pathology samples and unused blood and bone marrow collected for this protocol may be stored at the ECOG Pathology Coordinating Office or the Central Laboratory. These pathology samples and remaining blood and bone marrow may be used for future research that could include genetic research (about diseases that are passed on in families). This research will not have an effect on my care, therefore, neither I nor my doctor will receive results of this testing. No medical report will be added to my records. My medical records may be reviewed in the future for purposes of obtaining more information about my health but my name and address will remain confidential and will not be released. The blood, bone marrow, and pathology samples will be used for research purposes only, it will not be sold and may not have a direct benefit to me or my cancer.**

If I decide now that my blood, bone marrow, and pathology samples can be kept for research, I can change my mind at any time. I just need to contact my doctor and withdraw my consent for the use of my blood, bone marrow, and pathology samples for research.

I have read all of the above, asked questions and received answers concerning areas that I did not understand. I willingly consent to allow my blood, bone marrow, and pathology samples to be stored for future research.

* *

(Patient Signature) **(Date)**

(Witness Signature) **(Date)**

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APPENDIX II

Average Body Weight for Heights

Height		Weight (Male)		Weight (Female)	
Feet	Inches	Lbs.	Kgs.	Lbs.	Kgs.
4	11	122	55.5	116	52.7
5	0	124	56.4	118	53.6
	1	126	57.3	120	54.4
	2	128	58.2	122	55.5
	3	131	59.6	125	56.8
	4	134	60.9	129	58.6
	5	138	62.7	132	60
	6	142	64.5	136	61.8
	7	146	66.4	140	63.6
	8	150	68.2	144	65.5
	9	154	70	148	67.3
	10	158	71.8	152	69.1
	11	163	74.1	155	79.1
6	0	169	76.8	159	72.3
	1	175	79.5	-	-
	2	181	82.3	-	-
	3	187	85	-	-

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APPENDIX III

COMMON TOXICITY CRITERIA

		0	1	2	3	4
Leukopenia	WBC x 10^3 Granulocytes/Bands	≥4 ≥2 ≥2	3 - 3.9 1.5 - 1.9 1.5 - 1.9	2 - 2.9 1 - 1.4 1 - 1.4	1 - 1.9 0.5 - 0.9 0.5 - 0.9	<1 <0.5 <0.5
Thrombocyto-penia	Plt x 10^3	WNL	75 - normal	50 - 74.9	25 - 49.9	<25
Anemia	Hgb	WNL	10 - normal	8 - 10	6.5 - 7.9	<6.5
Hemorrhage	- - - - -	none	mild, no	gross, 1-2 units transfusion/episode	gross, 3-4 units transfusion/episode	massive, >4 units transfusion/episode
***Infection**	- - - - -	none	mild, no active Rx	Moderate, localized infection requires active Rx	severe, systemic infection requires active Rx, specify site	life-threatening, sepsis, specify site
Fever in absence of infection	- - - - -	none	37.1° - 38° C 98.7 °- 100.4° F	38.1 ° - 40°C 100.5 ° - 104° F	>40° C (>104° F) for less than 24 hours	>40° C (104° F) for >24 hrs or fever with hypotension
	• **Fever felt to be caused by drug allergy should be coded as allergy.** • **Fever due to infection is coded under infection only.**					
GU	Creatinine	WNL	< 1.5 x N	1.5 - 3 x N	3.1 - 6 x N	>6 x N
	Proteinuria	No change	1+ or <0.3g% or <3g/l	2-3+ or 0.3 - 1g% or 3 - 10g/l	4+ or >1g% or >10g/l	nephrotic syndrome
	Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion
	*BUN	<1.5 x N	1.5 - 2.5 x N	2.6 - 5 x N	5.1 - 10 x N	>10 x N
	• **Urinary tract infection should be coded under infection, not GU.** • **Hematuria resulting from thrombocytopenia should be coded under hemorrhage, not GU.**					
GI	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	- - - - -
	Vomiting	none	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	>10 episodes in 24 hrs or requiring parenteral support
	Diarrhea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	increase of 7-9 stools/day or incontinence, or severe cramping	increase of ≥10 stools/day or grossly bloody diarrhea, or need for parenteral support
	Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers, but can eat	painful erythema, edema or ulcers, and cannot eat	requires parenteral or enteral support
Liver	Bilirubin	WNL	- - - - -	<1.5 x N	1.5 - 3 x N	>3 x N
	Transaminase (SGOT, SGPT)	WNL	≤2.5 x N	2.6 - 5 x N	5.1 - 20 x N	>20 x N
	Alk Phos or 5'nucleotidase	WNL	≤2.5 x N	2.6 - 5 x N	5.1 - 20 x N	>20 x N
	Liver - clinical	no change from baseline	- - - - -	- - - - -	precoma	hepatic coma
	• **Viral Hepatitis should be coded as infection rather than liver toxicity.**					
Pulmonary	- - - - -	none or no change	asymptomatic, with abnormality in PFTs	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
	• **Pneumonia is considered infection and not graded as pulmonary toxicity unless felt to be resultant from pulmonary changes directly induced by treatment.**					

COMMON TOXICITY CRITERIA

		0	1	2	3	4
Cardiac	Cardiac dysrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring, or hypotension or ventricular tachycardia or fibrillation
	Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
	Cardiac--ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
	Cardiac--pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Blood Pressure	Hypertension	none or no change	asymptomatic, transient increase by >20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	recurrent or persistent increase by >20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis
	Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization; resolves within 48 hours of stopping the agent	requires therapy and hospitalization for >48 hours after stopping the agent
Skin	-----	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Allergy	-----	none	transient rash, drug fever <38° C, 100.4° F	urticaria, drug fever ≥ 38°C 100.4°F, mild bronchospasm	serum sickness, bronchospasm, requires parenteral meds	anaphylaxis
***Phlebitis**		none	arm	thrombophlebitis, leg	hospitalization	embolus
Local		none	pain	pain and swelling, with inflammation or phlebitis	ulceration	plastic surgery indicated
Alopecia	-----	no loss	mild hair loss	pronounced or total hair loss	-----	-----
Weight gain/loss	-----	<5%	5 - 9.9%	10 - 19.9%	≥20%	-----
NEUROLOGIC **Sensory**	neuro--sensory	none or no change	mild paresthesias; loss of deep tendon reflexes	mild or moderate objective sensory loss; moderate paresthesias	severe objective sensory loss or paresthesias that interfere with function	-----
	neuro--vision	none or no change	-----	-----	symptomatic subtotal loss of vision	blindness
	neuro--hearing	none or no change	asymptomatic hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness, not correctable
Motor	neuro--motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
	neuro--constipation	none or no change	mild	moderate	severe	ileus >96 hours
Psych	neuro--mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Clinical	neuro--cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation or hallucinations	coma, seizures, toxic psychosis
	neuro--cerebellar	none	slight incoordination, dysdiadokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
	neuro--headache	none	mild	moderate or severe but transient	unrelenting and severe	-----

Metabolic	Hyperglycemia	<116	116 - 160	161 - 250	251 - 500	>500 or ketoacidosis
	Hypoglycemia	>64	55 - 64	40 - 54	30 - 39	<30
	Amylase	WNL	<1.5 x N	1.5 - 2 x N	2.1 - 5 x N	>5.1 x N
	Hypercalcemia	<10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	≥13.5
	Hypocalcemia	>8.4	8.4 - 7.8	7.7 - 7	6.9 - 6.1	≤6
	Hypomagnesemia	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤0.5
Coagulation	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.5 x N	0.49 - 0.25 x N	≤0.24 x N
	Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.5 x N	1.51 - 2 x N	>2 x N
	Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3 x N	>3 x N

* denotes ECOG specific criteria

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APPENDIX IV

Bone Marrow (Engraftment) Toxicity Criteria

Grading is based on duration of cytopenia rather than nadir. Grade 5 refers to toxic death, while other toxicities are graded 0-4.

Grade	5	Death due to bacterial or fungal infection or hemorrhage associated with neutrophils < 500/ul or platelets < 10,000/ul more than 8 weeks after marrow transplantation.
	4	Neutrophils < 500/ul or platelets < 10,000/ul more than 8 weeks after marrow transplantation.
	3	Neutrophils < 500/ul and/or platelets < 10,000 4 to 8 weeks after marrow transplantation.
	2	Neutrophils < 500/ul and/or platelets < 10,000/ul for a duration of up to 4 weeks after marrow transplantation.
	1	Neutropenia and/or thrombocytopenia, but neutrophils never < 500/ul and platelets never < 10,000/ul.

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APPENDIX V

Criteria for Capillary or Vascular Leak Syndrome

Cardiac: Pericardial

Grade 1 = asymptomatic effusion, no intervention required

Grade 2 = pericarditis (rub, chest pain, EKG changes)

Grade 3 = symptomatic effusion; drainage required

Grade 4 = tamponade; drainage urgently required

Weight Gain

Grade 1 = 5 - 9.9%

Grade 2 = 10 - 19.9%

Grade 3 = $\geq$ 20%

Edema

Grade 1 = 1+

Grade 2 = 2+

Grade 3 = 3+; presacral and lower extremity edema

Grade 4 = 4+; generalized anasacra

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APPENDIX VI

Total Body Irradiation Guidelines
(For Patients Undergoing Bone Marrow Transplantation)

I. Equipment

Beam Energy: Treat only with megavoltage units: i.e., cobalt-60 or accelerator beams with nominal energy of no less than 4 MeV (million electron volts). High energy photons (6 MeV and above) must satisfy the same total dose requirements for skin surfaces. It will be necessary for each institution to establish, through experimental measurements, whether the combination of entrance plus exit beams satisfy these conditions in the first few millimeter of tissue.

Geometry: The treatment configuration shall be that the patient is entirely included within the treatment beam exclusive of the penumbra, i.e., the patient shall be situated well within the 90% decrement line at each depth. (The 90% decrement line is defined as a line in each plan perpendicular to the central axis connecting points which are 90% of the central axis dose in that plane.) It is essential that agreement between the light and radiation fields be established and verified for the extended TBI treatment distance.

Dose Rate: The dose rate shall be between 5 and 30 cGy/min defined at the midplane of the umbilicus. Dose rates outside this range will have to be approved prior to use by the Study Chair. Total elapsed time of treatment will be recorded to compute the effective dose rate per treatment field.

II. Prescription Doses and Fractionation

Prescription Point is defined as the point midplane at the level of the umbilicus.

Dose Definition: The dose shall be defined as centigray to muscle. No inhomogeneity corrections shall be made in the calculation of the dose to the prescription point.

Total Treatment Dose: The total treatment dose shall be 1320 cGy delivered in 6 fractions of 220 cGy per fraction. A hyperfractionation regimen of 2 fractions per day for 3 consecutive days shall be used. Thus, the patient shall be treated with 2 fractions per day at 220 cGy fraction, yielding a total daily dose of 440 cGy per day. There is a required time interval of at least 5 hours
Rev. 5/93, 2/95 between fractions on a given day. The time of day for each treatment should be recorded on the chart. All fields should be treated during each fraction. On day -6 a 400 cGy electron boost to the testes will be delivered to male patients. For example:

Rev. 2/95

Session	Day	Time	Beam Direction	Energy (MeV)	Dose (cGy)	Notes
1	-6	7:30	AP/PA	10X	220	TLD
			AP	electron	400	testes-male
2	-6	12:30	AP/PA	10X	120	TLD
3	-5	7:30	AP/PA	10X	220	
4	-5	12:30	AP/PA	10X	220	
5	-4	7:30	AP/PA	10X	220	
6	-4	12:30	AP/PA	10X	220	

II. Dose Hemogeneity and Off-Axis Reference Points

Reference Points:

a. Head: This reference point is defined at the level of pituitary fossa.

b. Neck: This reference point is defined at midplane at the level of the thyroid cartilage.
c. Mid-mediastinum: This reference point is defined along the patient's longitudinal axis at the level of the angle of Louis, at midplane.

d. Umbilicus: This is the point of prescription, at midplane.

e. Pelvis: This reference point is defined along the patient's longitudinal axis in the center of the pelvis at a level which is 1 cm superior to the symphysis pubis.

f. Knee: This reference point is defined along the midline in the midplane of the knee at the level of the middle of the patella.

g. Ankle: This reference point is defined along the midline at the midplane of the ankle at the level of the lateral malleolus.

h. Lung: This reference point is defined along the patient's longitudinal axis at the level of the angle of Louis, at the center of the right lung.

IV. Treatment Technique

Equally weighted parallel opposed portals shall be used. AP, PA and bilateral opposed four-field techniques are acceptable. The collimator opening and treatment distance shall be such that the patient will be included entirely within the treatment beam and that no part of the patient extends into the penumbra region as defined by the 90% decrement line. Usually, the treatment distance, either source-to-skin (SSD) or source-to-axis (SAD), will be at least 3 m; greater dose unformity will be achieved at increased distances.

Rev. 5/93

Patients may be treated in any position that is compatible with the homogeneity requirements and allows for the reproducibility of setup the patient dosimetry. Tissue compensation will be used when necessary to improve dose homogeneity. If used, a complete description of the compensation technique and its effect on the prescription dose and dose distribution shall be reported as submitted or part of the quality control documentation. Skin bolus (e.g., blankets or other body covers) or a large lucite plate will be used when necessary to bring up the superficial dose to satisfy the homogeneity requirements. The dose to the skin should be as high as reasonably achievable and must be at least 90% of the dose maximum at 5 mm depth.

V. Calculations and Treatment Planning

Rev. 5/93

It is recommended that the calculation method be based upon measurements that are made in a unit density phantom 35 x 35 x 35 cm^3 in size. All measurements should be made at the appropriate TBI extended SSD. The method of calculation should be specific to the institution's methods, clearly documented. "*In vivo*" dosimetry (TLD, diodes, etc.) is optionaL, but should be performed initially to confirm the accuracy and the general method of radiation treatment. Such measurements should be performed on at least one patient prior to protocol entry of patients. Alternately, or in addition, dosimetric measurements shall be conducted employing an anthropomorphic phantom in the TBI treatment geometry.

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APPENDIX VII

Radiotherapy Guidelines for Prophylactic Cranial Irradiation and Therapeutic Cranio-Spinal Irradiation

1.0 General Principles

Rev. 2/95
Rev. 10/05

Patients, who do not present with occult CNS disease and who are not receiving allogeneic or autologous BMT, are to receive prophylactic whole brain radiotherapy to a dose of 24 Gy in 12 fractions over 2 to 3 weeks between intensification and the start of consolidation (see section 5.311 CNS Prophylaxis).

If CNS leukemia is present at diagnosis, methotrexate 12.5 mg is given intrathecally or via an Omaya Reservoir weekly until blasts are absent from the spinal fluid. Cranial irradiation to a dose of 24 Gy and spinal axis irradiation to a dose of 12 Gy should be administered concurrently with Phase II (see 5.213 Spinal Fluid Examination).

2.0 Equipment

Beam Energy: Treat only with megavoltage units: i.e., cobalt-60 or accelerator beams with a nominal energy of no less than 4 MV.

Machine Geometry: The minimum acceptable source-axis distance is 80 cm.

Simulation: The use of a simulator for both the prophylactic cranial and the therapeutic cranio-spinal irradiation is recommended.

3.0 Treatment Techniques

3.1 Patient Position

3.11 For prophylactic cranial irradiation, patients may be treated supine or prone.

3.12 For cranio-spinal irradiation, the patient should be placed prone. It is suggested that the patient's trunk be elevated from the treatment couch so that the neck is relatively straight. Delivering the cranial irradiation with the patient in the oblique or supine position is discouraged, because of the difficulty in matching fields.

3.2 Treatment Volume

3.21 For prophylactic cranial irradiation, the cranium is to be treated with opposed lateral fields which include the entire calvarium as well as the brain stem to the level of the bottom of C2. The entire subarachnoid space and optic nerves should be included in the field. Eye blocking should be used, but should not extend posteriorly behind the lateral canthus or superiorly into the anterior cranial fossa. The fields should not be exactly parallel; instead, the gantry should be angled slightly to spare the contralateral eye. Inferiorly, the border of the cranial field should be at least 0.5 cm below the base of the skull. There must be fall-off from the scalp anteriorly, superiorly and posteriorly.

3.22 For therapeutic cranio-spinal irradiation, the cranium and brain stem should be treated as above (section 3.21), and the collimator should be rotated so that it parallels the divergence of the spinal field. It is recommended that the cranial field abut the spinal field directly on the neck in the mid-sagittal plane. It is optional whether to move the field junction once or twice during the course of radiation.

The spine should be treated with a posterior field which extends from the lower margin of the cervical extension of the cranial field to the inferior border of the second sacral segment. The spinal field should extend laterally on both sides to cover the entire vertebral bodies with at least 1 cm margin on either side, thus including the width of the spinal cord and CSF recesses. A spade to cover sacroiliac joints (and sacral nerve roots) is not required, but is allowable.

If the entire length of the spine cannot be included in a single field, the field may be divided into two fields, preferably with the junction below L2. An appropriate gap calculation should be performed so that the fields abut at the level of the spinal cord. It is optional whether this gap is moved once or twice during treatment of the spinal field.

4.0 Treatment Dose

4.1 Prescription Point

The cranial dose should be calculated at the midplane. The dose to the spinal cord will be taken at the depth along the central axis from the posterior skin to the posterior margin of the vertebral bodies as determined by lateral x-ray of the spine.

4.2 Dose Definition

Doses are defined as absorbed dose in cGy to muscle tissue at the prescription point. No correction should be made for tissue homogeneity.

4.3 Total Treatment

The total cranial dose is 2400 cGy. The total spinal dose is 1200 cGy.

5.0 Time-Dose Considerations

A daily dose of 200 cGy is recommended for both the prophylactic cranial and the therapeutic cranio-spinal irradiations.

We recommend that treatments be given 5 days per week. The 2400 cGy cranial irradiation should be given over 16-19 days, while the 1200 cGy spinal axis irradiation should be given over 8 days. There will be no adjustments for interruption in treatment.

6.0 Radiation Oncology Clarification

Questions regarding the radiotherapeutic aspects of this protocol should be addressed to the radiotherapy co-chairman:

Rev. 7/04

Richard Whittington, M.D.
University of Pennsylvania Hospital
Department of Radiation oncology
2 Donner
3400 Spruce Street
Philadelphia, PA 19104-4283
Tel: (215) 662-6515

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APPENDIX VIII

Rev. 12/04 **NOTE: As of Addendum #14, Erwinia Asparaginase use as a substitute for L-Asparaginase or PEG-Asparaginase has been discontinued as the drug is no longer available.**

Erwinia L-asparaginase

Rev. 7/04 Sponsorship of the IND relating to Erwin L-asparaginase (BB IND 290) has been transferred from the National Cancer Institute (NCI) to Porton Products Ltd.. Distribution services of Erwinia L-asparaginase on behalf of Porton Products Ltd. will be provided by McKesson BioServices Corporation.

Please place all orders for Erwinia L-asparaginase in writing (preferably by fax) to:

Rev. 7/04

McKesson BioServices Corporation
14665 Rothgeb Drive
Rockville, Maryland 20850
Tel: (301) 315-8460
Fax: (301) 738-2478

Each order should state:

1. The quantity of vials required
2. The protocol identification number
3. A patient identifier code and/or initials
4. A purchase order number for invoicing reference
5. The shipping address
6. The billing address if different from the shipping address
7. Your name, department and telephone number
8. The patient's diagnosis
9. A statement regarding the reason for ordering Erwinia L-asparaginase (hypersensitivity reaction to E.Coli L-asparaginase)
10. Physicians's name and telephone number

Formerly the NCI was purchasing Erwinia L-asparaginase from Porton and supplying the user free of charge. Under the new system the FDA has approved that Porton make a charge for this drug.

Rev. 7/04 Porton's US affiliate, Ipsen Pharmaceuticals, Inc will invoice the requesting institutions $96.50 per 10,000 I.U. vial of Erwinia L-asparaginase which includes shipping and handling. Terms are net 30 days. All purchase orders for Erwinia L-asparaginase should indicate that payment will be made to Ipsen Pharmaceuticals, Inc. 30401 Agoura Road, Suite 102, Agoura Hills, CA 91301-2009.

For any queries other than billing and payment terms outlined above, please contact Dr PN Robinson in the Maidenhead UK office directly by telephone or fax:

(011) 441628 771417 telephone
(011) 441628 770211 fax

Rev. 7/04 Questions regarding billing or payment should be directed to Mr. Scott Shrock, Controller, Ipsen Pharmaceuticals, Inc. telephone (818) 879-2200.

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Rev. 12/04 **NOTE: As of Addendum #14, Erwinia Asparaginase use as a substitute for L-Asparaginase or PEG-Asparaginase has been discontinued as the drug is no longer available.**

ERWINIA L-ASPARAGINASE SHIPMENT REQUEST FORM

Photocopy as needed

Please place all orders for Erwinia L-asparaginase by completing this form and send via Fax to:

Rev. 7/04

McKesson BioServices Corporation, Rockville, MD 20850
Tel: (301) 315-8460 Fax: (301) 738-2478

Please complete **legibly** the following to assure a quick response:

1. Quantity of vials required: _____ * Date Needed _____
2. Protocol Identification Number: _____
3. Patient identification Code and/or Initials: _____
4. Purchase Order Number: _____
   (required for Invoicing Reference)
5. Ship to Address:

6. Billing Address if different from shipping address:

7. Your Name, Department, Telephone and Fax number:

Name _____ Dept: _____
Tel: _____ Fax: _____

8. Patient's Diagnosis

_____

9. Statement regarding the reason for ordering Erwinia L-asparaginase (Hypersensitivity reactions to E. Coli L-asparaginase)

_____

10. Physician's Name and Telephone Number:

Name _____
Tel: _____ Fax: _____

Rev. 5/99

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APPENDIX IX

Pathology Submission Guidelines

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates (CRAs))
2. Instructional memo to submitting pathologists
3. List of Required Materials for E2993
4. ECOG Pathology Material Submission Form (# 638)

GUIDELINES FOR SUBMISSION OF PATHOLOGY MATERIALS

The following items should always be included when submitting pathology materials to the ECOG Pathology Coordinating Office:

- Institutional Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG Pathology Material Submission Form (# 638)

Instructions:

1. Place the Patient ID label provided by the ECOG Coordinating Center in **Part A** of the ECOG Pathology Material Submission Form.

   If a label is not available **TYPE or PRINT** the following information in Part A of the form:

   - Patient's name (last, first)
   - Protocol number
   - Protocol case number (the patient's ECOG sequence number; for intergroup studies, include both the ECOG and other group's sequence numbers)
   - Patient's hospital number
   - Institution
   - Affiliate (if appropriate)

2. Complete blank areas of the pathologist's instructional memo, and forward it, along with the List of Required Material and the ECOG Pathology Material Submission Form, to the appropriate pathologist.

   The pathologist should return to you the required pathologic samples and pathology reports, along with the completed ECOG Pathology Material Submission Form (# 638) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.

3. Keep a copy of the ECOG Pathology Material Submission Form (# 638) for your records (the original should be sent to the PCO).

4. Double check that **ALL** required forms, reports, and pathology samples are included in the package to send to the Pathology Coordinating Office (see appropriate List of Required Material).

   Pathology specimens submitted for a patient WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.

5. Mail pathology materials to:

Rev. 7/04

Elisabeth Paietta, Ph.D.
Our Lady of Mercy Cancer Center
600 East 233rd Street
6th Floor, Immunology Laboratory
Bronx, NY 10466-2967

If you have any questions concerning the above instructions, or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG Pathology Coordinating Office TEL: (718) 920-9992 or FAX: (718) 920-1161.

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MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D.
Chair
Rev. 7/04 ECOG Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: *Submission of Pathology Materials for E2993: Phase III Randomized Trial of Autologous and Allogeneic Bone MarrowTransplantation versus Intensive Conventional Chemotherapy in Acute Lymphoblastic Leukemia in First Remission*.

The patient named on the attached ECOG Pathology Material Submission Form (# 638) has been entered onto an ECOG protocol by _____*(ECOG Investigator).* This protocol requires the submission of pathology materials for pathology review.

Please complete **PART B** of the Submission Form. Keep a copy for your own records, and return the completed Submission Form, the pathology report, the slides, and any other required material (see attached List of Required Material) to the Clinical
Rev. 7/04 Research Associate (CRA). The CRA will forward all required pathology material to the ECOG Leukemia Translational Studies Laboratory.

Rev. 7/04

Results will be distributed to you upon completion of the review.

Rev. 2/03, 7/04 If you have any questions regarding this request, please feel free to contact the Leukemia Transitional Studies Laboratory at TEL: (718) 920-9992 or FAX: (718) 920-1161.

The ECOG CRA at your institution is:

Name: _____

Address: _____

_____

Phone: _____

Thank you.

LIST OF REQUIRED MATERIAL

Protocol E2993	*Phase III Randomized Trial of Autologous and Allogeneic Bone Marrow Transplantation versus Intensive Conventional Chemotherapy in Acute Lymphoblastic Leukemia in First Remission*.

Pre-Treatment:

1. ECOG Pathology Material Submission Form (# 638) -- Part B completed.
2. Institutional pathology report ***(must be included with EVERY pathology submission).***

Rev. 7/04 3. Two (2) unstained bone marrow biopsy slides from the initial diagnostic biopsy.

Rev. 7/04 4. When insufficient material is available, at least two (2) peripheral blood smears must be forwarded.

Rev. 7/04 5. If cytochemical stains have been performed please submit these for review.

INSTRUCTIONS: Please complete and submit this form **along with all pathology material and corresponding pathology reports** requested by the protocol. **See list of required materials specific to EACH protocol.**

PART A: TO BE COMPLETED BY DATA MANAGER

Date sample sent to ECOG _____ / _____ / _____ **(M,D,Y)**

Data Manager _____

Telephone No. ( ) _____ _____

FAX No. ( ) _____ _____

ECOG Parent Prot. No. _____ **Seq. No.** _____

PLACE ID LABEL HERE

Patient's Name _____

ECOG Prot. No. _____ **ECOG Patient Seq. No.** _____

Participating Group Prot. No. _____ **Participating Group Patient ID No.** _____

Group _____ **Institution** _____

Step No. _____ **Affiliate** _____

PART B: TO BE COMPLETED BY THE SUBMITTING PATHOLOGIST

	STATUS * (see Below)	DATE SPECIMEN COLLECTED (M,D,Y)	DISEASE SITE	NUMBER OF SLIDES	TYPE OF STAIN	SPECIMEN ID NUMBERS
COMPLETE FOR SLIDES		/ /				
		/ /				
		/ /				
	STATUS * (See Below)	**DATE SPECIMEN COLLECTED (M,D,Y)**	**DISEASE SITE**	**NUMBER OF BLOCKS**	**TYPE OF FIXATIVE**	**SPECIMEN ID NUMBERS**
COMPLETE FOR BLOCKS		/ /				
		/ /				

*** STATUS:** Please **identify** the clinical status of the sample. **List ALL that apply.**

1. Original Diagnostic Material
2. Pre-Protocol Treatment Biopsy
3. Post-Protocol Treatment Biopsy
4. Post-Surgery Biopsy
5. Relapse/Recurrence
6. Remission/Response
7. Other, Specify_____

Submitting Pathologist _____

Telephone No. ( ) _____ _____

Address _____

_____

_____

INSTITUTION COMMENTS _____

_____

Can this sample be retained by the ECOG Central Tissue Repository? _____ **Yes** _____ **No**

NOTE: Samples submitted for protocols requiring submission for tissue banking **will not be** returned except for purposes of individual patient management. For this reason, the **submitting pathologist should retain at least one paraffin block** at their institution.

[A block has been retained at the submitting institution: _____ **Yes** _____ **No]**

Please **CIRCLE THE REASON** for non-submission and **INCLUDE** a formal letter of explanation:
State Regulations, Institutional Policy, Insufficient Tissue, Patient Refusal, Other specify other _____ Pathologist or Investigator's Signature _____.

PART C: ECOG COORDINATING CENTER USE ONLY

Date Sample Received by ECOG _____ / _____ / _____ (M / D / Y)

Date Sent to Central Lab _____ / _____ / _____ (M / D / Y)

Date Sample Sent to Reviewer _____ / _____ / _____ (M / D / Y)

Items Received **(if different from above)** _____

Name of Reviewer _____

NOTES: _____

INVESTIGATOR: Keep a copy for your files and submit original form to destination specified in protocol. 2/96